Neurobiology of Aging 141 (2024) 182–193

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

Lifespan differences in hippocampal subregion connectivity patterns during movie watching

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ARTICLE INFO

Keywords:
Aging
Episodic memory
Hippocampus
Functional connectivity

ABSTRACT

Age-related episodic memory decline is attributed to functional alternations in the hippocampus. Less clear is how aging affects the functional connections of the hippocampus to the rest of the brain during episodic memory processing. We examined fMRI data from the CamCAN dataset, in which a large cohort of participants watched a movie (N = 643; 18–88 years), a proxy for naturalistic episodic memory encoding. We examined connectivity profiles across the lifespan both within the hippocampus (anterior, posterior), and between the hippocampal subregions and cortical networks. Aging was associated with reductions in contralateral (left, right) but not ipsilateral (anterior, posterior) hippocampal subregion connectivity. Aging was primarily associated with increased coupling between the anterior hippocampus and regions affiliated with Control, Dorsal Attention and Default Mode networks, yet decreased coupling between the posterior hippocampus and a selection of these regions. Differences in age-related hippocampal-cortical, but not within-hippocampus circuitry selectively predicted worse memory performance. Our findings comprehensively characterize hippocampal functional topography in relation to cognition in older age, suggesting that shifts in cortico-hippocampal connectivity may be sensitive markers of age-related episodic memory decline.

1. Introduction

Episodic memory entails the ability to encode, store, and retrieve past events, and is known to decline throughout the lifespan (Cabeza et al., 1997; Grady, 1999; Grady et al., 1998; Naveh-Benjamin et al., 2003; Nyberg et al., 2003, 2012). Studies have attributed age-related episodic memory decline to structural and functional changes to the hippocampus (Raz et al., 2005), the key brain region for encoding and retrieving episodic memories (Eichenbaum, 2001; Konkel and Cohen, 2009; Moscovitch et al., 2016; Scoville & Milner, 1957). The hippocampus is not a homogenous structure but shows hemispheric and long-axis functional specialization (Poppenk et al., 2013). Hippocampal subregions run anterior to posterior along the long-axis of the hippocampus and are functionally connected to one another as well as a distributed set of regions including but not limited to the anterior temporal, frontal, posterior medial, and parietal cortices (Libby et al., 2012). Due to their differential connectivity with these areas, anterior and posterior subregions contribute to different aspects of episodic memory formation (Diana et al., 2007; Horner et al., 2015; Ranganath, 2010). However, little is known about how the subregions' connectivity profiles differ cross-sectionally and relate to individual differences in cognition and especially, episodic memory functioning.

Naturalistic paradigms, such as movie watching, offer a unique window into understanding age-related shifts in how we process and encode our experiences in everyday life (Campbell and Schacter, 2017; Finn and Bandettini, 2021; Grall and Finn, 2022; Hasson, Landesman, et al., 2008; Meer et al., 2020). Movie watching, much like the encoding of everyday events, involves continuous exposure to chronologically related, temporally unfolding events rich in spatiotemporal, emotional, social, and narrative details (Kringelbach et al., 2023; Sonkusare et al., 2019). While we cannot predict the information we will need to encode and subsequently remember when watching a movie, our perception is tuned towards, and attention enhanced by, affective and salient information. In this way, movie watching puts viewers under conditions in

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https://doi.org/10.1016/j.neurobiolaging.2024.06.006
Received 10 December 2023; Received in revised form 17 May 2024; Accepted 22 June 2024
Available online 30 June 2024

which functional patterns relevant to episodic memory encoding are likely to emerge. Indeed, previous work has shown that viewers spontaneously and continuously engage episodic memory processes during movie watching – with individuals recollecting a considerable amount of movie specific details following passive, incidental viewing instructions (Fenerci et al., 2023; Hasson, Furman, et al., 2008; Shin et al., 2015). As well, studies have shown that hippocampus is highly engaged during movie watching, and the extent of this engagement predicts subsequent memory for the movie content (Hasson, Furman, et al., 2008). In the current study, we leveraged movie watching as a proxy for episodic memory encoding to study how hippocampal functional connectivity during this task differs across the lifespan and relate to individual differences in cognition.

When examining hippocampal functional connectivity, especially with respect to episodic memory processing, it is important to consider its functionally specialized subregions along the longitudinal axis and across the two hemispheres. First, evidence points to a gradient of processing resolution, such that the anterior hippocampus represents coarse-grained, conceptual information and posterior hippocampus, fine-grained, sensory-perceptual information (Brunec et al., 2018; Robin and Moscovitch, 2017; Sheldon et al., 2019; Sheldon and Levine, 2016). Second, in addition to its long-axis specialization, hippocampal memory functions are also highly lateralized (Persson and Söderlund, 2015). A large body of work has shown that the left hippocampus is preferentially involved in processing and encoding verbal information, whereas the right hippocampus is particularly tuned to processing pictorial or spatially oriented details (Gabrieli et al., 1997; Golby et al., 2001; Kelley et al., 1998; Stern et al., 1996). The distinct roles played by the subregions emerge from their functional connectivity with one another (Banich and Belger, 1990; Reuter-Lorenz and Mikels, 2005; Reuter-Lorenz and Stanczak, 2000; Wang et al., 2014). That is, the subregions respond to and process different kinds of information and communicate with one another to bind together the processed details and form coherent episodic memories (Cohen et al., 1997, 1999; Konkel and Cohen, 2009).

Hippocampal subregions are embedded within larger cortical networks distributed across the whole brain (Blessing, Beissner, Schumann, Brünner, and Bär, 2016; Robinson, Salibi, and Deshpande, 2016; Wang, Ritchey, Libby, and Ranganath, 2016; Frankland and Bontempi, 2005). During episodic memory tasks, the distinct component processes of hippocampal subregions are bolstered by large-scale cortical networks (Rugg and Vilberg, 2013) including the Default, Dorsal Attention, and Control networks (DN, DAN, CN). The DN forms internal representations of experiences by carrying information about narrative content (Andrews-Hanna et al., 2014; Baldassano et al., 2017; Buckner et al., 2008; Buckner and DiNicola, 2019; Chen et al., 2017; Lee and Chen, 2022; Spreng and Andrews-Hanna, 2015). The DAN supports top-down attentional control, particularly when processing and encoding external stimuli (Corbetta et al., 2002; Corbetta and Shulman, 2002). The CN supports effortful cognitive control processes (Corbetta and Shulman, 2002; Niendam et al., 2012; Spreng et al., 2010). Evidence suggests that hippocampal connectivity with each of these networks varies along its long axis (Grady, 2020). In younger adults, meta-analytic and functional imaging studies have shown that the anterior hippocampus shows preferential connectivity with the DN, as well as Limbic, and Somatomotor networks, whereas posterior hippocampus is particularly tuned to the Visual Network and the DAN (Blessing et al., 2016; Kahn et al., 2008; Robinson et al., 2016).

