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Functional Brain Networks Associated with Long-term Memory Consolidation: Changes in the Roles of the Hippocampus and Neocortex with the Age of the Memory

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Functional Brain Networks Associated with Long-term Memory Consolidation:

Changes in the Roles of the Hippocampus and Neocortex with the Age of the Memory

A Dissertation submitted in partial satisfaction of the requirements
for the degree Doctor of Philosophy

in

Experimental Psychology

by

Catherine Walsh Tallman

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Professor Robert Clark
Professor John Serences

2023

The Dissertation of Catherine Walsh Tallman is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California San Diego

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ABSTRACT OF THE DISSERTATION

Functional Brain Networks Associated with Long-term Memory Consolidation:

Changes in the Roles of the Hippocampus and Neocortex with the Age of the Memory

by

Catherine Walsh Tallman

Doctor of Philosophy in Experimental Psychology

University of California San Diego, 2023

Professor Christine Smith, Co-Chair
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As time passes after learning, connections between the hippocampus and neocortex gradually change. The exact time course of these changes is not well established and competing theories of memory consolidation debate if the role of the hippocampus in memory retrieval changes with the age of the memory. Functional

magnetic resonance imaging (fMRI) can measure changes in retrieval-related brain function associated with the age of the memory to characterize the roles of the hippocampus and neocortex in memory consolidation. This dissertation aims to identify common functional brain networks associated with long-term memory consolidation by examining how these networks change with the age of the memory. Three fMRI studies in healthy adults were conducted to examine changes in retrieval-related brain function associated with different memory ages and types of memoranda. Each study measured whole-brain changes in retrieval-related brain activity, hippocampal functional connectivity, and ventromedial prefrontal cortex connectivity.

In Chapter 1, I examine changes in brain function during retrieval of natural scenes learned 1 month to 1 hour prior to test. I demonstrate changes consistent with systems consolidation theory can be detected across short time periods. In Chapter 2, I examine changes in brain function during retrieval of three-word sentences learned 1 month to 1 hour prior to test. I similarly demonstrate changes consistent with systems consolidation theory can be detected across short time periods. In Chapter 3, I examine changes in brain function during retrieval of news events learned 1 year to 30 years prior to test. I demonstrate changes both consistent and inconsistent with memory consolidation theories are observed across long time periods. In the discussion, I compare commonalities between the brain networks identified in Chapters 1 and 2 which similarly change across short time periods but for different types of memoranda. I also compare the commonalities between the brain networks identified in Chapters 2 and 3 which change across both short and long time periods for similar memoranda. In sum, common changes in the functional roles of the hippocampus and neocortex consistent with

memory consolidation can be detected across different types of memoranda and memory ages.

GENERAL INTRODUCTION

Long-term memory consolidation is the gradual process in which declarative memories become stabilized from a labile to enduring state. Changes between the connections of the hippocampus and neocortex facilitate the stabilization of long-term memories. The exact nature of the changes in the roles of the hippocampus and neocortex is unknown. Neurocomputational models suggest that the hippocampus is “fast-acting” and guides the “slow-learning” neocortex to establish memories that will be resistant to interference (McClelland, 2013; McClelland et al., 1995). Psychological theories of long-term memory consolidation formulated predictions regarding the necessity of the hippocampus and neocortex in retrieval with memory age from patients exhibiting amnesia.

In several studies, patients with hippocampal or medial temporal lobe (MTL) damage demonstrated temporally-graded retrograde amnesia and were able to retrieve memories from the remote (several years or more) but not recent past for both semantic (Bayley et al., 2006; J.R. Manns et al., 2003) and autobiographical (Bayley et al., 2003; Kirwan, Bayley, Galvan, et al., 2008) memories. Similar patterns of amnesia can be observed in animals with hippocampal lesions although over short time scales, occurring over days to weeks (Clark et al., 2002; Kim et al., 1995; Winocur, 1990; S. Zola-Morgan & L. R. Squire, 1990). Systems consolidation theory (SCT) predicts that the hippocampus and other MTL structures are not necessary for remote but necessary for recent declarative memory retrieval (Marr, 1971; Squire & Alvarez, 1995). Alternative theories such as multiple trace theory/transformation theory (MTT/TT) (Moscovitch et al., 2005; Nadel & Moscovitch, 1997) posit that the hippocampus and MTL are always necessary for episodic recent and

remote memory retrieval. This phenomenon was observed in patients that exhibited ungraded amnesia for recent and remote memories (Steinvorth et al., 2005)

