Adult lifespan effects on functional specialization along the hippocampal long axis

Abbreviated title: Hippocampal long axis specialization in aging

Caitlin R. Bowman[1], Cara I. Charles[1], & Saisha M. Birr[1]

[1]Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, WI USA 53211

Correspondence: bowman2@uwm.edu (C.R.B.)

Number of pages: 44

Number of figures: 7

Number of tables: 4

Abstract: 237 words

Introduction: 697

Discussion: 1,499

Conflicts of interest. The authors declare no competing financial interests.

Acknowledgements. This work was supported by internal funding from the University of Wisconsin-Milwaukee, including an Advanced Opportunity Fellowship awarded to C.I.C. The authors thank the members of the Cognition, Aging, and Brain Imaging Lab and UW-Milwaukee Neuroscience Area for their feedback on this work.

Abstract

There has been increasing attention to differences in function along the hippocampal long axis, with posterior regions proposed to have properties that are well suited to representing fine-grained details and coarser representations in anterior regions. Whether long axis functional specialization persists into older age is not well understood, despite well documented memory changes in older age. In this study, we used a large database of fMRI data (n =323 humans of both sexes included) from across the adult lifespan (ages 18-88) to determine the degree of functional differentiation across the hippocampal posterior-anterior axis. Our first approach was to measure the similarity among signals within each hippocampal subregion. We found that intra-region signals within the most posterior hippocampal subregion became more similar in older age, but did not relate to episodic memory performance. As a second approach, we measured functional connectivity between hippocampal subregions and the rest of the brain. The functional connectivity profiles of the posterior and anterior hippocampal subregions became more distinct from one another with increasing age, and age-related reductions in connectivity were strongest for the intermediate portion of the hippocampus. In contrast, anterior hippocampal functional connectivity remained relatively stable across the adult lifespan, and stronger anterior hippocampus connectivity with the anterior cingulate was associated with better episodic memory in older adults, suggesting that the anterior hippocampus may help some older adults compensate for age-related changes to more posterior hippocampal regions to preserve episodic memory.

Significance Statement

There is an increasing understanding that differences across the hippocampal long axis help give rise to multifaceted episodic memories. Yet, whether hippocampal long axis differentiation persists into older age is not well understood. Here, we show that older age exaggerates the differentiation along the hippocampal long axis due largely to changes in posterior and intermediate portions of the hippocampus. Anterior hippocampal signals were more stable and were sometimes associated with better episodic memory performance in older age. These findings suggest that functional declines in posterior hippocampus may be a normal part of healthy aging, but that some older adults offset this decline by upregulating anterior hippocampal function, which in turn helps maintain episodic memory.

The hippocampus is critical for episodic memory function (Scoville & Milner, 1957) and shows structural and functional decline in healthy (Hu & Li, 2020; Leal & Yassa, 2015; O'Shea et al., 2016) and pathological aging (Anand & Dhikav, 2012; Peng et al., 2014). A functional differentiation along the hippocampal long axis has been proposed, with posterior hippocampus representing fine-grained information and anterior hippocampus having coarser representations that integrate across larger temporal and spatial windows (Brunec et al., 2018; Poppenk et al., 2013). This long axis differentiation may emerge due to differences in the granularity of signals within the hippocampus. A prior study in young adults showed less correlated signals across voxels within the posterior hippocampus compared to those within the anterior hippocampus (Brunec et al., 2018). The authors took this as evidence that the posterior hippocampus is well suited to encoding information over narrow spatial and temporal windows, because its more variable and dynamic signals would be capable of capturing idiosyncratic, fine-grained details. However, a later study found a different patten: signals were least similar to one another in intermediate portions of the hippocampus and more similar in the furthest anterior and posterior portions (Thorp et al., 2022). Thus, there remains some question of the nature of intra-hippocampal signals across the hippocampal long axis. A prior aging study showed increases in the similarity of signals within the posterior medial temporal lobe, including the posterior hippocampus, and that these increases were associated with poorer episodic memory abilities (Salami et al., 2016) providing initial evidence that disruptions to intra-hippocampal signals contribute to age-related declines in episodic memory.

Patterns of structural and functional connectivity between the hippocampus and the rest of the brain may also contribute to hippocampal long axis specialization (Catenoix et al., 2011; Duvernoy et al., 2005; Fanselow & Dong, 2010; Frank et al., 2019; Jung et al., 1994; Kahn et al., 2008). Prior work in healthy young adults has shown that parts of lateral prefrontal cortex and lateral parietal cortex have stronger functional connectivity with the posterior than the anterior hippocampus, while the ventromedial prefrontal cortex showed greater coupling with the

anterior compared to posterior hippocampus (Frank et al., 2019). Other work has positioned the hippocampal functional gradient within larger medial temporal lobe (MTL) systems (Libby et al., 2012; Ranganath & Ritchey, 2012; Rugg & Vilberg, 2013). According to this framework, the posterior hippocampus is part of the posterior medial system that includes the parahippocampal cortex, retrosplenial cortex, posterior cingulate, precuneus, angular gyrus, and anterior thalamus. The anterior hippocampus is part of the anterior temporal system, which includes the perirhinal cortex, lateral orbitofrontal cortex, amygdala, and temporal pole. In older adults, separable posterior medial and anterior temporal networks have been detected (Das et al., 2015), healthy aging is associated with weaker within-network connections for both the posterior medial and anterior temporal networks (Hrybouski et al., 2023). A prior study that included older adults is a sample that was predominantly children, young, and middle aged adults showed age-related decreases in connectivity between the posterior hippocampus and the anterior cingulate and medial superior frontal gyrus (Panitz et al., 2021). Yet, the extent to which these effects are driven by differences in advanced age and their relationship to memory abilities remains unclear.

We tested whether patterns of hippocampal functional specialization persist across the adult lifespan and how any age-related differences in hippocampal specialization contribute to known age-related declines in episodic memory (Fraundorf et al., 2019; Old & Naveh-Benjamin, 2008; Spencer & Raz, 1995; Toner et al., 2009). We used resting-state fMRI data from individuals aged 18-88 (n = 323) from the Cambridge Centre for Ageing and Neuroscience (CamCAN) dataset (Shafto et al., 2014). We compared signals across three anatomically defined segments along the hippocampal posterior-anterior axis (tail, body, head) in terms of both the similarity of signals within each hippocampal subregion and functional connectivity between each subregion and the rest of the brain. We related these metrics to age-related differences in performance on an episodic memory task. Based on the proposed role of the posterior hippocampus in representing fine-grained details in memory and known age-related

decline in episodic memory, we expected to find disproportionate age-related differences in posterior hippocampal function.

Materials and Methods

Data and Code Availability

The raw data come from a publicly available dataset (https://www.cam-can.org). Intervoxel similarity values, functional connectivity values, scores on the behavioral tasks we used, and nuisance covariates for individual subjects are publicly available through the Open Science Framework (https://osf.io/qba8n/). Analytic code is also available.

Subjects

All data came from the publicly available CamCAN dataset (Shafto et al., 2014). From the larger dataset, we obtained resting state fMRI scans, anatomical MRI scans, and behavioral data from 653 individuals aged 18-88. To ascertain cognitive health, all participants underwent cognitive testing with the Mini-Mental State Exam (MMSE). Those who scored >24/30 points and who did not report any neurological conditions were invited to participate in the fMRI portion of the study. Of the 653 participants obtained, we excluded one subject due to missing functional data and another due to failed parcellation of their anatomical images. We excluded 24 subjects because they had fewer than 10 voxels in one or more hippocampal subregion. We also excluded for excessive motion. Our threshold for complete exclusion was having any single framewise displacement value greater than or equal to 1 mm or having fewer than 5 minutes of timepoints included after scrubbing (details below). These strict motion exclusions are necessary because functional connectivity analyses of rest data are especially sensitive to motion (Power et al., 2012, 2014). This procedure led to an additional 269 participants excluded. Thirty-five additional participants were excluded for having both excessive motion and too few voxels in a hippocampal subregion. The final sample for analyses involving only the neuroimaging data was 323 subjects. Because the emotional memory task that served as the

best measure of episodic memory abilities was only administered to half of the participants in the original CamCAN study, a subset of the sample used for neuroimaging analyses was carried forward to analyses linking brain indices to behavior. The sample for brain-behavior analyses included 157 subjects. For further details about the distribution of age, sex, and MMSE scores in these samples, see Table 1.

Table 1

Sample characteristics separated by decades-based age groups

	fMRI data only analyses			**Brain-behavior analyses**		
Age Group	**N included**	**% Female**	**Mean MMSE Score**	**N included**	**% Female**	**Mean MMSE Score**
18-29	51	55%	29.2	26	46%	29.4
30-39	67	46%	29.2	32	50%	29.3
40-49	71	46%	29.2	33	55%	29.3
50-59	43	63%	29.4	24	62%	29.6
60-69	45	42%	28.9	19	42%	28.8
70+	46	33%	28.1	23	30%	28.1
Total	323	47%	29.0	157	48%	29.1

Experimental design

Participants in the Cam-CAN study completed a series of behavioral tasks across a Stage 1 interview phase. They then completed a Stage 2 phase involving detailed cognitive testing and MRI. Testing occurred over three sessions (Shafto et al., 2014).

MRI Data Acquisition

Full details of the MRI acquisition protocol have been previously reported (Shafto et al., 2014). From the larger dataset, we used the resting state functional run and the T1-wighted and T2-weighted structural images. During the resting state functional run, participants were asked

to keep their eyes closed while 261 EPI volumes were acquired (1.97 second TR, 3 mm x 3 mm x 4.44 mm voxel), with a total acquisition time of 8 minutes and 40 seconds.

Anatomical data preprocessing and regions of interest selection

We defined anatomical regions of interest in each subject's native space from Freesurfer 7.1.1 (Fischl, 2012). We applied Freesurfer's standard cortical parcellation and subcortical segmentation to the T1-weighted anatomical image. Afterwards, we further segmented the hippocampus by applying Freesurfer's segmentHA_T2 protocol using both the T1-weighted and T2-weighted anatomical images as inputs (Iglesias et al., 2015). From the hippocampal segmentation, we selected the tail, body, and head (separately for the right and left hemispheres) as our posterior, intermediate, and anterior hippocampal ROIs, respectively (Figure 1A). We used the cortical parcellation and subcortical segmentation to define anatomical regions of interest to serve as targets in the functional connectivity analysis. We used 42 distinct anatomical labels (84 regions across left and right hemispheres) from the Desikan-Killiany cortical atlas and the subcortical segmentation (excepting the hippocampus since it served as the seed). For a full list of target regions, see Table S1. This approach averages across many voxels to increase the reliability of the signal and reduces the number of pairwise connections to correct for when multiple comparison corrections are needed. Using a whole-brain ROI approach also aids in interpreting findings by allowing us to leverage the known structural and functional properties of these regions (Ritchey & Cooper, 2020). We used the mutual information algorithm from Advanced Normalization Tools (ANTS) version 2.1.0 to register and transform the anatomical images to functional space.