Together, these studies indicate that episodic memory encoding involves the concerted interplay between hippocampal subregions and cortical networks (Ranganath and Ritchey, 2012), which likely show age-related alterations. Indeed, aging is associated with functional connectivity alterations in large-scale brain networks, which points to parallel changes in the subregions' connectivity patterns (Campbell et al., 2015; Geerligs et al., 2015; Geerligs and Campbell, 2018; Grady et al., 2016). Compared to younger adults, older adults demonstrate weaker within-network connectivity and stronger between-network connectivity (Andrews-Hanna et al., 2007, 2014; Betzel et al., 2014; Chan et al., 2014; Damoiseaux et al., 2008). This pattern of network dedifferentiation, linked to age-related episodic memory decline, has become a hallmark of functional reorganization in healthy aging (Koen et al., 2020; Koen and Rugg, 2019). It remains to be determined whether hippocampal subregions follow a similar trajectory with age, where connectivity profiles demonstrate less selectivity and hemispheric specificity in favor of more integration.

2. Current study

Functional interactions within the hippocampus as well as between the hippocampal subregions and the rest of the brain are central for episodic memory, which suggests that shifts in subregion connectivity profiles may underlie age related episodic memory decline. In the current study, we examined differences in hippocampal functional connectivity across the lifespan and how these differences relate to cognitive functioning. Specifically, we probed hippocampal connectivity patterns at two levels, both within the hippocampus and between the hippocampus and cortical networks. We then assessed whether these patterns vary with cognitive functioning and episodic memory ability, specifically standard measures of story recall. Given the known functional and hemispheric specialization in the hippocampus, we considered subregion connectivity patterns in the context of laterality differences. To this end, we leveraged functional magnetic resonance imaging (fMRI) and neuropsychological data from a large-scale, healthy, population-based cohort of healthy adults. Based on previous work, we reasoned that if subregion connectivity patterns parallel age-related network dedifferentiation, then the subregions should show a more integrated (less distinct) pattern of connectivity in older age. Finally, if shifts in hippocampal connectivity underlie cognitive and episodic memory decline, then any age-related connectivity differences will be associated with lower cognitive and episodic memory performance.

3. Materials & methods

3.1. Participants

The data were acquired from the Stage II of Cambridge Centre for Aging and Neuroscience (Cam-CAN) data repository. This is a large-scale, population-based study of the healthy adult lifespan. All participants included in the study were cognitively healthy (Mini Mental State Examination $>$ 24), had normal or corrected-to-normal vision and hearing, were free of any medical, neurological or psychiatric conditions, and had English as their dominant language. Written, informed consent was collected from all participants and all study procedures were conducted in accordance with the ethical guidelines of Cambridge 2 Research Ethics Committee.

After data quality checks (outlined in section **Image Processing**), a sample of 520 participants ($M = 263$, $M_{age} = 52.58$, $SD_{age} = 18.24$) were included in the main analyses of this article. The demographic information for the final sample is provided, broken down by each age decade, in Table 1.

3.2. Stimuli

Participants watched an 8-minute, shortened version of the "Bang! You're Dead" episode from the television show, Alfred Hitchcock Presents (1961). The full 25-minute episode was cut due to time constraints but retained the central plot of the original narrative. The instructions were to watch, listen, and pay attention to the movie. None of the participants reported having seen the movie before.

Additional measures of interest included performance indices on select neuropsychological tests from the full battery included in the CamCAN protocol. Of particular interest to us were the attentional

Table 1
Summary of participant demographics across age decades.

Age Decade	N	Sex (F/M)	M_{age} (SD)	Handedness (L/R/A)
18–20	12	5/7	18.75 (0.87)	2/10/0
20–30	62	34/28	26.45 (2.34)	5/57/0
30–40	88	39/49	35.83 (2.90)	8/77/2
40–50	84	50/34	45.75 (2.77)	5/77/2
50–60	78	33/45	55.64 (3.05)	7/70/1
60–70	93	43/50	65.72 (2.74)	9/83/1
70–80	77	40/37	76.03 (3.08)	6/70/0
>80	26	13/13	83.58 (2.08)	1/24/1

Note: Handedness information was not available for 2 participants. L = left, R = right, A = ambidextrous, F = female, M = male, M_{age} = Mean, SD = standard deviation.

orientation, composite memory, fluency, language, visuospatial performance, and total scores from the Addenbrooke's Cognitive Examination (ACE-A; ACE-M; ACE-F; ACE-L; ACE-VS; ACE-R, respectively) as well as the Logical Memory Test (LMT) immediate and delayed recall tests from the Wechsler Memory Scale. In Wechsler LMT, participants read two short stories and freely recalled as many story details as they can immediately after reading the story and after a 20-minute delay. Participants' free recall data were scored for the number of correctly recalled story details for each time point. The scores for each cognitive test are provided, broken down by each age decade, in Supplementary Table 1.

3.3. MRI data acquisition

The data were collected using a Siemens 3T TIM Trio scanner with a 32-channel head coil at the MRC Cognition and Brain Sciences Unit, Cambridge, UK. Functional data during movie watching were acquired with a multi-echo T2* EPI sequence over 193 volumes [32 axial slices, 3.7 mm thick, 0.74 mm gap, TR = 2470 ms, TE = [9.4, 21.2, 33, 45, 57] ms, flip angle = 78°, FOV =192 × 192 mm, voxel size = 3 × 3 × 4.44 mm]. T1-weighted images were acquired with a 3D MPRAGE sequence [TR = 2250 ms, TE = 2.99 ms, TI = 900 ms, flip angle = 9°, FOV = 256 × 240 × 192 m, 1 mm isotropic voxels, GRAPPA acceleration factor = 2].

3.4. Image processing

The data were preprocessed with a combination of fMRIPrep 21.0.1 (Esteban, Markiewicz et al., 2019), which is based on Nipype 1.6.1 (Gorgolewski et al., 2011), and *tedana* (DuPre et al., 2021).

3.5. Anatomical

The T1-weighted (T1w) images were corrected for intensity non-uniformity, then skull-stripped. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w.

Hippocampal subregions, including the anterior and posterior hippocampus were automatically segmented using the Automatic Segmentation of Hippocampal Subfields (ASHS; Yushkevich et al., 2015; atlas: ashsT1_atlas_upennpmc_07202018). ASHS employs multi-atlas label fusion to automatically label hippocampal subregions in individual participants (Wang et al., 2013). This segmentation method was chosen based on recent work validating its rigor among manual and automated segmentation approaches (Bussy et al., 2021). Quality control was performed on these data, which involved three researchers (CF, RS & JS) visually inspecting the outputs for gross errors in segmentation. Specifically, the quality control criteria included (1) correct labelling of the hippocampus as a whole, (2) whether regions other than the hippocampus were labeled as such, and (3) presence of the uncal apex in the anterior hippocampus. Gross errors were observed in 41 participants, who were excluded from analyses. The resulting outputs of interest were four hippocampal segments: anterior and posterior subregions for each hemisphere (i.e., right/left). Intracranial volume (ICV) as well as gray matter volumes from each subregion were extracted as part of the ASHS protocol and volumes were summed to obtain the whole hippocampal volume.