The hallmark of functional magnetic resonance imaging (fMRI) provided the opportunity to examine how the roles of the hippocampus and neocortex change with memory age in individuals with normal cognition. Measuring changes in retrieval-related brain function with memory age can reveal patterns of activity or functional connectivity that are consistent with memory consolidation theories. For example, hippocampal/MTL function that decreases with memory age would support SCT whereas hippocampal/MTL function that increases or remains unchanged would support MTT/TT. The literature of fMRI studies examining long-term memory consolidation is vast and examines changes in the retrieval of many types of memoranda and across varying time periods (e.g., minutes to days or years to decades). fMRI studies that find patterns of change that support SCT are found across relatively short (e.g., Takashima et al., 2009; Takashima et al., 2006; Yamashita et al., 2009) and longer (e.g., Douville et al., 2005; Haist et al., 2001; Smith & Squire, 2009) time periods. Conversely, there are studies which find support for MTT/TT across both shorter (e.g., Bosshardt, Degonda, et al., 2005; Bosshardt, Schmidt, et al., 2005) and longer (E.A. Maguire & C.D. Frith, 2003; Maguire et al., 2001) time periods. The observed patterns of hippocampal and neocortical brain function with memory age are taken to support one memory consolidation theory over the other, yet no consolidation theory has prevailed from functional neuroimaging studies in humans.

There are significant confounds commonly observed across study designs that may contribute to the inconsistent results and bias one pattern to be observed over the

other. When examining changes in retrieval-related brain function, many studies evaluate one recent and one remote time period. This poses challenges when considering the statistical inferences of comparing fMRI activity to baseline activity at only two points in time (Tallman et al., 2022a). Examining multiple time points to evaluate patterns of change can ameliorate this issue. In addition, the nature of testing memory retrieval also invokes memory encoding, which is dependent on structures used for retrieval, particularly the medial temporal lobe (MTL) (Buckner et al., 2001). Lastly, changes in behavior associated with memory judgments (i.e., response time and confidence) can change in a similar pattern to observed changes in retrieval-related brain function. Changes in brain function associated with memory age could simply be tracking these behavioral changes rather than reflecting memory consolidation. Studies that address this issue commonly equate behavior of recent and remote time periods by only analyzing high confidence trials (e.g., Sterpenich et al., 2009; Yamashita et al., 2009), yet this disproportionately excludes remote trials.

The overarching aim of this dissertation is to identify a functional brain network associated with long-term memory consolidation. Commonalities in the functional roles of the hippocampus and neocortex with memory age were assessed by measuring retrieval-related brain function changing with memory age in three separate fMRI studies (described below). Retrieval-related brain activity, task-based hippocampal functional connectivity, and task-based ventromedial prefrontal cortex (vmPFC) functional connectivity were examined. In addition, each study was designed to address the three common confounds in fMRI studies of memory consolidation. Retrieval was measured at multiple timepoints to examine patterns of change in brain function. To validate the

observed changes in retrieval-related brain function, successful encoding-related activity was assessed through post-scan subsequent memory tests and secondary statistical models were carried out to minimize the effects of confidence and response time at the trial-level.

In Chapter 1, I examine changes in the brain function of younger adults with normal cognition during retrieval of natural scenes learned 1 month to 1 hour prior to test. In Chapter 2, I examine changes in brain function of older adults with normal cognition during retrieval of three-word sentences learned 1 month to 1 hour prior to test. I similarly demonstrate changes consistent with systems consolidation theory can be detected across short time periods. In Chapter 3, I examine changes in the brain function of the same older adults from Chapter 2 during retrieval of news events learned 1 year to 30 years prior to test. I demonstrate changes both consistent and inconsistent with consolidation theories are observed across long time periods. In the discussion, I compare commonalities between the brain networks identified in Chapters 1 and 2 which similarly change across short time periods but for different types of memoranda. I also compare the commonalities between the brain networks identified in Chapters 2 and 3 which change across both short and long time periods for similar memoranda. In sum, common changes in the functional roles of the hippocampus and neocortex consistent with memory consolidation can be detected across different types of memoranda and memory ages.

Chapter 1 Human Brain Activity and Functional Connectivity as Memories Age from One Hour to One Month

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Abstract

Theories of memory consolidation suggest the role of brain regions and connectivity between brain regions change as memories age. Human lesion studies indicate memories become hippocampus-independent over years, whereas animal studies suggest this process occurs across relatively short intervals, days to weeks. Human neuroimaging studies suggest that changes in hippocampal and cortical activity and connectivity can be detected over these short intervals, but many of these studies examined only two time periods. We examined memory and FMRI activity for photos of indoor and outdoor scenes across four time periods to examine these neural changes more carefully. Participants (N=21) studied scenes 1 hour, 1 day, 1 week, or 1 month before scanning. During scanning, participants viewed scenes, made old/new recognition memory judgments, and gave confidence ratings. Memory accuracy, confidence ratings, and response times changed with memory age. Brain activity in a widespread cortical network either increased or decreased with memory age, whereas hippocampal activity was not related to memory age. These findings were almost identical when effects of behavioral changes across time periods were minimized. Functional connectivity of the ventromedial prefrontal cortex with the posterior parietal cortex increased with memory age. By contrast, functional connectivity of the hippocampal with the parahippocampal

cortex and fusiform gyrus decreased with memory age. In sum, we detected changes in cortical activity and changes in hippocampal and cortical connectivity with memory age across short intervals. These findings provide support for the predictions of systems consolidation and suggest that these changes begin soon after memories are formed.