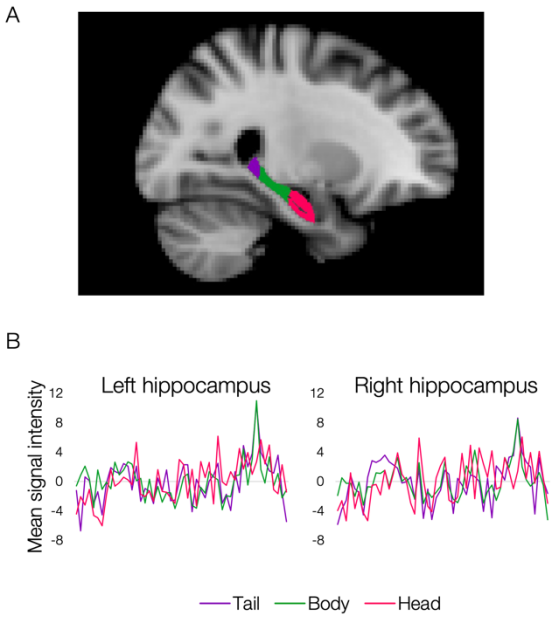

Figure 1. Hippocampal subregions of interest.
(A) The hippocampus was divided into three segments with the tail (purple) serving as the most posterior region, the body (green) serving as an intermediate region, and the head (pink) serving as the most anterior region. Boundaries between regions were determined by Freesurfer's hippocampal segmentation protocol and all analyses were computed in native space. For visualization purposes only, hippocampal regions of interest are depicted on a template T1-weighted anatomical image.
(B) Mean time courses for each hippocampal region are depicted separately for the right and left hemisphere. Because the number of timepoints differed across subjects based on motion exclusions, the first 50 usable timepoints were averaged for all subjects. The signal from each region was also mean-centered to emphasize the relative signal variability across regions in the visualization.

fMRI preprocessing

We first stripped the skull from each subject's resting state functional run using the Brain Extraction Tool from FSL (Jenkinson et al., 2006), then used FSL's MCFLIRT to motion correct the functional data, realigning all volumes to the middle volume. Using FEAT (fMRI Expert Analysis Tool) in FSL, the brain extracted, and motion corrected functional images were subjected to a high-pass temporal filter (100 sec) to remove low frequency drift in the scanner signal. Functional images were then minimally spatially smoothed using a 2-mm FWHM kernel.

Because functional connectivity measures can be especially sensitive to motion (Murphy et al., 2013; Power et al., 2012), we used the fMRI quality assurance tool

(https://github.com/poldrack/fmriqa) to identify subjects who moved excessively as well as individual timepoints with excessive motion. We computed framewise displacement (FD) scores, the temporal derivative of the signal variance over voxels (DVARS), translational and rotational motion, and the temporal derivatives of translational and rotational motion. We excluded all data from any subject who had any single FD value > 1 mm. For the remaining subjects, we identified individual timepoints with movement FD > .5 mm or DVARS > .5% and removed those timepoints as well as the timepoint immediately prior and two timepoints immediately after each motion-flagged timepoint. Subjects for whom fewer than 42% of their timepoints were usable (i.e., 5 minutes of data included) were excluded entirely. We used the 12 translational and rotational motion parameters, plus the mean signals from white matter, CSF, and whole brain and their temporal derivatives as volume-by-volume motion covariates when computing inter-voxel similarity within hippocampal subregions and functional connectivity between hippocampal subregions and the rest of the brain.

Inter-voxel similarity

Following pre-processing, we used the fslmeants function from FSL to extract a time course from each voxel within each hippocampal subregion separately from the right and left hemisphere of each subject (Figure 1B). We then used custom R code to compute the partial correlation between the timeseries of each pair of voxels in each subregion, controlling for volume-by-volume motion estimates. Following a Fisher's Z transformation of the resulting r-values, we averaged across the pairwise z-values for each subregion, leading to six inter-voxel similarity values for each subject (3 hippocampal subregions x 2 hemispheres).

Functional connectivity

We used the fslmeants function from FSL to extract a mean time course from each of the 84 target regions of interest (42 labels x right and left hemisphere). We then calculated the functional connectivity scores as a partial correlation between each hippocampal seed region (right and left hippocampal head, body, and tail = 6 seed regions) and each target region (right

and left of 42 cortical and subcortical targets = 84 target regions), controlling for volume-by-volume motion estimates. This procedure led to 504 pairwise connections for each subject. We then Fisher's Z transformed the resulting r-values and submitted these connectivity values to group-level analyses.

Episodic memory performance

From the cognitive measures obtained, only the emotional memory task tested episodic memory, and we therefore used it as our episodic memory measure. However, only half of the participants in the study were administered this task (the other half did an emotion regulation task instead). This led to 157 individuals who were included in imaging analyses and had episodic memory scores available.

In the emotional memory task, participants first underwent a study phase where they were shown a background picture for 2 seconds before an object would appear superimposed on the background. Participants were instructed to create a story linking the object to the background. After 8 seconds, the screen would advance to the next trial. There were 120 of these trials in the study phase, and participants were not told that there would be a memory test. The emotional component of the task came from the background pictures, which were from the International Affective Pictures Set (IAPS) (Lang et al., 1999). The background picture could depict a positive situation, a neutral situation, or a negative situation. There was a 10-minute retention interval between the study and test phases. There were three components of each test trial, testing different aspects of memory. First, as a measure of perceptual priming, participants saw a degraded version of an object and were asked to identify it. Next, as a measure of object recognition, they saw the full, non-degraded object image and were asked whether it was old (presented in the study phase) or new, also indicating their confidence. Lastly, as a measure of associative and contextual memory, participants were asked the valence (positive, neutral, or negative) of the background image presented with the object. There were 120 trials with old, studied objects and 40 trials with new objects. In our analyses, we included the object

recognition and background valence memory as indices of episodic memory. We averaged across the valence conditions. For object recognition, we computed the average hit rate (collapsed across confidence levels) across the three valence conditions, and we subtracted the single false alarm rate (Figure 2A). For the background valence memory, we computed the averaged hit rate across the three valence conditions and the average false alarm rate (e.g., a positive valence false alarm would be responding ‘positive’ to an object associated with a neutral or negative background image). We then computed the difference between the hit and false alarm rates (Figure 2B). These two metric were highly correlated with one another $r(157) = .73$, $p < .001$, so we created an episodic memory composite score by calculating z-scores for each measure, then averaged across the two resulting z-scores for each participant (Figure 2C). We also used scores from the Visual Short-Term Memory task to account for general cognitive and memory processes when assessing the relationship between hippocampal subregion function and episodic memory abilities. In this task, participants were presented with 1-4 colored discs at varying locations for 250 milliseconds. After a 900-millisecond blank display, one of the disc locations was highlighted with a border, and participants used a color wheel to indicate the color of the disc at that location, also indicating their confidence. From this task, we took the visual short-term memory capacity metric (K) as derived from the highest set size (4 items) (Zhang & Luck, 2008) (Figure 2D). The relationship between age and episodic memory performance was somewhat diminished but remained significant when visual short-term memory performance was accounted for, $r(151) = -.52$, $p < .001$, meaning that there were deficits in episodic memory above-and-beyond general cognitive or short-term memory deficits.

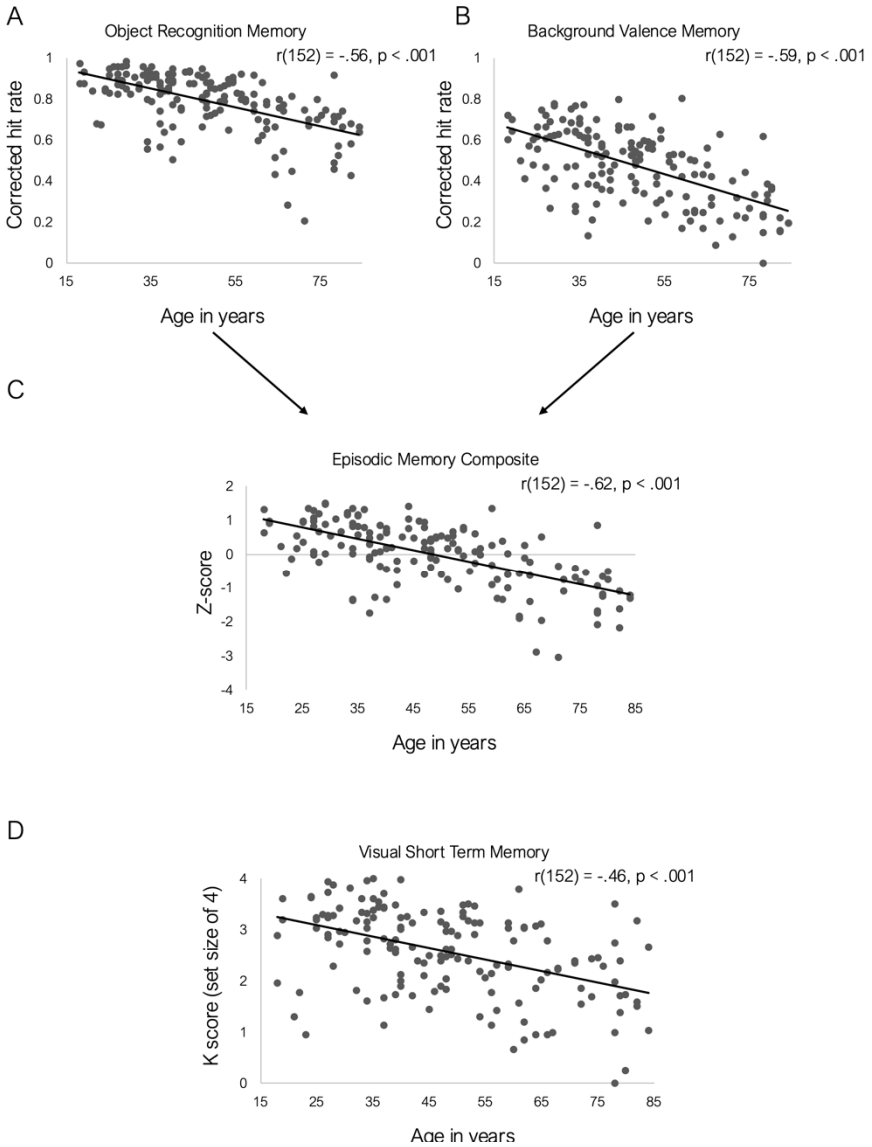

Figure 2. Relationship between age, episodic memory performance, and visual short-term memory.

The relationship between age and the corrected hit rate (hit rate – false alarm rate) for object recognition (A) and background picture valence (B) from the episodic memory task. (C) The relationship between age and the episodic memory composite derived from the object-emotional background task. The y-axis for the composite is the mean z-score across the two measures included in the composite (object recognition, and background valence memory). (D) The relationship between age and visual short-term memory at the highest set size test (4 items). The visual short-term memory task was used as a control for individual differences in general cognitive and memory abilities when determining the relationship between hippocampal subregion function and episodic memory abilities. In A-C, r values represent the partial correlation between age and the given behavioral metric, controlling for gender, motion, and hippocampal volume.

Statistical analysis

In all analyses that compared across ages, we included participant gender (dummy coded as female = 0, male = 1), subject-level motion (defined as the proportion of excluded timepoints), and overall bilateral hippocampal volume (measured as the proportion of total intracranial volume) as covariates. Thus, any age effects that emerged were above-and-beyond these other factors.

As a first test of differences in hippocampal functional specialization, we conducted an ANCOVA on the inter-voxel similarity values with age as a continuous predictor, hippocampal ROI (tail, body, head) and hemisphere (left, right) as categorical predictors, and the above covariates. We followed up on the resulting age interaction effect by conducting multiple linear regressions for each hippocampal subregion using age to predict intervoxel similarity, controlling for gender, motion, and hippocampal volume. We related the intervoxel similarity of each hippocampal subregion to each memory metric using multiple regression, also including age and the age x intervoxel similarity interaction effects as predictors of episodic memory performance, accounting for individual differences in visual short-term memory performance and with gender, motion, and hippocampal volume as covariates.