3.6. Functional

Data were minimally preprocessed using fMRIPrep, which is amenable to multi-echo functional images. Head-motion parameters with respect to the BOLD reference (i.e., transformation matrices, and six corresponding rotation and translation parameters) were estimated. BOLD runs were slice-time corrected to 1.2 s (0.5 of slice acquisition range 0–2.4 s) using 3dTshift from AFNI (Cox and Hyde, 1997). The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying the transforms to correct for head-motion.

The minimally pre-processed outputs of fMRIPrep were then submitted to *tedana* (DuPre et al., 2021). Multi-echo data were optimally combined, after which principal component analysis and the 'stabilized' Kundu component selection decision tree (Kundu et al., 2013) was applied for dimensionality reduction. Independent component analysis was then used to decompose the dimensionally reduced dataset. Component selection was performed to identify BOLD (TE-dependent), non-BOLD (TE-independent), and uncertain (low-variance) components using the Kundu decision tree (v2.5; Kundu et al., 2013). Output of *tedana* contains the denoised ICA coefficients, which were used to compute functional connectivity in the subsequent steps.

Additional steps were taken to reduce the effects of motion on the functional connectivity results. Wavelet despiking was applied to remove residual motion artefacts following *tedana* (Patel et al., 2014). Wavelet despiking identifies irregular events at different frequencies by detecting sequences of wavelet coefficients that are outliers. Outlying wavelet coefficients are then projected out of the denoised coefficient set. This approach has been previously applied to the CamCAN data (Caldinelli and Cusack, 2022; Geerligs et al., 2016, 2017; Henson et al., 2016; Lehmann et al., 2021) and has been shown to remove a variety of motion artefacts, including spin-history effects and higher frequency events such as spikes (Geerligs et al., 2017; Patel et al., 2014).

Denoised and wavelet despiked data were quality checked by three researchers (CF & RS & GB). The quality check criteria were (1) successful co-registration between the anatomical and functional scans, (2) a framewise displacement value less than 0.50, (3) DVARS less than 2, (4) sufficiently high temporal signal to noise ratio (calculated as the mean signal intensity of a voxel divided by its standard deviation across the timeseries with a cutoff of > 50), (5) greater than 10 retained BOLD-like components, and finally, (6) average spike percentage 2 SDs below the mean. As a result of these quality check steps, 86 participants were excluded from the analyses.

Next, a 400-region, 17 network, Schaefer parcellation (Schaefer et al., 2018) was projected to each participant's native surface space and the BOLD coefficient sets were extracted from each parcel, as well as from the left and right anterior/posterior hippocampal regions of interest.

3.7. Functional Connectivity

To assess functional connectivity, we computed the product-moment (r) correlation coefficients between our four regions of interest—left/right & anterior/posterior hippocampus— as well as between these regions and the 400 cortical parcels from the Schaefer atlas. A canonical Fisher's r-to-z transformation was applied to these correlation matrices to normalize the correlation values, which included a term to account for varying degrees of freedom (Kundu et al., 2013). This step resulted in a 4×4 square matrix for intra-hippocampal connectivity and a 4x400

rectangular matrix for cortico-hippocampal subregion connectivity for each participant.

3.8. Statistical analysis

3.8.1. Age effects on within-hippocampal connectivity and relationships to episodic memory

Prior to analyses, all continuous behavioural variables were mean centered.

Our first aim was to examine age effects on the connectivity between hippocampal subregions in relation to episodic memory. We used a linear mixed effects model (LMM) with the connectivity values as the dependent variable, and the connectivity type (contralateral vs. ipsilateral), chronological age, their interaction, ICV, gender, and the total hippocampal volume as fixed effects. We also included a connectivity type per participant random slope in the model to account for intra and inter-individual variability in subregion connectivity.

We conducted follow-up analyses across separate models to examine whether any observed changes in the contralateral or ipsilateral connectivity were driven by the anterior vs. posterior subregions or left vs. right hemisphere, respectively. In the model examining contralateral connectivity differences between the anterior and posterior hippocampus, we included hippocampal subregion, age, their interaction as well as ICV, gender and total hippocampal volume as fixed effects. The model examining ipsilateral connectivity differences between left and right hemispheres had a similar model structure, except with hemisphere (left vs. right) instead of hippocampal subregion as a fixed factor.

To examine whether within hippocampal connectivity related to behavioural measures, we used behavioural Partial Least Squares Correlation (bPLS; Krishnan et al., 2011; McIntosh and Lobaugh, 2004). bPLS is a multivariate method that captures latent patterns of maximal covariance between two sets of variables. The brain connectivity and behavioural matrices are cross-correlated, yielding a covariance matrix, which is then submitted to singular value decomposition to extract latent variables (LVs). LVs are orthogonal to one another and maximally capture relationships between the two matrices. For this analysis, the brain connectivity matrix was comprised of the contralateral (left anterior & right anterior; left posterior & right posterior) and ipsilateral (left anterior & left posterior; right anterior and right posterior) subregion connectivity (N = 4). The behavioural measures were those from the neuropsychological tests (N = 8). We conducted two hypothesis-driven bPLS analyses, one of which examined the association between within hippocampal connectivity and cognition due to age, and the other examined this association independently of age. For the latter, prior to the bPLS, we regressed out chronological age from all cognitive measures to assess whether within hippocampal connectivity related to cognition above and beyond age.

3.8.2. Age effects on cortico-hippocampal subregion connectivity and relationships to episodic memory

To examine cortico-hippocampal subregion connectivity across the lifespan we used the bPLS analysis. To run the bPLS, we first created separate data matrices storing each of the brain connectivity and the behavioural variables. Each row of the brain connectivity matrix corresponded to a vector of a participant's subregion connectivity with the 400 parcels, which was then ordered by the hippocampal subregion. The behavioural matrix consisted of participants' chronological age in the same order as the brain connectivity matrix.

As described above, we submitted the brain connectivity and behavioural matrices to bPLS. We extracted three measures of interest for each LV from bPLS: (1) a left singular value, representing the brain connectivity patterns that best characterizes the covariance, (2) a scalar singular value, containing covariance strength between the chronological age and connectivity, and (3) a right singular vector representing the weighted behavioural variable. The amount of variance each LV accounted for was calculated by dividing the square of each LV's singular value by the sum of squares of all singular values (hereon referred to as percent cross-block covariance). The bPLS additionally assigns each individual participant a brain connectivity score by calculating the dot product of the left singular value and each participant's connectivity matrix. Brain connectivity scores represent how strongly each participant expresses a given LV for each hippocampal subregion. For each LV, stronger positive values represent stronger expression of warmer colors, whereas stronger negative values represent stronger expression of cooler colors.