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Chapter 2 Human Brain Activity and Functional Connectivity Associated with Verbal Long-term Memory Consolidation Across One Hour to One Month

Introduction

Long-term memory consolidation is the time-dependent neural reorganization that establishes enduring memories from unstable memory traces. According to standard systems consolidation theory (SCT), as time passes after learning, declarative memories that were initially dependent on the hippocampus become stabilized in the neocortex and can eventually be retrieved independently of the hippocampus (Marr, 1971; McClelland, McNaughton, O'Reilly, et al., 1992; McClelland et al., 1995; Squire & Alvarez, 1995). Patients with lesions restricted to the hippocampus demonstrated that memories several years old can be retrieved independent of the hippocampus, and this pattern of temporally-graded retrograde amnesia extended further when the parahippocampal gyrus was also damaged (Bayley et al., 2006; J. R. Manns et al., 2003). However, competing theories of memory consolidation such as multiple-trace/transformation theory (MTT/TT) (Moscovitch et al., 2005; Nadel & Moscovitch, 1997; Sekeres et al., 2017) and contextual binding theory (CBT) (Yonelinas et al., 2019) debate the dependence on the hippocampus for remote episodic memory retrieval and posit that the hippocampus is always necessary for memory retrieval. The theories described above are in agreement that semantic memories become hippocampus independent over time.

Although the predictions of long-term memory consolidation theories consider whether or not the hippocampus is *necessary* for remote memory retrieval, noninvasive imaging techniques such as functional magnetic resonance imaging (fMRI) allow for the examination of relative changes in retrieval-related brain function over time. Time-dependent decreases in MTL brain activity associated with semantic (“fact”) memory retrieval across several years demonstrated changes in brain function consistent with SCT (Douville et al., 2005; Haist et al., 2001; Smith & Squire, 2009). Studies of time-

dependent changes associated with autobiographical memory retrieval are less consistent as some studies demonstrated decreases in hippocampal activity (e.g., Gilboa et al., 2004; E. A. Maguire & C. D. Frith, 2003) or increases in hippocampal activity (e.g., Piolino et al., 2004; Rekkas & Constable, 2005) across several years. Overall, the examination of changes in retrieval-related brain activity in humans across years reveals that decreasing dependence can be detected at these time intervals.

In animals with hippocampal lesions, the time-dependent changes of systems consolidation appears to be shorter, with memories becoming hippocampus independent over days to weeks (Kim & Fanselow, 1992; Winocur, 1990; S. M. Zola-Morgan & L. R. Squire, 1990). Studies of hippocampal activity in animals across short time periods using markers of brain activity such as glucose metabolism or immediate early gene activity also reveal evidence that hippocampal activity decreases with memory age (Bontempi et al., 1999; Frankland et al., 2004; Maviel et al., 2004; Wheeler et al., 2013). Nevertheless, there are reports of hippocampal activity that was similar or that increased for recent and remote retrieval of spatial memory (Makino et al., 2019; Teixeira et al., 2006), suggesting that patterns of hippocampal findings are not entirely consistent within the animal literature.

In concordance with the animal literature, studies of human neuroimaging and consolidation have also tried to detect changes in hippocampal activity over short time scales (minutes to months). Several studies observed hippocampal activity decreases with memory age, supporting the predictions of systems consolidation theory (left, Bosshardt, Schmidt, et al., 2005; Dandolo & Schwabe, 2018; Du et al., 2019; Furman et al., 2012; Harand et al., 2012; Milton et al., 2011; Ritchey et al., 2015; Sekeres et al.,

2018; Smith et al., 2010; Sterpenich et al., 2009; Takashima et al., 2009; Takashima et al., 2006; Yamashita et al., 2009). However, other studies have found increases or no changes in hippocampal activation associated with memory age (Bosshardt, Degonda, et al., 2005; Bosshardt, Schmidt, et al., 2005; Gais et al., 2007; Smith et al., 2010; Vanasse et al., 2022). These latter findings can be taken to support for the idea that memory traces increase within the MTL as time passes after learning, as predicted by MTT/TT. Additionally, several studies have found no change in retrieval-related hippocampal activity associated with memory age at varying time intervals up to ~45 days (Davis et al., 2009; Du et al., 2019; Janzen et al., 2008; Stark & Squire, 2000; Suchan et al., 2008; Tallman et al., 2022b; Tompary & Davachi, 2017; Vilberg & Davachi, 2013).