To assess the degree of similarity in the functional connectivity profiles of the hippocampal subregions, we computed a correlation between the entire series of connectivity values for each pair of ipsilateral hippocampal subregions for each participant. We computed a Fisher's Z transformation on the resulting r-values and submitted them to a 3 (hippocampal subregion comparison) x 2 (hemisphere) x age (continuous) ANCOVA. To follow-up on the significant age x hippocampal subregion comparison x hemisphere interaction, we computed separate correlations relating age to the degree of similarity for each pair of hippocampal subregions in each hemisphere.

Next, we investigated age-related differences in functional connectivity along the hippocampal long axis. We confirmed that there were differences in functional connectivity

along the hippocampal long axis by submitting functional connectivity values to a 3 (hippocampal ROI: head, body, tail) x 2 (hippocampal hemisphere: left, right) x 42 (cortical and subcortical target ROIs) x 2 (target hemisphere: left, right) repeated-measures ANCOVA with covariates. We focused on main effects of hippocampal ROI and age x hippocampal ROI interaction effects, but complete ANCOVA results for each target region are available in the OSF repository (https://osf.io/qba8n/). We followed up on the significant hippocampal ROI x target ROI interaction by computing separate age (continuous) x 3 (hippocampal ROI: head, body, tail) x 2 (hippocampal hemisphere: left, right) x 2 (target hemisphere: left, right) mixed-factors ANCOVAs for each target ROI. We used the Holm-Bonferroni method to correct for multiple comparisons given the 42 separate regressions performed. To follow up on significant age x hippocampal subregion effects in connectivity, we computed correlations between continuous age and connectivity strength separately for each hippocampal subregion.

We then sought to determine the behavioral relevance of age-related differences in hippocampal long axis connectivity. For each region showing age-related moderation of hippocampal long axis connectivity, we computed a multiple regression using age, the strength of connectivity with each hippocampal subregion, and the interaction between age and hippocampal subregion connectivity as predictors of episodic memory scores. We also accounted for visual short-term memory performance and standard covariates. To follow up on significant age x hippocampal subregion interaction effects, we separated the sample into those age 18-49 and those aged 50+ and re-computed the multiple regression without age or age interaction effects. These larger age ranges were chosen for exploring interactions based on the smaller sample size for analyses including the behavioral data (18-49 n = 91; 50+ n = 66).

Results

Age-related signal differences within hippocampal subregions

Our first approach to understanding the impact of age on hippocampal function specialization was to compare signals from within each of the three hippocampal regions. As in

prior studies, we computed the correlation across timeseries for each pair of voxels within each hippocampal region ('inter-voxel similarity') (Brunec et al., 2018; Thorp et al., 2022). Higher values on this metric indicate that the voxels within a given hippocampal subregion have more similar signals to one another, with higher similarity proposed to subserve integration across memories and generalization as opposed to specificity and discrimination (Bowman & Zeithamova, 2018; Brunec et al., 2018; Collin et al., 2015; Poppenk et al., 2013; Schlichting et al., 2015). The group-level inter-voxel similarity values across all ages are depicted in Figure 3A. Across all age groups, inter-voxel similarity values were numerically *highest* in the tail of the hippocampus and relatively less similar to one another in the body and head. However, the main effect of hippocampal region was not significant when participant gender, motion, and hippocampal volume were included in the model as covariates, $F(1.9,486.9) = .65$, $p = .52$, $\eta_p^2 = .003$. There was, however, a significant age x hippocampal subregion interaction, $F(122.2,486.9) = 1.47$, $p = .003$, $\eta_p^2 = .27$. Figure 3B presents the inter-voxel similarity values for the left and right hippocampus separated into six decades-based age groups. Visual inspection suggests that the general pattern from Figure 3A is apparent across age groups with the exception of the 18–29-year-old group in the right hippocampus, which shows the highest inter-voxel similarity in the body of the hippocampus. In addition, the pattern of higher inter-voxel similarity in the hippocampal tail vs body and head becomes more pronounced in older age groups.

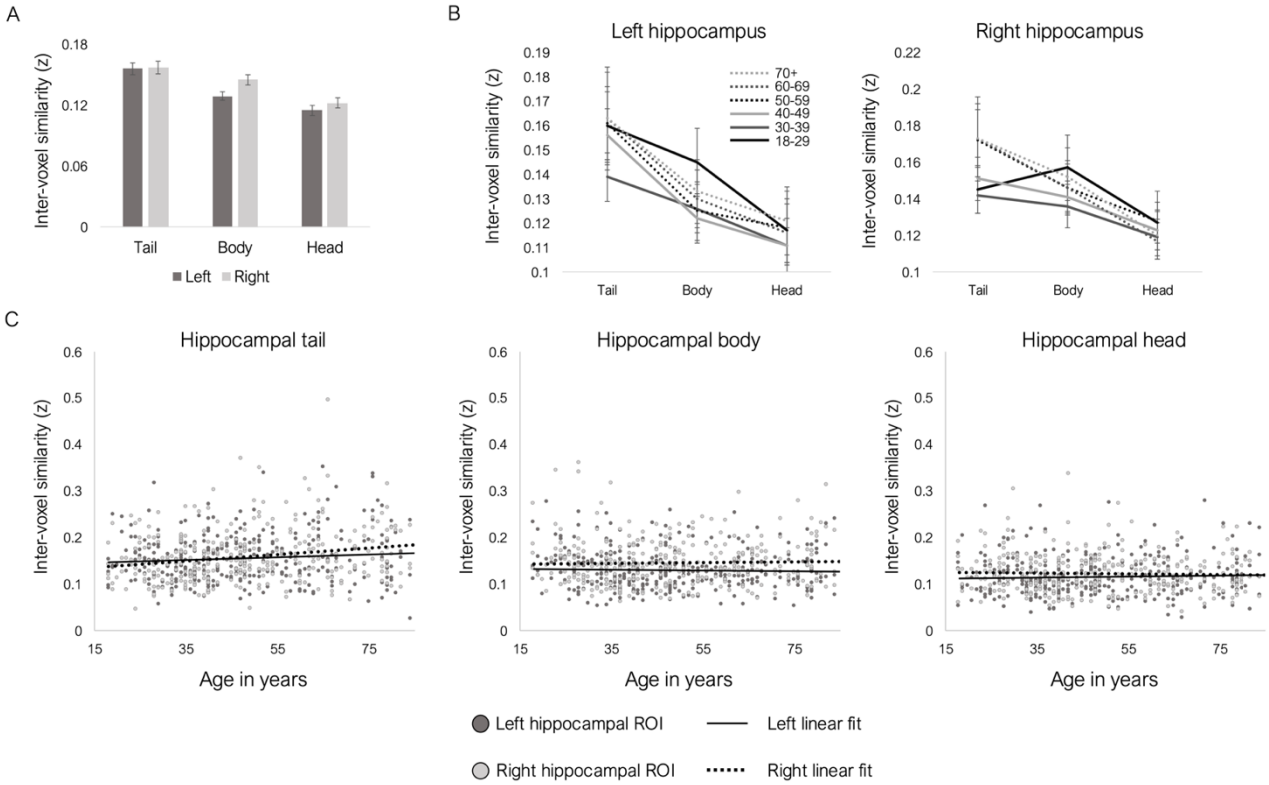

Figure 3. Age-related differences in the correlation among intra-hippocampal signals.
(A) Mean inter-voxel similarity separated by hippocampal subregion and left (dark bars) vs. right (light bars) hemisphere across all ages.
(B) Mean intervoxel similarity values for the left and right hippocampal subregions separated by approximately decades-based age groups. Solid lines represent younger age groups (18-49), and dashed lines represent older age groups (50+). Within each of those groups, darker lines represent younger groups, and lighter lines represent older groups.
(C) The relationship between continuous age and inter-voxel similarity in each hippocampal subregion. Each circle represents one participant, with darker circles for the left hippocampus and lighter circles for the right hippocampus. Trendlines represent the zero-order relationship between age and intervoxel similarity. Solid lines represent linear trends for the left hippocampus, and dashed lines represent linear trends for the right hippocampus.
In A-B, error bars represent 95% confidence intervals. In A-C, inter-voxel similarity is the mean Fisher's Z transformation of the correlations between all pairs of voxels within a given hippocampal subregion.

To quantify patterns of age-related change in the intra-hippocampal subregion signal similarity, we examined the relationship between age and inter-voxel similarity for each hippocampal subregion separately for the left and right hemisphere (Figure 3C). We conducted multiple linear regressions for each hippocampal subregion using age to predict intervoxel similarity, controlling for gender, motion, and hippocampal volume. Results showed a significant

positive relationship between age and IVS in the right hippocampal tail, ß = .138, t = 2.49, p = .013. There was a notable outlier on the IVS metric for the right hippocampal tail, but the positive age-IVS relationship remained significant even with that subject excluded. The age-IVS relationship was also directionally positive in the left hippocampus but was not significant, ß = .059, t = 1.03, p = .31. In contrast, the age-IVS relationships in the body and head of the hippocampus in both hemispheres were numerically negative (ß range -.002, -.104) but no relationship reached significance (p-value range .97, .07). Thus, it seems that the overall age x hippocampal subregion interaction was driven by the most posterior subregion being on a different trajectory than the intermediate and anterior regions, with more correlated signals in older age potentially reflecting dedifferentiation of posterior hippocampal signals.

Next, we sought to relate differences in intra-hippocampal signals to differences in episodic memory performance. We related the intervoxel similarity of each hippocampal subregion to the episodic memory score using multiple regression, also including age and the age x intervoxel similarity interaction effects as predictors of episodic memory performance, accounting for individual differences in visual short-term memory performance and with gender, motion, and hippocampal volume as covariates. To simplify the regression model and because right and left IVS for a given hippocampal subregion were correlated with one another (tail r = .362, body r = .37, head r = .57, all p's < .001), we averaged IVS values across hemispheres for each subregion. Full results are presented in Table 2. While the overall model was quite successful in accounting for differences in episodic memory, $F(11,145) = 12.11$, $p < .001$, adjusted $R^2 = .44$, and the overall effect of age on episodic memory no longer reached significance (p = .103), none of the individual IVS predictors or age x IVS interaction effects were significant. This lack of a significant IVS-episodic memory relationship remained when we ran separate regressions for each hippocampal subregion (all IVS and age x IVS interaction effects p > .29), when we ran separate regressions for the right and left hemispheres (all VIS and age x IVS interaction effects p > .22), and when we removed covariates (all IVS and age x

IVS interaction effects p > .20). Thus, despite signs of age-related differences in the similarity of signals within the hippocampus, intra-hippocampal signals at rest were not reliable predictors of age-related differences in episodic memory performance.