To determine the significance of the LVs, we used permutation testing (N = 1000), in which the rows of the brain connectivity matrix were randomly reordered to create a new *permutation sample*. A new bPLS was then re-run for each of the resampled data set to obtain a set of singular values representing the sampling distribution under the null hypothesis. Statistical significance was determined as the probability that the permuted singular values are greater than the observed singular value for a given LV ($p < 0.05$; McIntosh and Lobaugh, 2004). Following permutation testing, we then used bootstrap resampling with replacement (N = 500) to assess the stability of the connectivity weights. For each resampling, a new bPLS was run and a bootstrap ratio (BSR) was calculated as the bootstrap estimated mean connectivity weight divided by the standard error. In this way, higher BSR values represent more stable connectivity weights for a given LV. We used a threshold of ±1.96, which represents the 95 % confidence interval.

To examine the relationship between cortico-hippocampal connectivity and performance on the cognitive tasks, we derived brain connectivity scores for each of the observed patterns from the bPLS. We then calculated the correlation between participants' brain connectivity scores and performance on the neuropsychological tests.

4. Results

4.1. Aging reduces contralateral functional connectivity of the anterior and posterior hippocampus

We first examined age effects on contralateral (e.g., left vs. right anterior) and ipsilateral (e.g., anterior vs. posterior) within-hippocampal connectivity (i.e., 4×4 square matrix). The LMM with the within hippocampal functional connectivity as the outcome revealed a significant interaction between connectivity type (contralateral vs. ipsilateral) and age [ß = 1.42, t(517) = 3.49, p < 0.001], indicating that contralateral connectivity showed a greater decline across the lifespan compared to ipsilateral connectivity (see Fig. 1A). We found significant main effects of both age [ß = −0.70, t(537) = −4.11, p < 0.001], indicating reduced functional connectivity regardless of connectivity type across the lifespan, and connectivity type [ß = −1.58, t(518) = −14.88, p < 0.001]. In other words, functional connectivity values decreased overall across the lifespan, and contralateral connectivity was greater than ipsilateral connectivity. No other significant main effects emerged (all ps > 0.40).

We next examined whether the reduced contralateral connectivity across the lifespan was most related to the anterior or posterior hippocampus. The LMM with the contralateral functional connectivity as the outcome variable and hippocampal subregions (anterior vs. posterior) collapsing across hemispheres, chronological age, as well as their interaction, ICV, gender, and total hippocampal volume revealed a significant main effect of chronological age [ß = 1.42, t(517) = 3.49, p < 0.001] as well as ICV [ß = 1.42, t(517) = 3.49, p < 0.001]. No other significant interaction or main effects were observed (See Fig. 1B). This finding suggests that neither the anterior nor the posterior hippocampus differ in the extent to which they show reductions in contralateral connectivity across the lifespan (see Fig. 1C).

Finally, we assessed whether the observed null effect on ipsilateral connectivity across the lifespan was stable across hemispheres (left vs. right). The LMM with the above model structure, except with ipsilateral connectivity as the outcome variable and hemisphere (left vs. right) as

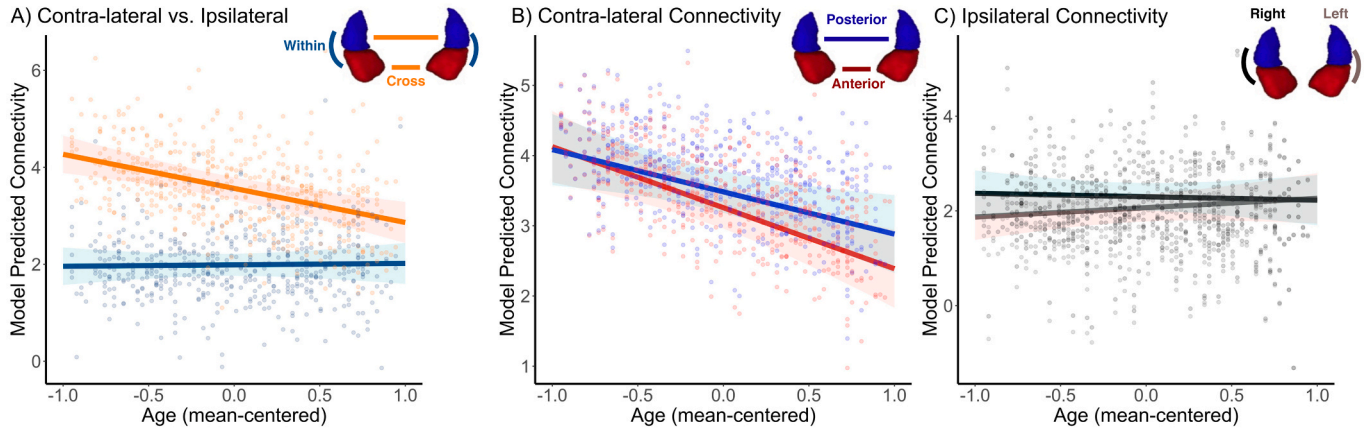

Fig. 1. Model predicted, fisher-z transformed, functional connectivity values for Linear Mixed Effects Models contrasting (A) contralateral vs. ipsilateral connectivity, (B) contralateral connectivity for the anterior vs. posterior hippocampus, and (C) ipsilateral connectivity for the right and left hemisphere across the lifespan.

the fixed factor, revealed no significant interactions nor main effects (all *ps* > 0.07), indicating no hemispheric differences in the stable patterns of ipsilateral subregion connectivity.

Next, we examined whether within hippocampal connectivity (N=4) was related to cognition by conducting bPLS analyses. No significant associations between within hippocampal connectivity and cognition were found (all ps>0.3).

4.2. Age differences in anterior and posterior hippocampal-cortical connectivity patterns

We computed a bPLS to investigate how cortico-hippocampal connectivity patterns differ across the lifespan. This analysis revealed two significant LVs.

The first LV (43 % cross-block covariance, permuted $p < 0.001$) revealed a connectivity pattern that varied with chronological age and was shared among the bilateral anterior hippocampus and to a lesser extent, the right posterior hippocampus (see Fig. 2A). BSR values for each significant parcel are presented in Supplementary Table 2. Regionally, these parcels were predominantly right lateralized (92 %) and involved the lateral (Control A) and ventro-lateral prefrontal cortex, inferior parietal lobule (Control B), precuneus, posterior cingulate (Default A), ventral prefrontal cortex as well as the temporal lobe (Default B) and regions in the superior parietal (Dorsal Attention B) and post-central cortices (Dorsal Attention B). These regions showed increased connectivity with the bilateral anterior and posterior subregions. In contrast, these subregions showed decreased connectivity with parcels in the left hemisphere (66 %) and included regions within the left medial prefrontal cortex (Default A). BSR values for these regions are projected on to a template brain surface in Fig. 2B. Taken together, these age-related differences point to less specific connectivity patterns of the hippocampal subregions (i.e., reduced asymmetry), with increased coupling to regions in the right hemisphere.