There are several methodological factors to consider (e.g., experimental design, time interval between recent and remote timepoints) which may explain these inconsistent findings across studies. In particular, it is unclear if the type of memoranda used is relevant to discern a common pattern of hippocampal activity changes. Several studies have examined memory for verbal material, and the pattern of hippocampal activity changes remains variable. Some studies identified decreases in hippocampal activity with memory(left hippocampus; Bosshardt, Degonda, et al., 2005; associative memory; Du et al., 2019; Ritchey et al., 2015), others identified increases (Bosshardt, Degonda, et al., 2005; right hippocampus; Bosshardt, Schmidt, et al., 2005; Gais et al., 2007), or failed to detect any changes in activity (Davis et al., 2009; item memory; Du et al., 2019).

Theories of long-term memory consolidation are dependent on changing hippocampal-cortical and cortico-cortical *connections*. Thus, assessing time-dependent changes in functional connectivity, rather than overall differences in brain activity, may be

a more reliable measure for detecting long-term memory consolidation effects. Changes in hippocampal functional connectivity of semantic memory have not yet been examined, although studies of autobiographical memory exhibited decreasing hippocampal-cortical functional connectivity across several years or more (Gilmore et al., 2021; Sheldon & Levine, 2013; Söderlund et al., 2012). Time-dependent decreases in hippocampal-cortical functional connectivity were also detected over short time periods of one day in humans (Brodt et al., 2016; Takashima et al., 2009) and similarly across days in animals (Bontempi et al., 1999; Wheeler et al., 2013; Wirt & Hyman, 2019). Assessing more direct changes in the relationship between the MTL and cortex with functional connectivity may reveal more consistent patterns of brain function associated with long-term memory consolidation, particularly over short time periods.

Therefore, we examined brain activity and functional connectivity associated with retrieval of unique sets of three-word sentences studied one hour, one day, one week, or one month (four memory ages) before a memory retrieval test. Our aim was to identify time-dependent patterns of retrieval-related brain activity and functional connectivity associated with memory age. Secondary analyses were conducted to ensure additional factors that changed with memory age (i.e., changes in confidence and response time, re-encoding of targets) did not influence our primary analyses.

Methods

Participants

Twenty-eight participants (12 female; mean age = 72.6 yrs ± 1.5 yr; range = 65–91 yrs; mean education = 16.6 yrs ± 0.4 yr) were recruited from the San Diego community and underwent MRI scanning. One participant was excluded due to technical issues while MRI scanning, one participant was excluded due to excessive motion during scanning,

and two participants were excluded due to difficulty understanding of the task instructions. Twenty-four participants (10 female; mean age = 72.6 ± 1.3 yr; range = 65–91 yrs; mean education = 16.6 yrs ± 0.5 yr) were included in the reported statistical analyses.

Memory task design

Each participant completed the study protocol across four visits which consisted of 1) four study sessions outside of the scanner, 2) one recognition memory test while undergoing fMRI scanning, and 3) one surprise posttest outside of the scanner. Study sessions were administered using Qualtrics online surveys and occurred at one month, one week, one day, and one hour before an in-scanner recognition memory test (Figure 2.1A; Visits 1-4). Participants learned a unique set of 60 fact-like, three-word sentences (e.g., LID SEALED JAR) at each of the four study sessions. Sentences were created such that no words were repeated across the stimuli. Each sentence was individually presented on the screen for 4 seconds followed by a question that encouraged deeper encoding (Could you picture what was described in the sentence?) with unlimited time to respond. To aid memory retention, the set of sentences was repeated 4 times at the study session.

Participants completed a recognition memory test of the previously learned sentences while undergoing fMRI scanning (Figure 2.1B; Visit 4). Within the scanning session, 240 three-word target sentences (60 from each study phase) and 120 novel three-word sentences and 282 digit baseline trials were presented. Each three-word sentence trial was presented for 6.4 sec during which participants made a recognition memory judgment using confidence ratings (1 = definitely new, 2 = probably new, 3 = maybe new, 4 = maybe old, 5 = probably old, and 6 = definitely old). Confidence ratings were completed by selecting a number (1–6) on the screen with an MRI-compatible

mouse (Current Designs, Philadelphia, PA). The starting location of the mouse cursor on the screen was randomized before each sentence trial with the intention of decorrelating rightward and leftward movements with the right and left sides of the 1-6 scale. After each sentence trial, zero to seven digit baseline trials were presented (mean = 1.95 trials). For each baseline trial, a single digit (1–8) was presented and participants selected with the mouse whether it was even or odd (3.2 sec) (Stark & Squire, 2001). The scanning session consisted of six 8.8 min runs, with each run containing 60 sentences (40 target sentences [10 from each memory age condition] intermixed with 20 novel foil sentences).