Table 2
Multiple regressions relating intervoxel similarity in each hippocampal region to episodic memory performance

Effect	ß	t-value	p-value
Gender (0 = F, 1 = M)	**-.166**	**-2.641**	**.009**
Hippocampal volume	-.055	-.844	.400
Motion	< .001	.002	.998
Visual short-term memory	**.227**	**3.250**	**.001**
Age	-.530	-1.639	.103
Tail IVS	.125	.626	.532
Body IVS	-.194	-.990	.324
Head IVS	.013	.057	.954
Age x Tail IVS	-.152	-.503	.616
Age x Body IVS	.159	.505	.614
Age x Head IVS	-.004	-.012	.990

Note: IVS = intra-voxel similarity

Age-related differences in hippocampal-whole brain functional connectivity

Looking beyond intra-hippocampal signals, functional specialization along the hippocampal long axis has been shown to emerge in part due to different patterns of connectivity with the rest of the brain (Catenoix et al., 2011; Duvernoy et al., 2005; Fanselow & Dong, 2010; Frank et al., 2019; Jung et al., 1994; Kahn et al., 2008). To test for age-related differences in patterns of functional connectivity along the hippocampal longitudinal axis, we computed functional connectivity between each hippocampal subregion and 42 cortical and subcortical regions in each hemisphere (84 total targets across hemispheres) defined from the Desikan-Killiany Atlas (Desikan et al., 2006). Figure 4 depicts functional connectivity values for all target regions separated by hippocampal subregion and approximately decade-based age groups (18-29, 30-39, 40-49, etc.).

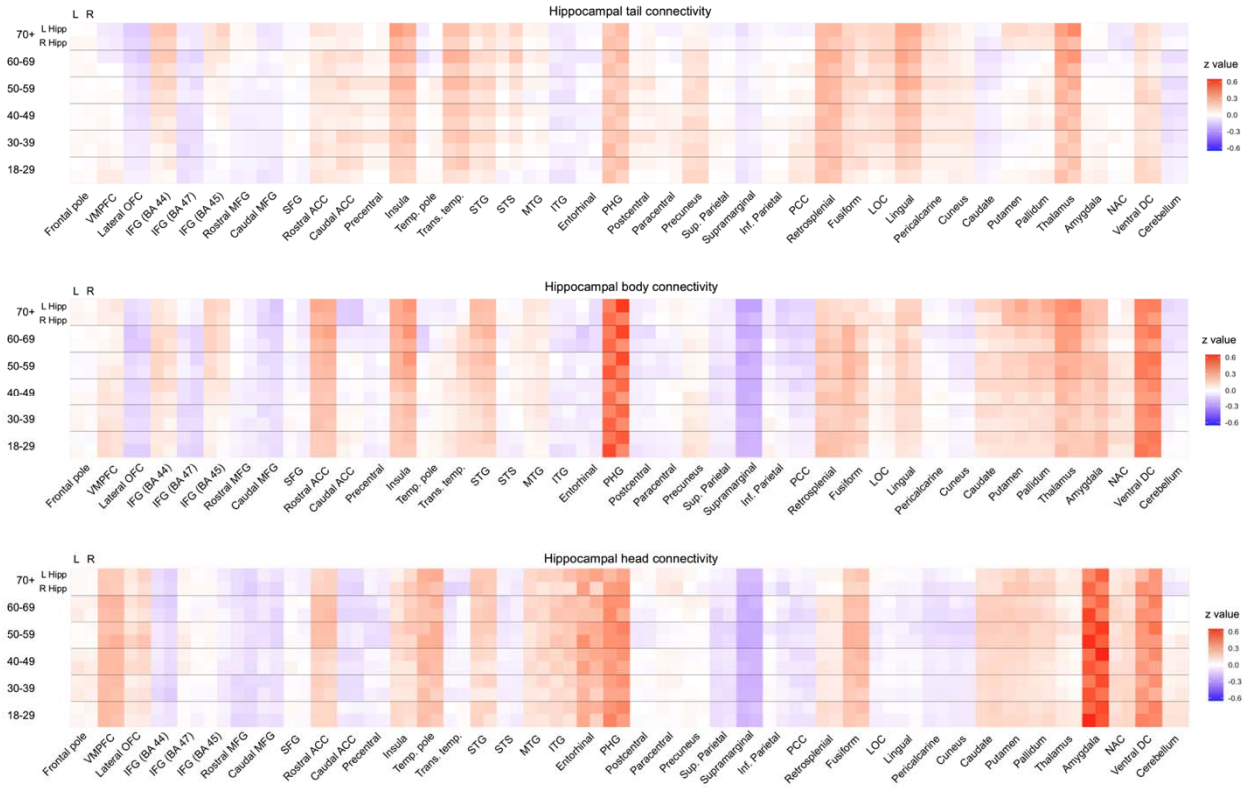

Figure 4. Functional connectivity for each hippocampal subregion and target region across the adult lifespan.
Functional connectivity was computed as the Fisher-z transformed partial correlation between timecourses in each hippocampal seed region and 84 cortical and subcortical target regions across both hemispheres. Functional connectivity values are presented separately for the (A) hippocampal tail, (B) hippocampal body, and (C) hippocampal head. In A-C, participants are separated into categorical age groups to visualize age effects (rows separated by grey line). Left (L) and right (R) hippocampal seeds are presented in adjacent rows, and left and right target regions are presented in adjacent columns. Full names and atlas labels for abbreviated target regions are presented in Table S1.

Our first approach was to determine the degree of overlap in the whole-brain connectivity profiles of each pair of hippocampal subregions and whether similarity in connectivity profiles differed across the adult lifespan. We used an approach similar to representational similarity analyses that are typically used to determine the similarity between patterns of functional activation (Kriegeskorte et al., 2008), substituting patterns of connectivity strength across target regions. In each individual subject, we computed the correlation between the unthresholded pattern of connections for each pair of ipsilateral hippocampal segments (e.g., left tail connectivity map similarity to left body connectivity map). This process resulted in

six Fisher's Z transformed correlation values for each subject (tail-body, body-head, tail-head for left and right hippocampus). We then submitted to a 3 (hippocampal subregion comparison: tail-body, body-head, tail-head) x 2 (hemisphere) x age (continuous) ANCOVA to determine the extent to which subregions of the hippocampus showed more similar patterns of functional connectivity compared to other pairs of subregions. The overall effect of the hippocampal subregion comparison was not significant, $F(1.5,390.3) = 1.03$, $p = .34$, $\eta_p^2 = .004$, nor was the interaction between age and hippocampal subregion comparison, $F(97.9,390.3) = 1.07$, $p = .33$, $\eta_p^2 = .21$, but there was a significant age x hippocampal subregion comparison x hemisphere interaction effect, $F(107.1,426.9) = 1.36$, $p = .01$, $\eta_p^2 = .26$. Figure 5A depicts the mean similarity in connectivity profiles for each subregion comparison separately for each hemisphere, collapsed across all ages. Overall, the connectivity profile for the body of the hippocampus was most similar to the tail, but also showed strong similarity to the connectivity profile of the head. This finding is notable since a common scheme for splitting the hippocampus into two segments collapses across the body and tail of the hippocampus in defining the posterior subregion and leaves the head as the anterior subregion (Poppenk et al., 2013). Our results suggest that the body may be more of a mix of 'tail-like' 'head-like' connectivity, with a slight bias toward the hippocampal tail. In contrast, the overlap in connectivity profiles was substantially lower for the tail and head, representing the extreme posterior and extreme anterior hippocampal subregions. Together, these findings are in line with different functional properties along the hippocampal long axis. Similarity scores for each subregion comparison and their relationship to continuous age are depicted in Figure 5B for the left hippocampus and Figure 5C for the right hippocampus. Based on visual inspection, it seems that the overall effect from Figure 5A is present in the left hippocampus across the lifespan, with slight age-related reductions in the similarity of connectivity profiles for all subregion comparisons across the lifespan. In contrast, in the right hippocampus, the body shows comparable similarity to the head and tail in early adulthood. The

similarity of the body-head and the tail-head connectivity profiles declines with age while the similarity between the tail and body profiles remains quite constant. To quantify this pattern, we conducted separate correlations between age and similarity scores for each pair of hippocampal subregions. All of the age-similarity score relationships in the left hippocampus were numerically negative but did not reach significance (tail-body $r(323) = -.02$, $p = .67$; body-head $r(323) = -.002$, $p = .97$; tail-head $r(323) = -.07$, $p = .21$). In the right hippocampus, the age-similarity score relationship was marginally negative for the body-head comparison, $r(323) = -.11$, $p = .054$, and significantly negative for the tail-head comparison, $r(323) = -.19$, $p < .001$. The relationship was numerically positive for the tail-body comparison but was not significant, $r(323) = .02$, $p = .74$. Taken together, aging results show that the specialization of functional connectivity profiles across hippocampal subregions is established in the left hippocampus in the youngest subjects tested here. However, that pattern is established somewhat later in the right hippocampus, driven by decreases in similarity between the head from the more posterior subregions, with the tail and the body maintaining or even slightly increasing the overlap in their connectivity profiles across the adult lifespan.

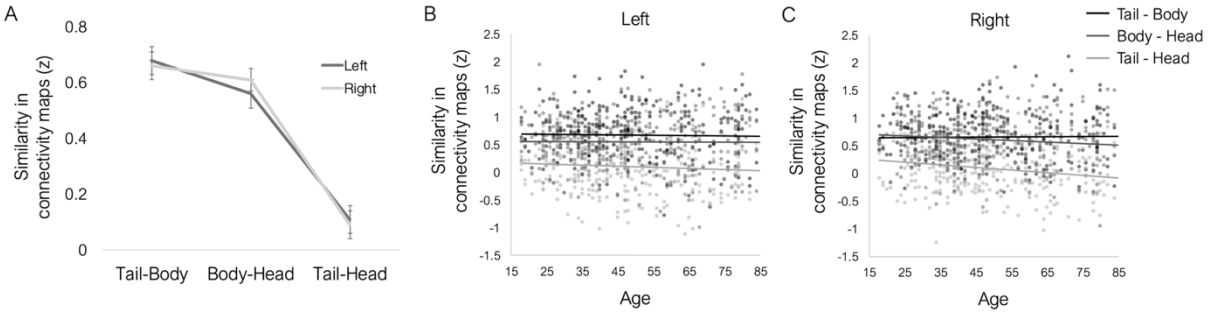

Figure 5. Regions showing significant connectivity gradients and the of overlap in connectivity profiles between hippocampal subregions.
(A) Similarity in unthresholded functional connectivity profiles between pairs of hippocampal subregions (body and tail, body and head, tail and head). Similarity values are the Fisher's Z transformation of the Pearson's correlation between the connectivity values for all target regions across both hemispheres associated with each pair of hippocampal subregions. Results are presented separate for the left (dark line) and right (light line) hippocampus. Error bars represent 95% confidence intervals for the mean across subjects.
The relationship between continuous age (in years) and similarity in unthresholded functional connectivity profiles between pairs of hippocampal subregions in the (B) left and (C) right hippocampus.

Next, we sought to understand the specific connections that differ between hippocampal subregions and any age-related differences in the pattern of connectivity across hippocampal subregions and the rest of the brain. We first confirmed that there were overall differences in patterns of functional connectivity across the hippocampal subregions. We computed a 3 (hippocampal subregion: head, body, tail) x 2 (hippocampal hemisphere: left, right) x 42 (cortical and subcortical target ROIs) x 2 (target hemisphere: left, right) repeated-measures ANCOVA with age, gender, hippocampal volume, and motion as covariates. As expected, there was a significant hippocampal subregion x target region interaction effect, $F(22.0,7008.8) = 2.11$, $p = .001$, $\eta_p^2 = .007$, indicating differences in functional connectivity patterns across the hippocampal subregions. We next sought to determine the nature of these function connectivity differences and test for age-related differences in functional connectivity patterns by computing separate age (continuous) x 3 (hippocampal subregion: head, body, tail) x 2 (hippocampal hemisphere: left, right) x 2 (target hemisphere: left, right) mixed-factors ANCOVAs for each target region. Results from the main effect of hippocampal ROI and the age x hippocampal ROI interaction from these ANCOVAs are presented in Table 3.