The second LV (29 % cross-block covariance, permuted $p < 0.05$) captured a distinct connectivity pattern that covaried with age for bilateral posterior hippocampus (see Fig. 3A). BSR values for each significant parcel are presented in Supplementary Table 2. Increased age was associated with increased connectivity of the posterior hippocampus with the left intraparietal sulcus (Control A), left extrastriate superior (Visual Peripheral), right medial prefrontal cortex (Default A), as well as the left medial parietal and right ventro-lateral prefrontal cortices (Salience/Ventral Attention A & B). In contrast, increased age was associated with reduced connectivity of posterior hippocampus with parcels in the medial prefrontal cortex (Default A), temporal lobes in the left hemisphere (Default B), and precuneus/posterior cingulate, medial prefrontal (Default A) and dorsal prefrontal cortices (Default B) in the right hemisphere. Additionally, we observed reduced posterior hippocampal connectivity with the bilateral temporal pole (Limbic A), extrastriate (Visual Peripheral) and striate cortices (Visual Central) as well as the left superior parietal lobule (Dorsal Attention A) and right auditory cortex (Somatomotor B). BSR values for these regions are projected on to a template brain surface in Fig. 3B.

4.3. Age related differences in cortico-hippocampal subregion connectivity are associated with episodic memory performance

Finally, we assessed whether the above reported patterns of cortico-hippocampal subregion connectivity changes in older age were related to cognitive and standardized measures of story recall (Fig. 2C & 3C). In LV1, for both left and right anterior hippocampus, higher brain connectivity scores were negatively associated with delayed memory recall performance on the Wechsler LMT [LANT: $r(520) = -0.12$, $p < 0.01$; RANT: $r(520) = -0.16$, $p < 0.01$]. In addition, brain connectivity scores for the right anterior hippocampus were negatively associated with immediate recall [$r(520) = -0.14$, $p < 0.01$] as well as ACE-Memory and ACE-total scores [ACE-M: $r(520) = -0.12$, $p < 0.01$; ACE-R: $r(520) = -0.12$, $p < 0.01$; Fig. 2C]. Overall, these findings indicate that greater connectivity between the anterior hippocampus and cortical networks such as the Control, Dorsal Attention as well as Default Networks is associated with worse episodic memory performance. Scatterplots relating brain connectivity scores to cognition are provided in Supplemental Figure 2.

In LV2, higher brain connectivity scores were significantly negatively associated with delayed memory recall performance for the left posterior hippocampus [$r(520) = -0.11$, $p < 0.01$; Fig. 3C]. Thus, reduced connectivity between the posterior hippocampus and the Default, Visual, and Limbic Networks is associated with worse episodic memory performance. Scatterplots relating brain connectivity scores to cognition for each LV are provided in Supplemental Figure 3A & B.

5. Discussion

Episodic memory emerges from the functional interactions within the hippocampus and with the cortical mantle. Shifts in subregion connectivity patterns may be critical to age-related episodic memory decline. We tested this proposal by first examining hippocampal connectivity patterns during movie watching, then relating these patterns to performance on cognitive tests and standard measures of story recall. First, we observed reduced contralateral connectivity between the hippocampal subregions in older age. Examining cortico-subregion connectivity profiles revealed greater bilateral anterior hippocampal connectivity with regions predominantly located in the Control, Dorsal

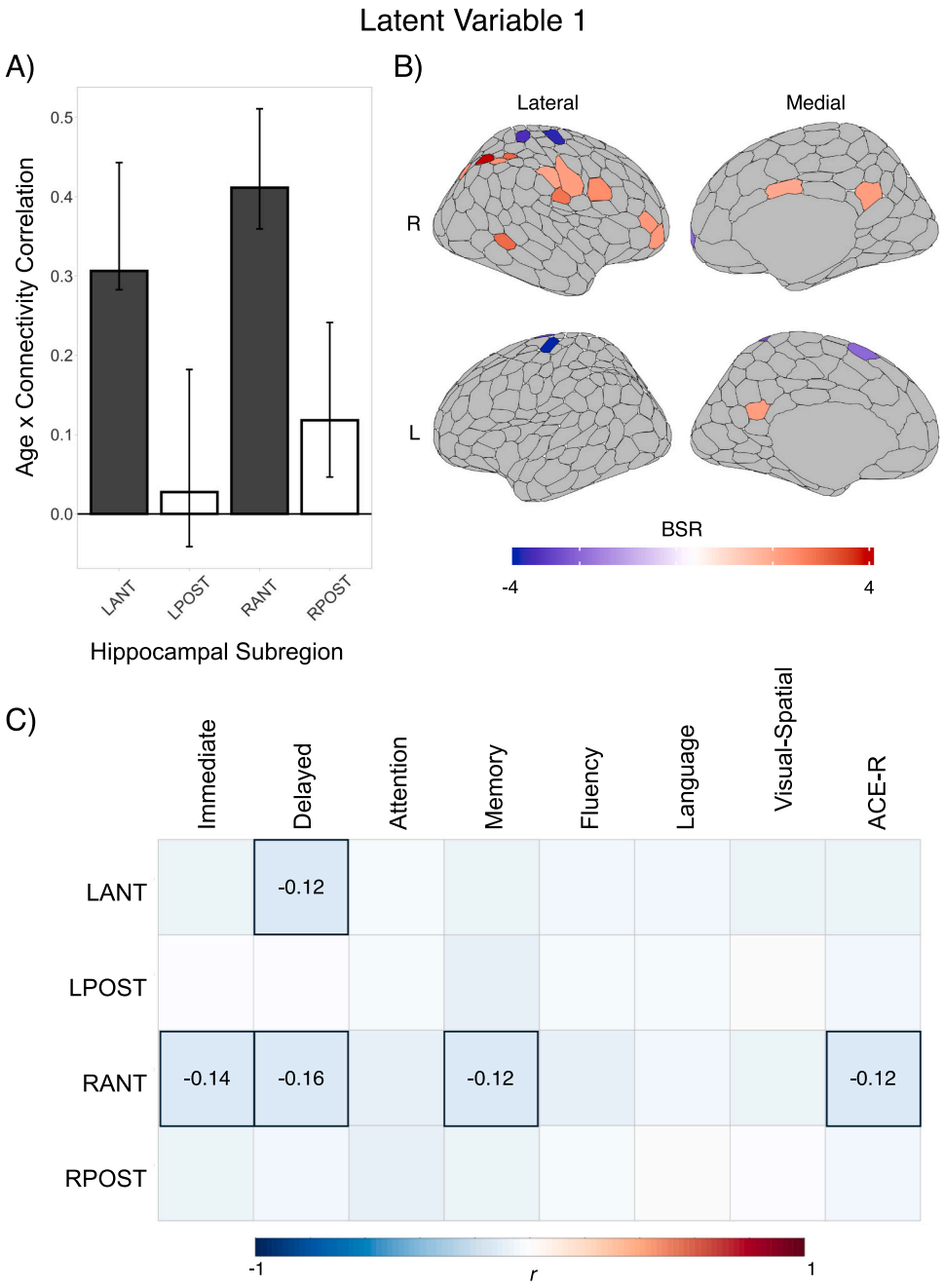

Fig. 2. A) Age-connectivity correlation profile for Latent Variable (LV) 1. This LV explained 43 % of the cross-block covariance (permuted $p < 0.001$) and captured a pattern expressed more by the bilateral anterior and to some extent right posterior hippocampus. Error bars represent 95 % confidence intervals derived from bootstrap estimation. B) BSR values projected on the brain surface. Warm colors represent regions that show increased coupling with the anterior hippocampus in older age. Cool colors show the opposite of this pattern (*right panel*). C) Brain connectivity scores for each hippocampal subregion for LV1 correlated with the cognitive measures. LANT = left anterior, LPOST = left posterior, RANT = right anterior, RPOST = right posterior, BSR = bootstrap ratio, ACE-R = Addenbrooke's Cognitive Examination-Revised total score.