A surprise post test to assess subsequent memory of in-scanner foils was administered immediately following the fMRI scan (Figure 2.1C). Participants were presented with the 120 foil three-word sentences viewed in the scanner (now considered to be targets) intermixed with 60 novel foil three-word sentences across 6 runs. The same recognition judgement scale was used, and participants had unlimited time to indicate if the sentence was old (previously seen in the scanner), or new (first time encountering the sentence in the study). The presentation of sentences was counterbalanced across participants so that each set of sentences had an equal chance of being presented during one of the study phases, during the test phase as a target or foil, or during the post-scan recognition memory test as a foil.

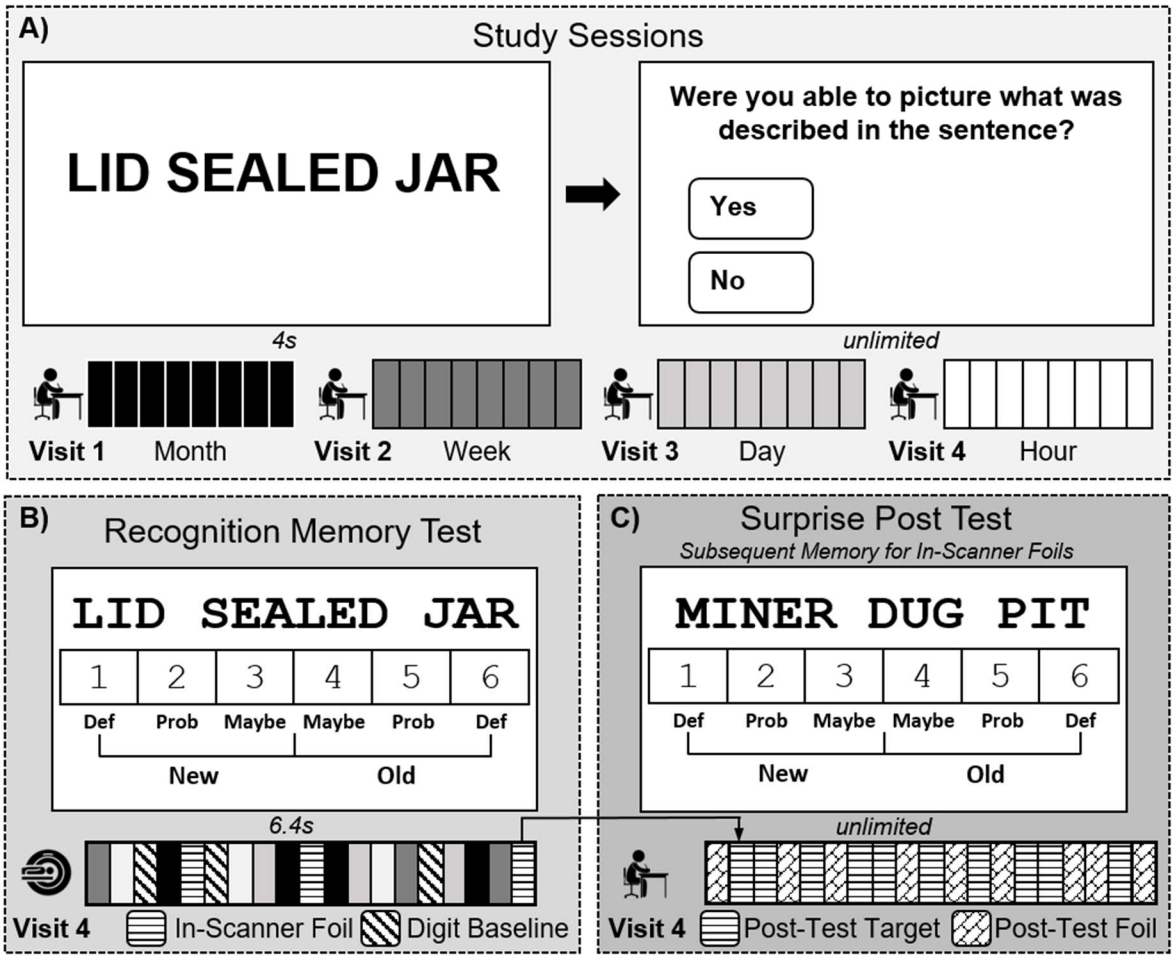

Figure 2.1: Three-word sentences task design. (A) Participants studied a unique set of fact-like, three-word sentences one month (black, Visit 1), one week (dark grey, Visit 2), one day (light grey, Visit 3), and one hour (white, Visit 4) before the MRI. (B) During Visit 4, participants completed a test in the scanner where they made old/new recognition memory judgments using confidence ratings (1 = definitely new to 6 = definitely old) in response to each three-word sentence studied previously (240 studied sentences; white, light grey, dark grey, and black bars) intermixed with 120 novel sentences (in-scanner foil; horizontal striped bars), and made even/odd judgments in response to digits (baseline trials; diagonally striped bars). (C) At the end of Visit 4, participants completed a surprise post test outside of the scanner to examine subsequent memory for the in-scanner foils. Participants made memory judgments using the same confidence scale in (B), but in response to the 120 post test targets (previously presented in-scanner foils, horizontal striped bars) intermixed with a completely novel set of 120 sentences (post test foils, diagonal brick bars).

fMRI imaging protocol

Scanning was conducted on a 3T General Electric MR750 Discovery MRI scanner at the Center for Functional MRI (University of California San Diego) using a NOVA 32 channel head coil. Functional images were acquired using a gradient- echo, echo-planar, T2*-weighted pulse sequence, using parameters closely matched to the HCP Lifespan brain imaging protocol (800 msec TR; 37.0 msec TE; 104 × 104 matrix size; 20.8 cm field of view; 2 × 2 mm in-plane resolution; multiband acceleration factor = 8). Seventy-two axial slices (slice thickness = 2mm) were acquired covering the whole brain. Spin-echo fieldmap scans with opposite phase encoding directions (P>A & A>P) were acquired for susceptibility induced distortion correction after run 1 to correct functional runs 1-3 and after run 4 to correct functional runs 4-6. Following the third functional run, high-resolution structural images were acquired using a sagittal T1-weighted MPRAGE pulse sequence (25.6 cm field of view; 160 slices; 1 mm slice thickness; 256 × 256 matrix size). PROMO (PROspective MOtion correction; White et al., 2009) was used to adaptively compensate for motion during structural scanning resulting in little to no loss of anatomical data due to subject motion.

Data Analysis

Behavioral data analysis