Table 3

Results for the main effect of hippocampal ROI and age x hippocampal ROI interaction from hippocampal ROI x hippocampal hemisphere x target hemisphere ANOVAs

	Hippocampal ROI main effect			Age x Hippocampal ROI interaction			
Target ROI	F-value	p-value	η_p^2	Effect	F-value	p-value	η_p^2
Regions showing greatest connectivity with the hippocampal tail							
IFG (BA 44)	6.57	.002	.025	T > B > H	1.25	.057	.24
Caudal ACC*	**5.35**	**.006**	**.021**	**T > B > H**	**1.74**	**< .001**	**.30**
Cuneus	4.23	.019	.016	T > B ~ H	0.78	.95	.16
Regions showing greatest connectivity with the hippocampal head							
VMPFC	13.12	< .001	.05	H > B > T	1.11	.23	.22
Amygdala	5.89	.006	.02	H > B > T	1.08	.29	.21
Regions showing greatest connectivity with the hippocampal body							
PHG	3.99	.02	.02	B > H > T	1.14	.18	.22
Thalamus	**5.75**	**.007**	**.02**	**B > T > H**	**1.30**	**.039**	**.25**
Regions showing no overall differences across hippocampal segments							

Frontal pole	1.22	.30	.005	--	1.28	.050	.24
Lateral OFC	3.24	.052	.01	--	1.13	.20	.22
IFG (BA 47)	**1.16**	**.32**	**.005**	**--**	**1.31**	**.035**	**.25**
IFG (BA 45)	**0.44**	**.61**	**.002**	**--**	**1.13**	**.042**	**.24**
Rostral MFG	3.17	.053	.012	--	1.22	.09	.23
Caudal MFG*	**0.21**	**.78**	**.001**	**--**	**1.49**	**.003**	**.27**
SFG	**1.83**	**.17**	**.007**	**--**	**1.51**	**.022**	**.28**
Rostral ACC	**2.73**	**.07**	**.01**	**--**	**1.37**	**.014**	**.26**
Precentral	0.12	.89	< .001	--	0.92	.71	.19
Insula	2.15	.12	.008	--	1.23	.06	.24
Temp. Pole	**2.78**	**.08**	**.01**	**--**	**1.42**	**.010**	**.26**
Trans. Temp.	2.34	.10	.009	--	1.25	.058	.24
STG	0.69	.48	.003	--	0.90	.76	.18
STS	1.15	.31	.004	--	0.91	.71	.19
MTG	0.49	.58	.002	--	1.02	.43	.20
ITG	0.36	.65	.001	--	1.18	.13	.23
Entorhinal	2.42	.11	.009	--	0.84	.85	.17
Postcentral	1.75	.18	.007	--	0.94	.66	.19
Paracentral	2.40	.10	.009	--	1.02	.45	.20
Precuneus*	**2.94**	**.06**	**.01**	**--**	**1.53**	**.002**	**.28**
Sup. Parietal	0.55	.56	.002	--	1.08	.29	.21
Supramarginal	2.18	.12	.008	--	1.05	.35	.21
Inf. Parietal*	**1.18**	**.31**	**.005**	**--**	**1.54**	**.001**	**.28**
PCC	0.34	.70	.001	--	1.25	.053	.24
Retrosplenial	0.10	.89	< .001	--	1.26	.054	.24
Fusiform	2.14	.13	.008	--	1.00	.48	.20
LOC	0.81	.43	.003	--	0.71	.98	.15
Lingual	1.53	.22	.006	--	1.11	.23	.22
Pericalcarine	2.41	.10	.009	--	0.87	.83	.18
Caudate	2.28	.11	.009	--	1.08	.29	.21
Putamen	1.15	.31	.004	--	1.14	.18	.22
Pallidum	1.71	.19	.007	--	1.07	.32	.21
NAC	3.09	.057	.01	--	1.14	.16	.22
Ventral DC	2.55	.09	.01	--	0.91	.74	.19
Cerebellum	1.61	.21	.006	--	1.25	.07	.24

Note: Within each table section, regions are organized by cortical lobe followed by subcortical regions. Full names of target regions are presented in Table S1. H = head, B = body, T = tail, ‘>’ indicates a significant difference between hippocampal segments at alpha = .05, and ~ indicates a difference at p = .05 - .1. Bold text is for age interaction effects that are significant at uncorrected alpha = .05 and starred labels indicate those surviving a Holm-Bonferroni correction for multiple comparisons.

Most target regions did not show significant differences in connectivity across hippocampal subregions (35/42, 83%). Two regions – the amygdala and VMPFC – showed an anterior to posterior functional connectivity gradient with the strongest connectivity to the head of the hippocampus and weakest connectivity to the tail. These findings align well with prior work on the role of the hippocampus in affective and motivational processing in connection with the amygdala (Fastenrath et al., 2014; Ghosh et al., 2013; Smith et al., 2006; Vaisvaser et al., 2013). Increased connectivity with the ventromedial prefrontal cortex is consistent with the anterior hippocampus playing an outsized role in memory abstraction and generalization (Bowman & Zeithamova, 2018; Collin et al., 2015; Zeithamova et al., 2012). Also notable is that neither of these regions showed significant age-related moderation, suggesting that the strongest connections with the hippocampal head are relatively stable across the adult lifespan. Three regions – caudal ACC, IFG-BA 44, and the cuneus – showed the reverse posterior to anterior functional connectivity gradient. Of these, the caudal ACC showed significant age-related moderation of its connectivity pattern, which we unpack below. IFG-BA 44 showed a marginal age-related effect. Thus, we have initial evidence that connections to the hippocampal tail differ more substantially with age than those of the hippocampal head. Lastly, two regions – PHG and the thalamus – showed highest connectivity with the body of the hippocampus. The body-thalamus connection showed age-related moderation that did not pass correction for multiple comparisons.

Next, we followed-up on the relationship between age and connectivity strength differences across hippocampal subregions for each of the four target regions where the age x hippocampal subregion interaction effect passed a correction for multiple comparisons (Table 3; see Figure S1 for additional regions that passed an uncorrected alpha = .05). Mean connectivity values for each hippocampal subregion separated by approximately decades-based age groups are presented in Figure 6A-D. The relationship between continuous age and connectivity

strength are depicted in Figure 6E-H. Across all four regions showing an age effect that passed correction, there was a significant negative relationship between age and connectivity with the hippocampal body (caudal ACC $r(323) = -.37$, $p < .001$; caudal MFG $r(323) = -.12$, $p = .03$; precuneus $r(323) = -.19$, $p < .001$; inferior parietal $r(323) = -.24$, $p < .001$). There was also a marginal negative age relationship for tail-caudal ACC connectivity, $r(323) = -.11$, $p = .053$. With the exception of the age relationship to tail-caudal MFG connectivity that was numerically positive, $r(323) = .02$, $p = .79$, age was associated with numerically or significantly weaker connectivity across all hippocampal subregions and target regions. Thus, it seems that older age tended to weaken hippocampal connectivity with these regions, but that tendency was especially strong for the body of the hippocampus. However, weaker hippocampal connectivity with age was not universal, as the regions that did not pass correction for multiple comparison tended to show increased connectivity strength with older age (see Supplement). Instead, it seems that weakening connectivity with the hippocampal body was relatively specific to these frontal and parietal regions.

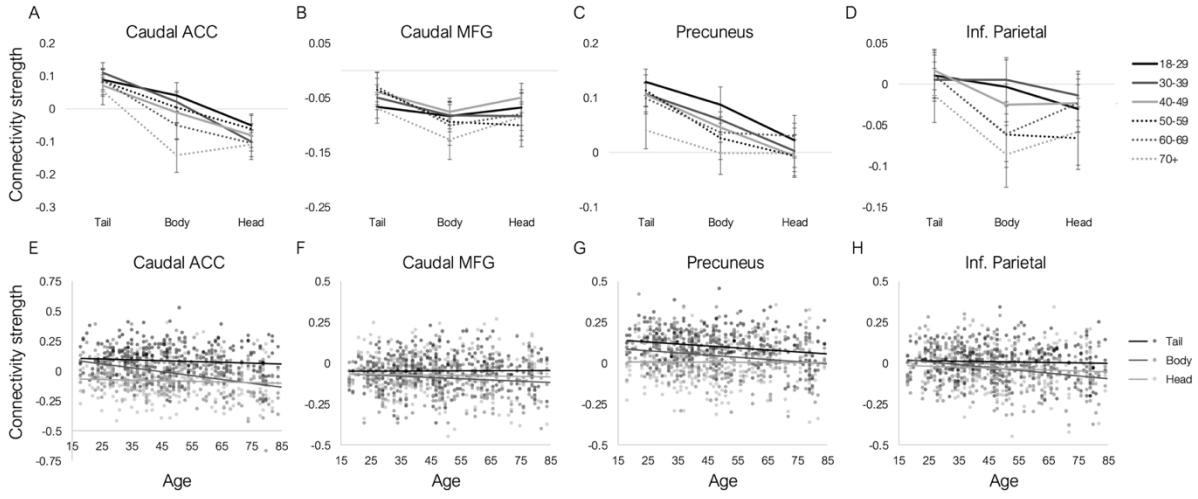

Figure 6. Age effects in functional connectivity with hippocampal subregions.
Top row (A-D): Connectivity for each hippocampal subregion separated into six approximately decades-based age groups in regions that showed a significant age x hippocampal subregion effect that passed a correction for multiple comparisons (see Table 3). Solid lines represent the youngest age groups (18-49), and dashed lines represent older age groups (50+). Within each set of lines, darker lines represent younger age groups and light lines represent older age groups. Error bars depict the 95% confidence interval of the mean across subjects.

Bottom row (E-H): The relationship between continuous age and functional connectivity strength for each hippocampal subregion and the same target regions that showed significant age moderation. Dots represent individual subjects and lines represent linear age trends. The darkest dots and lines are for the hippocampal tail, the medium grey dots and lines are for the hippocampal body, and the lightest grey are for the hippocampal head.

Lastly, we tested the extent to which age differences in hippocampal subregion connectivity patterns and connection strength with particular target regions explained age-related differences in memory abilities. For each target region showing a significant overall age x hippocampal subregion interaction effect, we computed a regression with age, connectivity with each hippocampal subregion (tail, body, head), and their interactions as predictors of episodic memory performance. We also included visual short term memory performance in the model to identify effects that were relatively specific to episodic memory in addition to standard gender, motion, and hippocampal volume covariates. Full results from these regressions are presented in Table 4. In all cases, the full model explained a significant amount of variance in episodic memory performance (R^2 .44-.46). However, age remained a significant predictor of episodic memory performance for all models, meaning that hippocampal subregion connectivity did not fully explain age differences in episodic memory. Visual short term memory performance was also a significant predictor of episodic memory performance in all cases, indicating that there are likely some general cognitive or memory abilities that are, once again, not fully explainable by hippocampal subregion connectivity. However, we also found that hippocampal head-caudal ACC connectivity was a marginal overall negative predictor of episodic memory performance, and that the relationship between connectivity strength and episodic memory was significantly moderated by age. To better understand this interaction effect, we computed separate regressions for the 18-49 vs. 50+ age groups, including the overall connectivity strength for each hippocampal subregion without their age interaction effects. Figure 7A depicts the resulting regression coefficients and their standard errors separately for each subregion and for each group. Stronger hippocampal head-caudal ACC connectivity was associated with better

memory performance in the older half of the sample, but the relationship was directionally negative in the younger age group. Thus, it seems that upregulation of connectivity between this frontal region and the hippocampal head played a compensatory role for older adults, helping to maintain episodic memory performance for some older adults. The results of similar regressions for the other regions showing age moderation of hippocampal connectivity are presented in Figure 7B-D. We also computed regressions linking functional connectivity to episodic memory performance in the regions that showed some evidence of age moderation of hippocampal connectivity but did not pass correction for multiple comparisons (Table S2). No additional regions showed a significant connectivity – behavior relationship or age moderation of a connectivity – behavior relationship. Thus, the age-related compensatory effect we found for anterior-caudal ACC connectivity was relatively unique.