Attention, and Default Networks and reduced bilateral posterior hippocampal connectivity with regions in the Visual, Limbic, and Default Networks. Both patterns were related to lower performance on the standard story recall measures. Broadly, these results align with the well-reported pattern of neural dedifferentiation in older age, suggesting that functionally specialized hippocampal subregions become increasingly integrated in older age. Together, our findings establish a significant role for the hippocampal subregions in age-related episodic memory deficits, indicating that shifts in subregion connectivity profiles may be sensitive markers of how aging alters the ability to encode complex events.

5.1. Lifespan trajectory of within hippocampal connectivity patterns

When examining connectivity within the hippocampus, we found that advanced age was linked to reduced contralateral subregion connectivity (e.g., left anterior to right anterior), whereas ipsilateral subregion connectivity (e.g., left anterior to left posterior) remained stable across the lifespan. Prior work has typically examined age effects on hippocampal connectivity using extreme groups designs, comparing connectivity patterns between young and old adults (Eisenstein et al., 2021; Setton, Mwilambwe-Tshilobo, Sheldon, et al., 2022; Stark et al., 2021), whereas we examined differences in subregion connectivity

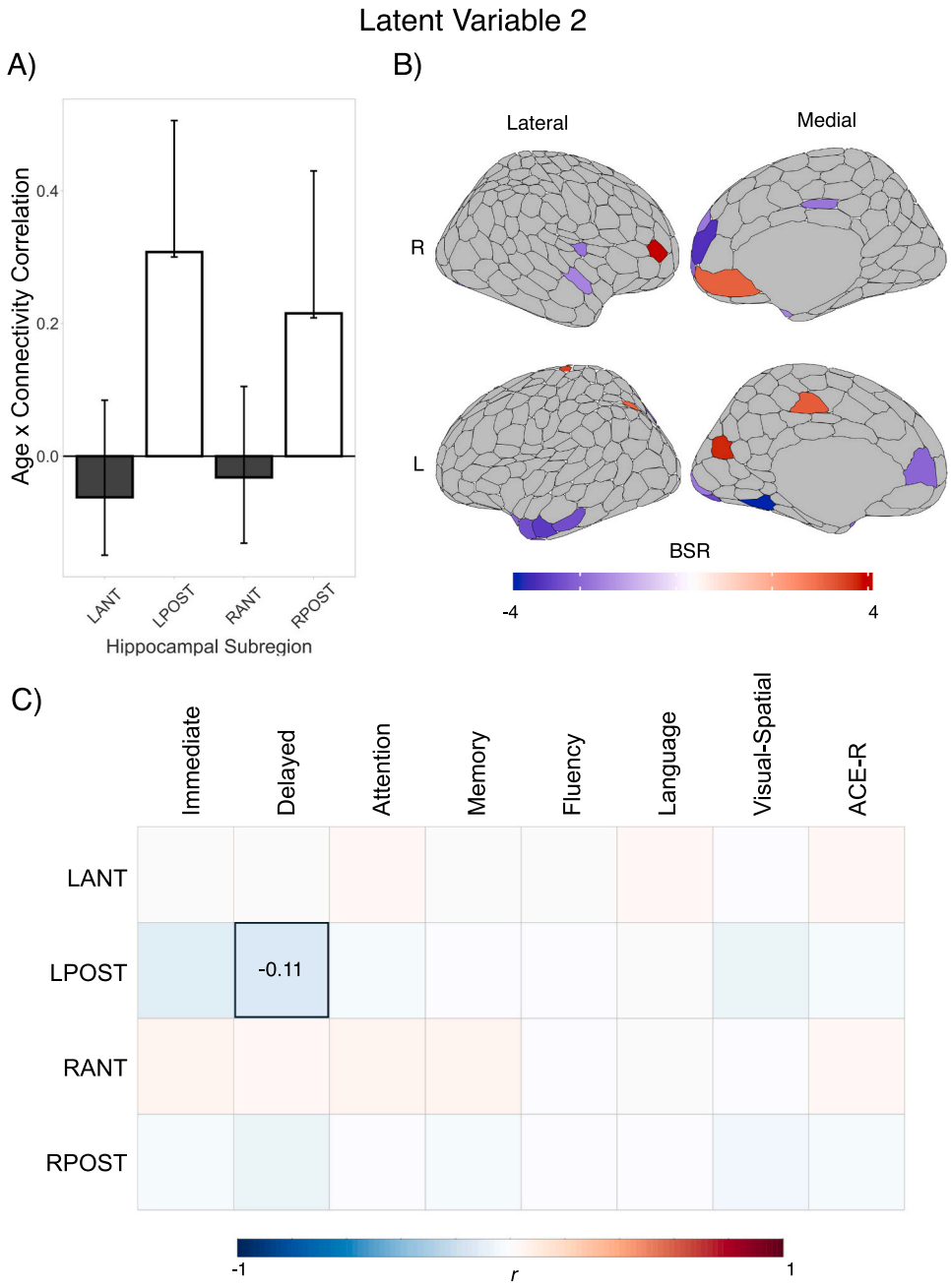

Fig. 3. A) Age-connectivity correlation profile for Latent Variable (LV) 2. This LV explained 29 % of the cross-block covariance (permuted $p < 0.05$) captured a pattern expressed only by the posterior hippocampus, bilaterally. Error bars represent 95 % confidence intervals derived from bootstrap estimation. B) BSR values projected on the brain surface. Warm colors represent regions that show greater coupling with the bilateral posterior hippocampus with older age. Cool colors show the opposite of this pattern (*right panel*). C) Brain connectivity scores for each hippocampal subregion for LV2 correlated with the cognitive measures. LANT = left anterior, LPOST = left posterior, RANT = right anterior, RPOST = right posterior, BSR = bootstrap ratio, ACE-R = Addenbrooke's Cognitive Examination-Revised total score.

patterns across the adult lifespan, identifying connectivity patterns that continuously scale with increasing age. To our knowledge, only one other study has tested the effects of age on within hippocampal connectivity across the lifespan (6.80–80.80 years) during an associative memory task (Langnes et al., 2020). This study found that ipsilateral subregion connectivity remained stable, whereas contralateral subregion connectivity showed a monotonic reduction with increasing age, aligning with the connectivity shifts we found during a more naturalistic encoding condition (i.e., movie watching).