Measures of discrimination, confidence, and response time for each memory age condition were calculated by taking the mean across all targets. Discriminability [d prime (d')] was also calculated using the following formula: Z(hit rate) – Z(false alarm rate) using Excel. Means and SEM are reported. Significant changes across memory age conditions were tested using repeated measures ANOVA.

fMRI data preprocessing

Results included in this manuscript come from preprocessing performed using fMRIPrep 21.0.2 (Esteban, Blair, et al., 2018; Esteban, Markiewicz, et al., 2018; RRID:SCR_016216) which is based on Nipype 1.6.1 (Gorgolewski et al., 2011; RRID:SCR_002502; Gorgolewski et al., 2018). Additional preprocessing and statistical modeling for the neuroimaging analyses was conducted using programs from Analysis of Functional NeuroImages (AFNI) (Cox, 1996).

fMRIprep anatomical data preprocessing

A total of 1 T1-weighted (T1w) images were found within the input BIDS dataset. The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al., 2010), distributed with ANTs 2.3.3 (Avants et al., 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 6.0.5.1:57b01774, RRID:SCR_002823, Zhang et al., 2001) Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1, RRID:SCR_001847, Dale et al., 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438, Klein et al., 2017). Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with antsRegistration (ANTs 2.3.3), using brain-extracted versions

of both T1w reference and the T1w template. The following template was selected for spatial normalization: ICBM 152 Nonlinear Asymmetrical template version 2009c [(Fonov et al., 2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym).

fMRIprep functional data preprocessing

For each of the 6 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 6.0.5.1:57b01774, Jenkinson et al., 2002). 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. These resampled BOLD time-series will be referred to as preprocessed BOLD in original space, or just preprocessed BOLD. The BOLD reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration (Greve & Fischl, 2009). Co-registration was configured with six degrees of freedom. Several confounding time-series were calculated based on the preprocessed BOLD: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, Power et al., 2014) and Jenkinson (relative root mean square displacement between affines, Jenkinson et al., 2002). FD and DVARS are calculated for each functional run, both using their implementations in Nipype (following the definitions by Power et al. 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain

masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (CompCor, Behzadi et al., 2007). Principal components are estimated after high-pass filtering the preprocessed BOLD time-series (using a discrete cosine filter with 128s cut-off) for the two CompCor variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by dilating a GM mask extracted from the FreeSurfer's aseg segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the k components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al., 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. The BOLD time-series were

resampled into standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964). Non-gridded (surface) resamplings were performed using mri_vol2surf (FreeSurfer).

Many internal operations of fMRIPrep use Nilearn 0.8.1 (Abraham et al., 2014, RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in fMRIPrep's documentation.