Table 4
Multiple regressions relating functional connectivity between each hippocampal subregion and target regions showing an age x hippocampal subregion interaction to episodic memory performance

Caudal ACC Model – $F(11,145) = 12.97$, $p < .001$, adjusted $R^2 = .46$			
Effect	ß	t-value	p-value
Gender (0 = F, 1 = M)	-.17	-.2.69	.008
Hippocampal volume	-.07	-1.10	.27
Motion	-.01	-0.10	.92
Visual short-term memory	**.24**	**3.43**	**< .001**
Age	**-.41**	**-4.67**	**< .001**
Tail – caudal ACC connectivity	.01	0.05	.96
Body – caudal ACC connectivity	-.03	-0.12	.90
Head – caudal ACC connectivity	-.37	-1.73	.09
Age x Tail – caudal ACC connectivity	-.04	-0.18	.86
Age x Body – caudal ACC connectivity	.05	0.22	.82
Age x Head – caudal ACC connectivity	**.45**	**2.08**	**.039**

Caudal MFG Model – $F(11,145) = 12.13$, $p < .001$, adjusted $R^2 = .44$			
Effect	ß	t-value	p-value
Gender (0 = F, 1 = M)	**-.13**	**-2.01**	**.046**
Hippocampal volume	-.06	-0.90	.37
Motion	-.01	-0.16	.88
Visual short-term memory	**.23**	**3.30**	**.001**
Age	**-.51**	**-5.69**	**< .001**
Tail – caudal MFG connectivity	.34	1.33	.19

Body – caudal MFG connectivity	-.20	-0.73	.47
Head – caudal MFG connectivity	-.04	-0.16	.88
Age x Tail – caudal MFG connectivity	-.30	-1.18	.24
Age x Body – caudal MFG connectivity	.21	0.77	.44
Age x Head – caudal MFG connectivity	.06	0.26	.79

Precuneus Model –
$F(11,145) = 12.95$, $p < .001$, adjusted $R^2 = .46$

Effect	ß	t-value	p-value
Gender (0 = F, 1 = M)	**-.16**	**-2.50**	**.01**
Hippocampal volume	-.04	-0.57	.57
Motion	.01	0.11	.92
Visual short-term memory	**.25**	**3.57**	**< .001**
Age	**-.56**	**-5.87**	**< .001**
Tail – precuneus connectivity	-.09	-0.41	.68
Body – precuneus connectivity	-.23	-0.85	.40
Head – precuneus connectivity	.41	1.68	.096
Age x Tail – precuneus connectivity	.11	0.50	.62
Age x Body – precuneus connectivity	.25	0.94	.35
Age x Head – precuneus connectivity	-.31	-1.23	.22

Inf. Parietal Model –
$F(11,145) = 13.18$, $p < .001$, adjusted $R^2 = .46$

Effect	ß	t-value	p-value
Gender (0 = F, 1 = M)	**-.16**	**-2.58**	**.01**
Hippocampal volume	-.05	-0.74	.46
Motion	.02	0.36	.72
Visual short-term memory	**.22**	**3.19**	**.002**
Age	**-.51**	**-6.97**	**< .001**
Tail – inf. parietal connectivity	-.02	-0.10	.92
Body – inf. parietal connectivity	-.37	-1.47	.14
Head – inf. parietal connectivity	.37	1.54	.13
Age x Tail – inf. parietal connectivity	.05	0.23	.82
Age x Body – inf. parietal connectivity	.43	1.72	.088
Age x Head – inf. parietal connectivity	-.28	-1.13	.26

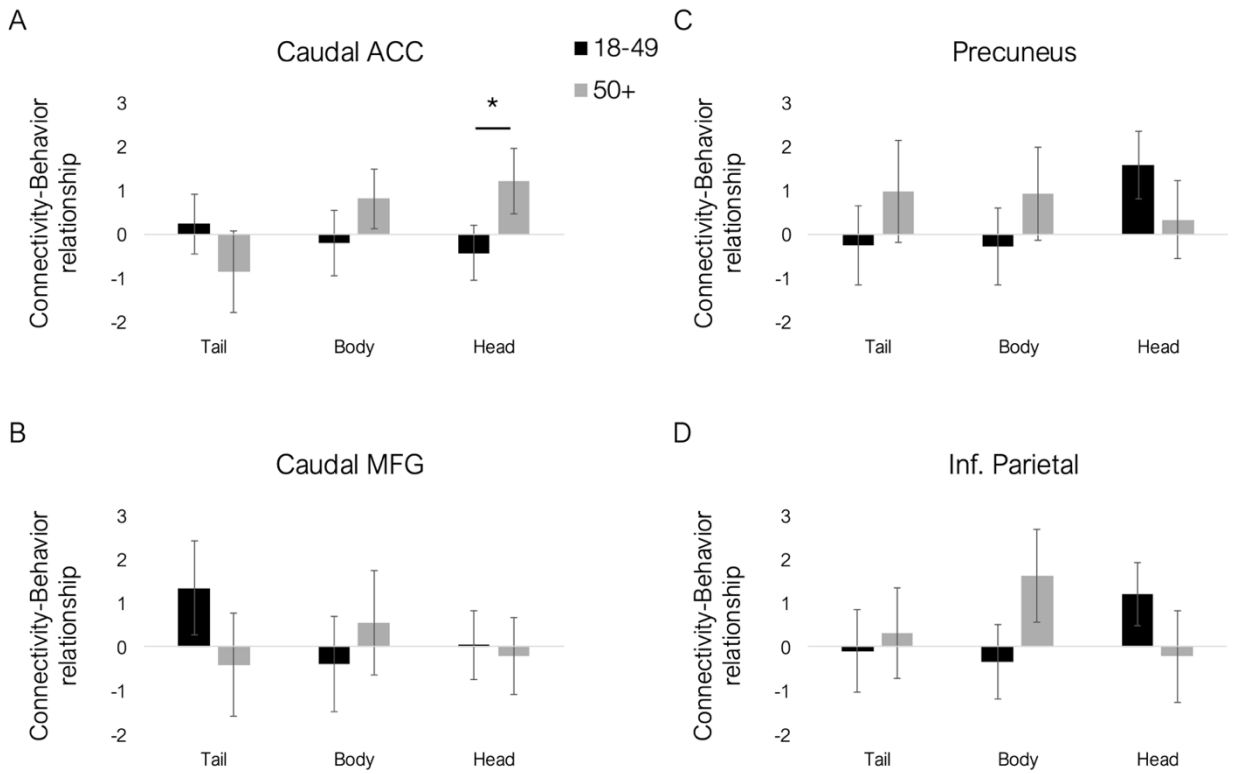

Figure 7. Age differences in the relationship between hippocampal subregion connectivity and episodic memory performance.
Non-standardized regression coefficients and their standard errors for regressions relating hippocampal subregion connectivity to episodic memory performance in (A) caudal ACC, (B) caudal MFG, (C) precuneus, and (D) inferior parietal. Regressions were computed separately for the younger half of the sample (ages 18-49) and older half (ages 50+) to elucidate potential age x connectivity interaction effects in the connectivity – memory performance relationship. Star indicates a significant age interaction effect (alpha = .05) in a multiple regression across all ages that also controlled for gender, motion, total hippocampal volume, and visual short term memory performance (Table 4).

Discussion

We aimed to test the degree of functional differentiation along the hippocampal long axis across the adult lifespan and its relationship to episodic memory. In terms of signals within the hippocampus, we found an age interaction where signals within the most posterior hippocampal subregion tended to become more similar to one another with increasing age, whereas the intermediate and most anterior regions tended to show less similar intra-region signals in older age. Yet, age-related differences in the similarity of signals within the hippocampus did not significantly predict episodic memory performance. We found that the whole-brain connectivity

profile of the right hippocampal head tended to become less similar to the profiles of the body and tail, whereas the similarity of the body and tail connectivity profiles did not differ with age. Several prefrontal and parietal regions also showed age moderation of hippocampal connectivity, which was driven by weaker connectivity with the intermediate part of the hippocampus in older age. Lastly, we found that connectivity between the anterior hippocampus and the anterior cingulate positively predicted episodic memory performance in older but not younger subjects, potentially reflecting compensation from the anterior hippocampus in light of age-related decline in the intermediate and posterior hippocampus.

One theory of hippocampal function is that there is a posterior to anterior gradient in which the posterior hippocampal representations are more detailed than anterior hippocampal representations (Poppenk et al., 2013). Compelling evidence for this theory came from a study examining the correlation of signals within the hippocampus, showing less correlated signals in the posterior versus anterior hippocampus (Brunec et al., 2018). The authors concluded that the low correlation among posterior hippocampal signals made the posterior hippocampus well suited to representing information with high resolution to support memory specificity. However, a more recent study tested multiple schemes for subdividing the hippocampus and compared them across two large datasets (Thorp et al., 2022). While there were differences based on the parcellation scheme, results generally pointed to higher similarity among signals in the posterior hippocampus once it was subdivided into more than two subregions. Our overall findings are most in line with the latter study: signals within the hippocampal tail were more correlated with one another than signals in the body and the head. One potential driver of differences across studies is that the Brunec et al. (2018) study used both resting state data and data from a navigation task, and the increase in intervoxel similarity from posterior to anterior was more prominent in the navigation task. Our study and the Thorp et al. (2022) study used only resting state data. Thus, it may be that intra-hippocampal signals are noisier during rest and will show

more variable patterns across the hippocampal long axis, but that these signaling patterns emerge when the hippocampus is engaged in a task.

Despite an overall pattern of intra-hippocampal signals that differed from predictions from theories of hippocampal long axis specialization, we found that intra-hippocampal signaling in the posterior hippocampus had a different trajectory across the adult lifespan compared to intermediate and anterior regions of the hippocampus, which is consistent with what we would predict based on known age-related declines in various measures of memory specificity (Hashtroudi et al., 1989; Naveh-Benjamin et al., 2003; Yassa et al., 2011). Signals within the posterior hippocampus tended to become more similar to one another with increasing age, the opposite trend for the intermediate and anterior hippocampal subregions. This finding is consistent with a prior study showing age-related increases in the strength of functional connectivity within posterior medial temporal lobes (Salami et al., 2016). Increasing similarity of signals in the posterior hippocampus is in line with neurocognitive aging theories suggesting dedifferentiation of neural signals in older age (Goh, 2011; Koen & Rugg, 2019; Park et al., 2012; Pauley et al., 2024): that neural responses become less selective and more broadly tuned in older age. Here we show that this effect may be specific to the posterior versus anterior regions of the hippocampus. Following from theories of hippocampal functional specialization, it would make sense for dedifferentiation of posterior hippocampal signals to hinder memory for episodic details. However, we did not find any significant relationship between intra-hippocampal signals and episodic memory performance, nor any age modulation of this relationship. It is possible that the measure of episodic memory did not sufficiently index memory for the kinds of episodic details affected by dedifferentiation of posterior hippocampal signals, or that dedifferentiation of these signals during rest is not predictive of functional specialization during a memory task. However, between the mixed findings on the nature of within-hippocampus signals across its long axis and the lack of a strong behavioral impact of

age differences in intra-hippocampal signals, it is also possible that differences in inter-voxel similarity are more an epiphenomenon than a key driver of episodic memory performance.