In considering the cognitive correlates of age-related reductions in contralateral hippocampal subregion connectivity, the evidence suggests that connectivity between contralateral hippocampal subregions is integral to bind and integrate information that is separately processed across the hemispheres into a coherent episodic memory representation (Gee et al., 2011; Stark et al., 2008). However, if this were the case, then one would expect a link between contralateral hippocampal subregion connectivity strength and episodic memory ability, which did not emerge in our study. Rather, a more plausible interpretation of our finding is that it speaks to the well-reported pattern of neural dedifferentiation in older age (Chan et al., 2014; Setton, Mwilambwe-Tshilobo, Girn, et al., 2022; Setton, et al., 2022). That is, given the well-reported functional specialization along the hippocampal long-axis, our finding of reduced contralateral functional connectivity in both the anterior and posterior hippocampus indicates that aging is associated with

non-selective shifts in how subregions support episodic memory encoding and integrate information.

5.2. Lifespan trajectory of cortical-hippocampal subregion connectivity patterns

We assessed subregion connectivity at the whole brain level in relation to episodic memory ability. Two important findings emerged. First, we found that the left and right anterior, as well as to some degree, the right posterior hippocampus showed increased functional connectivity with a set of right lateralized regions in the Control, Dorsal Attention and Default Networks – with the greater proportion of these regions being in the Control Network. This finding parallels previous work showing that during episodic memory encoding, older adults exhibit greater connectivity with anterior brain regions, especially the prefrontal cortex (Dennis et al., 2008). Older adults' greater reliance on prefrontal, cognitive control regions during episodic memory tasks have been attributed to a multitude of aging phenomena. For example, a large body of work considers greater prefrontal recruitment in older age as a compensatory strategy employed by older adults during a given task to offset age-related cognitive decline (Grady, 2012). The additional recruitment of brain regions confers performance benefits for older adults, "compensating" for episodic memory deficits (Cabeza and Dennis, 2012; Reuter-Lorenz and Cappell, 2008). However, we found that the increased hippocampal, Control Network connectivity was related to lower episodic memory ability, which speaks against the compensation view of aging. Our results better align with accounts proposing age-related functional dedifferentiation (Goh, 2011; Koen et al., 2020). This view suggests that aging is associated with difficulty recruiting domain-specific neural mechanisms for a given task, which results in upregulated recruitment of a general cognitive control network (S.-C. Li and Lindenberger, 1999). In accord with this proposal, in our study, we observed greater connectivity with the prefrontal regions for both the anterior and posterior hippocampus, suggesting that these functionally specialized regions become less differentiated in older age and commonly synchronize with the Control Network. The greater connectivity between the anterior hippocampus and prefrontal cortex could also index age-related distinctions in the processing style (Castel, 2005; Umanath and Marsh, 2014). Previous work has shown that anterior hippocampus – via its functional connections to prefrontal regions implicated in schema-based knowledge –supports the formation of coarse, gist-based representations of an event (Frank et al., 2019; Robin and Moscovitch, 2017; Sheldon et al., 2019). Given that older adults increasingly rely on prior knowledge (Castel, 2005; Umanath and Marsh, 2014) and more likely form more gist-based representations of events than younger adults (Fenerci et al., 2023; Grilli and Sheldon, 2022; Koutstaal and Schacter, 1997), the increased coupling between anterior hippocampus and prefrontal cortex can underlie these behavioural shifts in information processing.

Second, we found that with increased age, both left and right posterior hippocampus showed reduced connectivity with regions located predominantly in the Default Network, as well as those in the Visual and Sensorimotor Networks. In addition, the subregions showed increased connectivity with Default, and Salience/Ventral Attention Networks. The finding of age-related reductions in posterior hippocampal connectivity parallels previous cross-sectional and longitudinal work showing that aging disproportionately reduces posterior cortico-hippocampal connectivity, especially with regions in the posterior Default Network (Damoiseaux et al., 2016; Panitz et al., 2021; Salami et al., 2016; see exception: Blum et al., 2014). These results are commonly interpreted in the context of age-related microstructural changes to the posterior hippocampus (Dalton, McCormick, De Luca, et al., 2019; Damoiseaux, 2017; Salami et al., 2016) and reduced volume of this subregion in older age (Langnes et al., 2020; Setton, Sheldon, Turner, et al., 2022), leading to changes in brain activity during episodic memory encoding (Cabeza et al., 2002; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008; Snytte et al., 2022). Expanding on this work, we found that the reduced posterior-DN connectivity in older age was specific to the dorsomedial subsystem of the DN (Default B), whereas regions in the core DN (Default A) showed both increased and decreased connectivity with this subregion. The dorsomedial subsystem has been implicated in tasks that rely on semantic memory processes such as conceptual and abstract processing (Andrews-Hanna et al., 2019). One interpretation for this finding could be that aging is associated with a shift towards utilizing prior semantic knowledge during episodic memory tasks, which manifests as reduced connectivity between regions involved in processing fine-grained episodic information (i.e., posterior hippocampus) and semantic, schematic knowledge (i.e., temporal pole, medial prefrontal cortex). Broadly, the shared differences in the connectivity patterns of the left and right posterior hippocampus suggest that increased age is associated with a loss of hemispheric specialization in the hippocampus.

Even though our results closely align with the neural dedifferentiation accounts of aging, they extend several other neuro-cognitive frameworks (Davis et al., 2008; Koen et al., 2020; S.-C. Li and Lindenberger, 1999; Spreng et al., 2018). One of which is a framework suggesting that aging is associated with shifts in activation from more posterior to more anterior regions during episodic memory tasks (PASA; Davis et al., 2008). This account predominantly rests on the finding of reduced activation in posterior brain regions (e.g., visual cortex, occipitotemporal regions) coupled with age-related increases in prefrontal activity (Dennis et al., 2008; Grady et al., 1994). In accord with these activation patterns, we found a posterior to anterior shift in older age in cortico-hippocampal connectivity profiles – with anterior hippocampus primarily showing increases in connectivity with anterior cortical regions and posterior hippocampus showing decreased connectivity with posterior cortical regions. An earlier model, the Hemispheric Asymmetry Reduction in Older Adults (HAROLD; Cabeza, 2002), proposes that when younger adults primarily recruit left lateralized regions during episodic memory encoding, older adults additionally recruit right-lateralized regions during the same task (Stebbins et al., 2002). The greater reliance on right-lateralized regions by older adults was evident in our cortico-hippocampal connectivity results, where we found that most regions showing increased coupling with the anterior hippocampus were right lateralized.