Additional functional data preprocessing

After preprocessing using fMRIprep, each functional run was subsequently smoothed up to a kernel of 4mm (*3dBlurtoFWHMx)* and scaled so the mean activation for each voxel was 100. Timepoints identified as motion outliers by fMRIprep criteria were censored during subsequent statistical analysis (Power et al., 2014). One participant was excluded as more than 10% of their functional data was identified as motion outliers. The remaining subjects included in the statistical analyses (n=24) had on average 1.1% of their functional data censored due to motion artifacts.

General linear modeling

Multiple regression analyses were conducted using AFNI's *3dDeconvolve* to calculate beta coefficients for vectors of interest relevant to each analysis (described below). Confound regressors included in multiple regression analyses were selected using the aCompCor pipeline approach to optimize the removal of noisy signal when conducting task-related functional connectivity analyses (Mascali et al., 2021) and using fMRIprep. These regressors were the first 5 aCompCor components (principle components which capture anatomical noise) and 24 motion regressors (6 translation/rotation directions, 6 derivatives of translation/rotation directions, 6 squared translation/rotation directions, and 6 squared derivatives of translation/rotation directions).

The hemodynamic response function was independently modeled for each sentence trial using twenty-one TENT functions spanning 0–16 seconds after the onset of the sentences. Peak activation from 6.4–9.6 seconds post-stimulus onset was isolated for analysis. The deconvolution matrix was fit using generalized least square regression within *3dREMLfit* to reduce the influence of temporal autocorrelation. The resulting β coefficients for each vector of interest from the multiple regression model reflected the mean peak activation.

Region of interest analysis: Hippocampus

We defined an anatomical hippocampal region of interest (ROI) for each participant to examine brain activity changes associated with memory age as well as to use as a seed in the task-based functional connectivity analyses (described below). Bilateral hippocampal ROIs were created using FSL FIRST to segment each participant's T1-

weighted image co-registered to MNI space (Patenaude et al., 2011). The anterior and posterior hippocampus was defined by the MRI slice where the uncus was no longer visible and demarcated the beginning of the posterior hippocampal ROI.

Whole-brain voxel-wise analysis of brain activity

Primary Analysis: Memory Age

The purpose of this study was to identify retrieval-related brain activity that changed as a function of memory age and that was consistent with memory consolidation. We were interested in brain activity that increased or decreased in relatively monotonic *patterns* across the memory age conditions. The detection of a pattern of activity across several memory ages is likely more robust than detection of differential activity across only two memory ages. Therefore, we *a priori* tested for retrieval-related brain regions which demonstrated activity that followed a power law (Takashima et al., 2006; Tallman et al., 2022b), a pattern that corresponds to normal forgetting (Wickelgren, 1974; Wixted & Carpenter, 2007).

First, four vectors of interest were created that coded for the target trials for each memory age condition (1 hour, 1 day, 1 week, 1 month). A fifth vector coded for foil trials. Second, beta coefficients for each memory age condition were obtained from multiple regression analysis for each participant. Third, we carried out a group-level linear mixed effect model (LME) analysis to examine voxels where the beta coefficients changed across time periods according to a power function ($y= x^{-0.33}$) (Chen et al., 2013). Finally, significant clusters were identified using a voxel-wise probability value of $p < 0.001$ and a cluster-wise probability of $p < 0.05$ (Woo et al., 2014). All cluster labels are reported in the tables using the gyrus and region information from the Brainnetome atlas (Fan et al., 2016).

Secondary Analyses

The brain regions identified as changing as a function of memory age in the primary analysis could instead reflect processes such as behavioral changes or encoding/re-encoding, that also change with memory age. Therefore, we also carried out two secondary analyses to validate that our primary findings reflected memory retrieval. *Amplitude-modulated analysis*: The purpose of the amplitude-modulated analysis was to ensure clusters identified in the primary analysis reflected changes in retrieval-related activity associated with memory age and not concomitant changes in behavior. The in-scanner behavioral measures of memory resemble the predicted pattern of brain function and could interfere with the accurate detection of retrieval-related activity patterns (reported below, see Figure 2.2). The identified monotonic patterns of brain activity could be tracking changes in behavior rather than changes in memory age. Therefore, we conducted an additional multiple regression analysis which allowed for the examination of all trials while minimizing the trial-by-trial effects of behavior (as in Tallman et al., 2022b). The same multiple regression from the primary analysis was used with the addition of 8 new vectors, two new vectors for each of the four memory age condition which corresponded to trial-level memory confidence ratings and trial-level response times (*1dMarry*). The resulting beta coefficients associated with each memory age condition represented retrieval-related activity when the effects of the behavioral changes were minimized. The amplitude-modulated beta coefficients associated with each memory age condition were used in a second LME model identical to the primary analysis to obtain retrieval-related brain regions associated with memory age while minimizing the effects of behavior.