Yet, evidence for a functional specialization along the hippocampal long axis has also come from differences in patterns of structural and functional connectivity with the rest of the brain. Prior work has shown that the anterior hippocampus has structural and/or functional connections to the ventromedial prefrontal cortex (Blessing et al., 2016; Bowman & Zeithamova, 2018; Frank et al., 2019; Kier et al., 2004; Robinson et al., 2016; Wang et al., 2016; Zeithamova et al., 2012) and amygdala (Blessing et al., 2016; Duvernoy, 2013; Robinson et al., 2016), which we confirm by showing an overall anterior to posterior gradient in both regions. Likewise, connections between the posterior hippocampus and the anterior cingulate (Blessing et al., 2016; Panitz et al., 2021; Poppenk & Moscovitch, 2011; Robinson et al., 2016) and cuneus (Poppenk & Moscovitch, 2011) have been previously identified, and we show a posterior to anterior connectivity gradient in these regions, along with the part of the inferior frontal gyrus. We also showed relatively little overlap in connectivity profiles between the most posterior and most anterior hippocampal subregions, whereas the intermediate hippocampal subregion showed considerable overlap with both posterior and anterior hippocampus. Yet, there were still many regions that did not show strong connectivity differences across hippocampal subregions. Thus, we find evidence for a long axis gradient in hippocampal functional connectivity, but these differences are not universal and much of the brain shows comparable connectivity levels across hippocampal subregions.

We also found that older age moderated the pattern of connectivity across hippocampal subregions for part of the anterior cingulate, part of the middle frontal gyrus, the precuneus, and inferior parietal cortex. Age-related reductions in connectivity were strongest for the intermediate subregion of the hippocampus, with some evidence of weakening in the anterior cingulate-posterior hippocampus relationship as well. These findings are in line with the hypothesis that relatively posterior hippocampal regions are more impacted by aging (Bussy et al., 2021; Frisoni

et al., 2008; Y et al., 2023), but they are novel in that past work on age differences in posterior vs. anterior hippocampal connectivity have been mixed. One prior study used an extreme age groups design and showed age-related reductions in hippocampal functional connectivity with other regions of the medial temporal lobes during a mnemonic similarity task (Stark et al., 2021). Age differences tended to be comparable along the hippocampal long axis (perirhinal cortex) or greater in the anterior versus posterior hippocampus (parahippocampal cortex). Other work also using extreme age groups investigated differences in functional connectivity across the posterior-anterior axis with the rest of the brain and found a shift toward posterior connectivity in older age (Blum et al., 2014). Yet, there were also several regions with age reductions in connectivity with intermediate hippocampal subregions (Blum et al., 2014), including the precuneus and a parieto-occipital region, which is in line with the current findings. Thus, while further empirical evidence is needed to understand the nature of hippocampal long axis connectivity differences in older age, we provide novel evidence that age effects are most prominent in the intermediate and posterior hippocampus, with little evidence of age differences in anterior hippocampal connectivity.

Lastly, we found that functional connectivity between the anterior hippocampus and part of the anterior cingulate was associated with better episodic memory performance in older but not younger age. This anterior cingulate region showed the strongest connectivity with the posterior hippocampus when looking across all ages. Thus, this age effect may reflect a compensatory shift toward the anterior hippocampus among some older adults to help maintain episodic memory performance in the face of age-related changes to most posterior hippocampal regions. While upregulation of brain activity or connectivity can be a sign of age-related dysfunction (Cabeza et al., 2018; McDonough et al., 2022; Salami et al., 2014), here we see a clear, positive link to cognitive performance which suggests compensation. However, it is still possible that increasing connectivity to more anterior hippocampal regions had negative consequences for memory performance that were not identified by the episodic memory task

used here. Future studies using different memory tasks that tap into a wider range of memory abilities will clarify the implications of maintaining episodic memory performance through upregulation of connectivity with the anterior hippocampus.

References

Anand, K. S., & Dhikav, V. (2012). Hippocampus in health and disease: An overview. *Annals of Indian Academy of Neurology*, *15*(4), 239–246. https://doi.org/10.4103/0972-2327.104323

Blessing, E. M., Beissner, F., Schumann, A., Brünner, F., & Bär, K.-J. (2016). A data-driven approach to mapping cortical and subcortical intrinsic functional connectivity along the longitudinal hippocampal axis. *Human Brain Mapping*, *37*(2), 462–476. https://doi.org/10.1002/hbm.23042

Blum, S., Habeck, C., Steffener, J., Razlighi, Q., & Stern, Y. (2014). Functional connectivity of the posterior hippocampus is more dominant as we age. *Cognitive Neuroscience*, *5*(3–4), 150–159. https://doi.org/10.1080/17588928.2014.975680

Bowman, C. R., & Zeithamova, D. (2018). Abstract Memory Representations in the Ventromedial Prefrontal Cortex and Hippocampus Support Concept Generalization. *Journal of Neuroscience*, *38*(10), 2605–2614. https://doi.org/10.1523/JNEUROSCI.2811-17.2018

Brunec, I. K., Bellana, B., Ozubko, J. D., Man, V., Robin, J., Liu, Z.-X., Grady, C., Rosenbaum, R. S., Winocur, G., Barense, M. D., & Moscovitch, M. (2018). Multiple Scales of Representation along the Hippocampal Anteroposterior Axis in Humans. *Current Biology*, *28*(13), 2129-2135.e6. https://doi.org/10.1016/j.cub.2018.05.016

Bussy, A., Patel, R., Plitman, E., Tullo, S., Salaciak, A., Bedford, S. A., Farzin, S., Béland, M.-L., Valiquette, V., Kazazian, C., Tardif, C. L., Devenyi, G. A., & Chakravarty, M. M. (2021). Hippocampal shape across the healthy lifespan and its relationship with cognition. *Neurobiology of Aging*, *106*, 153–168. https://doi.org/10.1016/j.neurobiolaging.2021.03.018

Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., Lindenberger, U., Nyberg, L., Park, D. C., Reuter-Lorenz, P. A., Rugg, M. D., Steffener, J., & Rajah, M. N.

(2018). Maintenance, reserve and compensation: The cognitive neuroscience of healthy ageing. *Nature Reviews Neuroscience*, *19*(11), 701–710. https://doi.org/10.1038/s41583-018-0068-2

Catenoix, H., Magnin, M., Mauguiere, F., & Ryvlin, P. (2011). Evoked potential study of hippocampal efferent projections in the human brain—ClinicalKey. *Clinical Neurophysiology*. https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S1388245711003567?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1388245711003567%3Fshowall%3Dtrue&referrer=

Collin, S. H. P., Milivojevic, B., & Doeller, C. F. (2015). Memory hierarchies map onto the hippocampal long axis in humans. *Nature Neuroscience*, *18*(11), 1562–1564. https://doi.org/10.1038/nn.4138

Das, S. R., Pluta, J., Mancuso, L., Kliot, D., Yushkevich, P. A., & A. Wolk, D. (2015). Anterior and Posterior MTL Networks in Aging and MCI. *Neurobiology of Aging*, *36*(0 1), S141-S150.e1. https://doi.org/10.1016/j.neurobiolaging.2014.03.041

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Duvernoy, H. M. (2013). *The Human Hippocampus: An Atlas of Applied Anatomy*. J.F. Bergmann-Verlag.

Duvernoy, H. M., Cattin, F., Naidich, T. P., Raybaud, C., Risold, P. Y., Salvolini, U., & Scarabine, U. (2005). The Human Hippocampus: Functional Anatomy, Vascularization and Serial Sections with MRI, 3rd edition. *AJNR: American Journal of Neuroradiology*, *26*(10), 2702.

Fanselow, M. S., & Dong, H.-W. (2010). Are the Dorsal and Ventral Hippocampus Functionally Distinct Structures? *Neuron*, *65*(1), 7–19. https://doi.org/10.1016/j.neuron.2009.11.031

Fastenrath, M., Coynel, D., Spalek, K., Milnik, A., Gschwind, L., Roozendaal, B., Papassotiropoulos, A., & Quervain, D. J. F. de. (2014). Dynamic Modulation of Amygdala–Hippocampal Connectivity by Emotional Arousal. *Journal of Neuroscience*, *34*(42), 13935–13947. https://doi.org/10.1523/JNEUROSCI.0786-14.2014

Fischl, B. (2012). FreeSurfer. *NeuroImage*, *62*(2), 774–781. https://doi.org/10.1016/j.neuroimage.2012.01.021

Frank, L. E., Bowman, C. R., & Zeithamova, D. (2019). Differential Functional Connectivity along the Long Axis of the Hippocampus Aligns with Differential Role in Memory Specificity and Generalization. *Journal of Cognitive Neuroscience*, *31*(12), 1958–1975. https://doi.org/10.1162/jocn_a_01457

Fraundorf, S. H., Hourihan, K. L., Peters, R. A., & Benjamin, A. S. (2019). Aging and recognition memory: A meta-analysis. *Psychological Bulletin*, *145*(4), 339–371. https://doi.org/10.1037/bul0000185

Frisoni, G. B., Ganzola, R., Canu, E., Rüb, U., Pizzini, F. B., Alessandrini, F., Zoccatelli, G., Beltramello, A., Caltagirone, C., & Thompson, P. M. (2008). Mapping local hippocampal changes in Alzheimer's disease and normal ageing with MRI at 3 Tesla. *Brain*, *131*(12), 3266–3276. https://doi.org/10.1093/brain/awn280

Ghosh, S., Laxmi, T. R., & Chattarji, S. (2013). Functional Connectivity from the Amygdala to the Hippocampus Grows Stronger after Stress. *Journal of Neuroscience*, *33*(17), 7234–7244. https://doi.org/10.1523/JNEUROSCI.0638-13.2013

Goh, J. O. S. (2011). Functional Dedifferentiation and Altered Connectivity in Older Adults: Neural Accounts of Cognitive Aging. *Aging and Disease*, *2*(1), 30–48.