Together, our results expand on the above-reviewed work in important ways. First, ours is the first study to examine age effects on hippocampal subregion connectivity patterns during movie watching, mimicking the complexity and the nature of our everyday experiences (Campbell et al., 2015; Finn, 2021; Finn et al., 2020; Sonkusare et al., 2019). Given that functional connectivity during movie watching outperforms rest in predicting individual differences in cognition (Finn and Bandettini, 2021), this paradigm allowed us to draw a more complete picture of hippocampal functional topography as it relates to cognition in older age (Lacy and Stark, 2012). As well, we analyzed the largest sample reported to date to probe hippocampal connectivity patterns, which allowed for a well-powered examination of functional connectivity and its relation to episodic memory across the lifespan. We also employed a comprehensive approach to minimize age-related confounds and derive reliable measures of functional connectivity (e.g., motion artefacts, spatial normalization). We took advantage of the multi-echo data, which significantly mitigates motion artifacts after processing and denoising (Gotts et al., 2020), yielding a higher temporal signal-to-noise ratio (Kundu et al., 2013) and allowing reliable estimation of functional connectivity (Lynch et al., 2020). Second, we conducted our analyses in the participants' native space as well as with individualized hippocampal segmentation, circumventing issues with poor registration to standard, normalized templates, which are especially pervasive with older adult samples (Braga and Buckner, 2017; Wang et al., 2015).

However, our results deviate from other reports of age-related changes to functional brain connectivity at rest. For example, previous

work reported that older adults have reduced resting state functional connectivity in both ipsilateral and contralateral hippocampal subregions (Setton, Mwilambwe-Tshilobo, Sheldon, et al., 2022; but see Salami et al., 2014 and Damoiseaux et al., 2016 for different results). Although this inconsistency could be due to analytical differences (e.g., modeling age as a continuous vs. cohort variable; controlling for hippocampal volume in statistical models), it could also be because our study estimated connectivity profiles during movie watching, which is a more constrained, and ecologically valid assessment of connectivity that is known to differ from resting state scans in important ways (Finn and Bandettini, 2021; Kringelbach et al., 2023; Lacy and Stark, 2012; Meer et al., 2020).

Despite these advantages, our study was not without limitations. For example, in the CamCAN dataset, participants' memory for the movie was not tested. For this reason, episodic memory ability was measured using tests from a standardized neuropsychological battery which are limited in how much they relate to encoding and remembering complex events. This limitation might explain why we did not find a significant association between contralateral subregion connectivity and episodic memory performance as previously reported in neuropsychological studies (McCormick et al., 2018). The lack of memory measures for the encoded movie also precludes determining whether the observed functional connectivity patterns are driven by younger and older adults attending to different features of the movie. To this point, several studies using movie watching paradigms have shown differences in how events are processed by younger and older adults (Kurby and Zacks, 2019; Magliano et al., 2012; Zacks et al., 2006). For example, older adults show less agreement in where they perceive salient changes in a movie (Kurby and Zacks, 2019; Stawarczyk et al., 2020) as well as less hippocampal activity at these time points (Reagh et al., 2020) than younger adults. To examine whether age-related differences in hippocampal connectivity patterns relate to differences in attended movie features, current data can be supplemented by recent advances in fMRI analysis tools, which can reconstruct viewing behaviour from the MR-signal of the eyeballs (Frey et al., 2021; Nau et al., 2023).

Moreover, without collecting behavioural data associated with the movie-watching, it remains unclear whether the observed shifts in hippocampal connectivity patterns lead to age differences in how memories are represented by younger and older adults. A hypothesis in light of patterns reported here is that aging will be associated with qualitative shifts in the way memories are represented by younger and older adults (Grilli and Sheldon, 2022). In support of this hypothesis, emerging work finds differences in the recollected content from the same movie between younger and older adults (Davis et al., 2008; Fenerci et al., 2023; Henderson & Campbell, 2023). Future work can employ free recall paradigms in conjunction with in-scanner movie watching to map the observed patterns to the content younger and older adults use to remember the movie.

Last but not least, distinct from the subregions, the hippocampus is also composed of cytoarchitecturally distinct subfields, each of which playing an ascribed role in episodic memory processing (Mueller et al., 2011), showing dissociable cortical functional connectivity patterns (Chang et al., 2021; Dalton, McCormick, De Luca, et al., 2019; Dalton, McCormick, and Maguire, 2019; Vos de Wael et al., 2018) and selective age-related deterioration (de Flores et al., 2015; Frisoni et al., 2008; La Joie et al., 2010; Pereira et al., 2014). In the current study, it was not possible to assess age effects on hippocampal subfield connectivity given the high-resolution needed to reliably segment these subfields. Thus, an important future avenue is to characterize how aging affects hippocampal subfield connectivity in concert with changes in episodic memory (Dalton, McCormick, De Luca, et al., 2019). Future work should also examine age-related connectivity differences in extra-hippocampal, medial temporal lobe structures. Several studies have shown functional heterogeneity within the medial temporal lobes (Davachi, 2006; Eichenbaum et al., 2007; Graham et al., 2010; Wan et al., 1999). Content-based accounts have suggested that perirhinal cortex, as part of a broader anterior temporal network, supports item representations as well as related conceptual knowledge and parahippocampal cortex, embedded within a posterior medial network, supports context representations (Ranganath and Ritchey, 2012; Ritchey and Cooper, 2020). Since aging selectively impairs context, but not item memory (Naveh--Benjamin et al., 2003), this may be reflected in connectivity differences in these key medial temporal lobe regions, along with their associated networks.

6. Conclusions

To conclude, our study draws a comprehensive picture of hippocampal subregion connectivity patterns across the lifespan as they relate to episodic memory performance. We show that during movie watching – a proxy for naturalistic episodic memory encoding – age-related differences in subregion connectivity are apparent both within the hippocampus as well as between the hippocampus and the rest of the brain. These results suggest that advanced age is associated with a loss of hemispheric and to some extent, long-axis specialization of the hippocampal subregions, which might be a sensitive marker of age-related episodic memory decline.

CRediT authorship contribution statement

Signy Sheldon: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Investigation, Funding acquisition, Conceptualization. **R. Nathan Spreng:** Writing – review & editing, Supervision, Resources. **Jamie Snytte:** Writing – review & editing, Validation, Data curation. **Giulia Baracchini:** Writing – review & editing, Validation, Methodology, Data curation. **Roni Setton:** Writing – review & editing, Validation, Software, Methodology, Data curation, Conceptualization. **Can Fenerci:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Acknowledgements

We thank all participants as well as their primary care teams in Cambridge for participating in the Cam-CAN study. For further information on the CamCAN corporate authorship membership, please see: https://www.cam-can.org/index.php?content=corpauth#13. This work was supported by Natural Sciences and Engineering Research Council of Canada awarded to SS [Grant number RGPIN-04241].

Disclosure statement

The authors declare no conflict of interest in the conduct of this research.

Submission Declaration and Verification

We would like to note that our manuscript is original, is not previously published, and is not under consideration at another journal. We also confirm that there are no known conflicts of interest associated with this publication, there has been no significant financial support for this work that could have influenced its outcome.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.06.006.

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