Hashtroudi, S., Johnson, M. K., & Chrosniak, L. D. (1989). Aging and source monitoring. *Psychology and Aging*, *4*(1), 106–112. https://doi.org/10.1037/0882-7974.4.1.106

Hrybouski, S., Das, S. R., Xie, L., Wisse, L. E. M., Kelley, M., Lane, J., Sherin, M., DiCalogero, M., Nasrallah, I., Detre, J. A., Yushkevich, P. A., & Wolk, D. A. (2023). *Aging and Alzheimer's Disease Have Dissociable Effects on Medial Temporal Lobe Connectivity* (p. 2023.01.18.23284749). medRxiv. https://doi.org/10.1101/2023.01.18.23284749

Hu, S., & Li, C. R. (2020). Age-Related Structural and Functional Changes of the Hippocampus and the Relationship with Inhibitory Control. *Brain Sciences*, *10*(12), 1013. https://doi.org/10.3390/brainsci10121013

Iglesias, J. E., Augustinack, J. C., Nguyen, K., Player, C. M., Player, A., Wright, M., Roy, N., Frosch, M. P., McKee, A. C., Wald, L. L., Fischl, B., & Van Leemput, K. (2015). A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: Application to adaptive segmentation of in vivo MRI. *NeuroImage*, *115*, 117–137. https://doi.org/10.1016/j.neuroimage.2015.04.042

Jenkinson, M., Pechaud, M., & Smith, S. (2006, February 6). *BET2—MR-Based Estimation of Brain, Skull and Scalp Surfaces*.

Jung, M. W., Wiener, S. I., & McNaughton, B. L. (1994). Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. *Journal of Neuroscience*, *14*(12), 7347–7356. https://doi.org/10.1523/JNEUROSCI.14-12-07347.1994

Kahn, I., Andrews-Hanna, J. R., Vincent, J. L., Snyder, A. Z., & Buckner, R. L. (2008). Distinct Cortical Anatomy Linked to Subregions of the Medial Temporal Lobe Revealed by Intrinsic Functional Connectivity. *Journal of Neurophysiology*, *100*(1), 129–139. https://doi.org/10.1152/jn.00077.2008

Kier, E. L., Staib, L. H., Davis, L. M., & Bronen, R. A. (2004). MR Imaging of the Temporal Stem: Anatomic Dissection Tractography of the Uncinate Fasciculus, Inferior Occipitofrontal Fasciculus, and Meyer's Loop of the Optic Radiation. *American Journal of Neuroradiology*, *25*(5), 677–691.

Koen, J. D., & Rugg, M. D. (2019). Neural Dedifferentiation in the Aging Brain. *Trends in Cognitive Sciences*, *23*(7), 547–559. https://doi.org/10.1016/j.tics.2019.04.012

Kriegeskorte, N., Mur, M., & Bandettini, P. A. (2008). Representational similarity analysis—Connecting the branches of systems neuroscience. *Frontiers in Systems Neuroscience*, *2*. https://doi.org/10.3389/neuro.06.004.2008

Lang, P., Ohman, A., & Vaitl, D. (1999). *The International Affective Picture System* [Dataset]. University of Florida.

Leal, S. L., & Yassa, M. A. (2015). Neurocognitive Aging and the Hippocampus Across Species. *Trends in Neurosciences*, *38*(12), 800–812. https://doi.org/10.1016/j.tins.2015.10.003

McDonough, I. M., Nolin, S. A., & Visscher, K. M. (2022). 25 years of neurocognitive aging theories: What have we learned? *Frontiers in Aging Neuroscience*, *14*. https://doi.org/10.3389/fnagi.2022.1002096

Murphy, K., Birn, R. M., & Bandettini, P. A. (2013). Resting-state fMRI confounds and cleanup. *NeuroImage*, *80*, 349–359. https://doi.org/10.1016/j.neuroimage.2013.04.001

Naveh-Benjamin, M., Hussain, Z., Guez, J., & Bar-On, M. (2003). Adult age differences in episodic memory: Further support for an associative-deficit hypothesis. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *29*(5), 826–837. https://doi.org/10.1037/0278-7393.29.5.826

Old, S. R., & Naveh-Benjamin, M. (2008). Differential effects of age on item and associative measures of memory: A meta-analysis. *Psychology and Aging*, *23*(1), 104–118. https://doi.org/10.1037/0882-7974.23.1.104

O'Shea, A., Cohen, R. A., Porges, E. C., Nissim, N. R., & Woods, A. J. (2016). Cognitive Aging and the Hippocampus in Older Adults. *Frontiers in Aging Neuroscience*, *8*, 298. https://doi.org/10.3389/fnagi.2016.00298

Panitz, D. Y., Berkovich-Ohana, A., & Mendelsohn, A. (2021). Age-related functional connectivity along the hippocampal longitudinal axis. *Hippocampus*, *31*(10), 1115–1127. https://doi.org/10.1002/hipo.23377

Park, J., Carp, J., Kennedy, K. M., Rodrigue, K. M., Bischof, G. N., Huang, C.-M., Rieck, J. R., Polk, T. A., & Park, D. C. (2012). Neural Broadening or Neural Attenuation? Investigating Age-Related Dedifferentiation in the Face Network in a Large Lifespan Sample. *Journal of Neuroscience*, *32*(6), 2154–2158. https://doi.org/10.1523/JNEUROSCI.4494-11.2012

Pauley, C., Zeithamova, D., & Sander, M. C. (2024). Age differences in functional connectivity track dedifferentiation of category representations. *bioRxiv*, 2024.01.04.574135. https://doi.org/10.1101/2024.01.04.574135

Peng, G., Feng, Z., He, F., Chen, Z., Liu, X., Liu, P., & Luo, B. (2014). Correlation of Hippocampal Volume and Cognitive Performances in Patients with Either Mild Cognitive Impairment or Alzheimer's disease. *CNS Neuroscience & Therapeutics*, *21*(1), 15–22. https://doi.org/10.1111/cns.12317

Poppenk, J., Evensmoen, H. R., Moscovitch, M., & Nadel, L. (2013). Long-axis specialization of the human hippocampus. *Trends in Cognitive Sciences*, *17*(5), 230–240. https://doi.org/10.1016/j.tics.2013.03.005

Poppenk, J., & Moscovitch, M. (2011). A Hippocampal Marker of Recollection Memory Ability among Healthy Young Adults: Contributions of Posterior and Anterior Segments. *Neuron*, *72*(6), 931–937. https://doi.org/10.1016/j.neuron.2011.10.014

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, *59*(3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 320–341. https://doi.org/10.1016/j.neuroimage.2013.08.048

Ranganath, C., & Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nature Reviews Neuroscience*, *13*(10), 713–726. https://doi.org/10.1038/nrn3338

Ritchey, M., & Cooper, R. A. (2020). Deconstructing the Posterior Medial Episodic Network. *Trends in Cognitive Sciences*, *24*(6), 451–465. https://doi.org/10.1016/j.tics.2020.03.006

Robinson, J. L., Salibi, N., & Deshpande, G. (2016). Functional connectivity of the left and right hippocampi: Evidence for functional lateralization along the long-axis using meta-analytic approaches and ultra-high field functional neuroimaging. *NeuroImage*, *135*, 64–78. https://doi.org/10.1016/j.neuroimage.2016.04.022

Rugg, M. D., & Vilberg, K. L. (2013). Brain Networks Underlying Episodic Memory Retrieval. *Current Opinion in Neurobiology*, *23*(2), 255–260. https://doi.org/10.1016/j.conb.2012.11.005

Salami, A., Pudas, S., & Nyberg, L. (2014). Elevated hippocampal resting-state connectivity underlies deficient neurocognitive function in aging. *Proceedings of the National Academy of Sciences*, *111*(49), 17654–17659. https://doi.org/10.1073/pnas.1410233111

Salami, A., Wåhlin, A., Kaboodvand, N., Lundquist, A., & Nyberg, L. (2016). Longitudinal Evidence for Dissociation of Anterior and Posterior MTL Resting-State Connectivity in Aging: Links to Perfusion and Memory. *Cerebral Cortex*, *26*(10), 3953–3963. https://doi.org/10.1093/cercor/bhw233

Schlichting, M. L., Mumford, J. A., & Preston, A. R. (2015). Learning-related representational changes reveal dissociable integration and separation signatures in the hippocampus and prefrontal cortex. *Nature Communications*, *6*(1), 8151. https://doi.org/10.1038/ncomms9151

Scoville, W. B., & Milner, B. (1957). LOSS OF RECENT MEMORY AFTER BILATERAL HIPPOCAMPAL LESIONS. *Journal of Neurology, Neurosurgery, and Psychiatry*, *20*(1), 11–21.

Shafto, M. A., Tyler, L. K., Dixon, M., Taylor, J. R., Rowe, J. B., Cusack, R., Calder, A. J., Marslen-Wilson, W. D., Duncan, J., Dalgleish, T., Henson, R. N., Brayne, C., & Matthews, F. E. (2014). The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) study protocol: A cross-sectional, lifespan, multidisciplinary examination of healthy cognitive ageing. *BMC Neurology*, *14*(1), 204. https://doi.org/10.1186/s12883-014-0204-1

Smith, A. P. R., Stephan, K. E., Rugg, M. D., & Dolan, R. J. (2006). Task and Content Modulate Amygdala-Hippocampal Connectivity in Emotional Retrieval. *Neuron*, *49*(4), 631–638. https://doi.org/10.1016/j.neuron.2005.12.025

Spencer, W. D., & Raz, N. (1995). Differential effects of aging on memory for content and context: A meta-analysis. *Psychology and Aging*, *10*(4), 527–539. https://doi.org/10.1037/0882-7974.10.4.527

Stark, S. M., Frithsen, A., & Stark, C. E. L. (2021). Age-related alterations in functional connectivity along the longitudinal axis of the hippocampus and its subfields. *Hippocampus*, *31*(1), 11–27. https://doi.org/10.1002/hipo.23259

Thorp, J. N., Gasser, C., Blessing, E., & Davachi, L. (2022). Data-Driven Clustering of Functional Signals Reveals Gradients in Processing Both within the Anterior Hippocampus and across Its Long Axis. *The Journal of Neuroscience*, *42*(39), 7431–7441. https://doi.org/10.1523/JNEUROSCI.0269-22.2022

Toner, C. K., Pirogovsky, E., Kirwan, C. B., & Gilbert, P. E. (2009). Visual object pattern separation deficits in nondemented older adults. *Learning & Memory*, *16*(5), 338–342. https://doi.org/10.1101/lm.1315109

Vaisvaser, S., Lin, T., Admon, R., Podlipsky, I., Greenman, Y., Stern, N., Fruchter, E., Wald, I., Pine, D. S., Tarrasch, R., Bar-Haim, Y., & Hendler, T. (2013). Neural traces of stress: Cortisol related sustained enhancement of amygdala-hippocampal functional connectivity. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00313

Wang, S.-F., Ritchey, M., Libby, L. A., & Ranganath, C. (2016). Functional connectivity based parcellation of the human medial temporal lobe. *Neurobiology of Learning and Memory*, *134*, 123–134. https://doi.org/10.1016/j.nlm.2016.01.005

Y, X., Y, H., & K, H. (2023). Atrophy of hippocampal subfields relates to memory decline during the pathological progression of Alzheimer's disease. *Frontiers in Aging Neuroscience*, *15*. https://doi.org/10.3389/fnagi.2023.1287122

Yassa, M. A., Lacy, J. W., Stark, S. M., Albert, M. S., Gallagher, M., & Stark, C. E. L. (2011). Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. *Hippocampus*, *21*(9), 968–979. https://doi.org/10.1002/hipo.20808

Zeithamova, D., Dominick, A. L., & Preston, A. R. (2012). Hippocampal and ventral medial prefrontal activation during retrieval-mediated learning supports novel inference. *Neuron*, *75*(1), 168–179. https://doi.org/10.1016/j.neuron.2012.05.010

Zhang, W., & Luck, S. J. (2008). Discrete fixed-resolution representations in visual working memory. *Nature*, *453*(7192), 233–235. https://doi.org/10.1038/nature06860