Re-encoding analysis. Another potential confound when detecting changes in retrieval-related activity associated with memory age is the presence of encoding-related activity in the same brain regions. Due to forgetting across the memory age conditions (reported below, see Figure 2.2), more re-encoding would be experienced for weakly remembered targets in the remote conditions when compared to strongly remembered targets in the recent conditions. Therefore, differential levels of re-encoding-related activity would appear as increases in retrieval-related brain activity associated with memory age.

We assessed successful encoding during the experiment by testing subsequent memory for in-scanner foils (post test targets) during a surprise post test (see Figure 2.1C). We created two vectors to define in-scanner foils as subsequently remembered or subsequently forgotten based on post test responses. A multiple regression analysis was carried out with one vector coding for all target sentences, one vector coding for subsequently remembered in-scanner foils, and one vector coding for subsequently forgotten in-scanner foils. The subsequently forgotten beta coefficients for six subjects were excluded from analysis because they performed so well that they had 5 or fewer forgotten items according to the post test. Thus, the re-encoding analysis included the subsequently remembered beta coefficients for all participants (n=24) and the subsequently forgotten beta coefficients for a subset of subjects (n=18). There were 89 ± 4.6 subsequently remembered in-scanner foil trials and 31 ± 4.6 subsequently forgotten in-scanner foil trials per participant, when excluding those 6 participants. Because LME can handle missing data, we carried out group-level analysis of encoding-related activity using *3dLME* to contrast subsequently remembered and subsequently forgotten foils

(successful encoding: remembered > forgotten). Cluster significance testing was carried out at the same threshold as the primary analysis.

Whole-brain, voxel-wise analysis of functional connectivity

Generalized psychophysiological interaction (gPPI) analyses were carried out to examine functional connectivity changes associated with memory age. gPPI analyses are used to test the interaction between different psychological contexts and the relationship of a neural response in a particular seed region and the rest of the brain. (Cisler et al., 2014; Friston et al., 1997; McLaren et al., 2012). Thus, it is possible to assess whether variations in functional connectivity between a specific brain region (seed region) and the rest of the brain are responsible for differences in levels of a psychological context. Alternatively, this interaction can be understood as the impact of different levels of a psychological context on the variations between the seed region and the rest of the brain.

We created gPPI models to examine the interaction between different levels of memory age across 1 hour to 1 month and the functional connectivity between the *apriori* ROIs (hippocampus and vmPFC) and the rest of the brain. The hippocampal analysis used the bilateral anatomical ROI seed region, described above. For the vmPFC gPPI analysis, an anatomical vmPFC seed region was selected from a previous study (Takashima et al., 2006) where an increase in activity was observed as memory age increased from 1 day to 3 months. To create the vmPFC seed region, an 8mm sphere was dilated around their MNI coordinate (-2,32,10).

Functional connectivity changes are detected at the neural level rather than detected within changes in the BOLD signal (Gitelman et al., 2003), therefore we carried out a series of steps to prepare the BOLD signal from the primary analysis of memory

age (described above) for gPPI modeling. First, the baseline activity associated with the task regressors was extracted using *3dSynthesize* and subtracted from the concatenated and preprocessed functional runs using *3dcalc*. Neural interaction regressors were created to represent the neural activity in the seed region convolved with the trial onset times each memory age condition (1 hour, 1 day, 1 week, 1 month) and for foils. Next, we carried out the same general linear model as in the primary activation analysis of memory age, but with the addition of the neural interaction regressors and the seed region time course. The resulting four beta coefficients of the neural interaction regressors represent the magnitude of the effect of the seed region on the rest of the brain for each memory age, respectively. The same LME approach was used to calculate if hippocampal or vmPFC functional connectivity changed as a function of memory age. Similarly, functional connectivity analysis was also carried out using the amplitude-modulated regression model as its starting point, to identify functional connectivity networks when behavioral effects were minimized. In addition, successful encoding-related functional connectivity for hippocampus and vmPFC was carried out to determine if there was overlap with the retrieval-related connectivity maps.

Results

Behavioral Findings

During the recognition memory test in the scanner, old-new discriminability (*d'*), response time, and confidence ratings decreased while response times increased across time periods (Figure 2.2). Participants obtained old-new discriminability scores of 2.6 ± 0.2, 2.4 ± 0.2, 1.7 ± 0.2, and 1.0 ± 0.1, average response times (ms) of 3112.8 ± 115.4, 3235 ± 106.8, 3501 ± 99.4, and 3889.5 ± 95.4, and confidence ratings of 5.8 ± 0.06, 5.6 ± 0.11, 4.9 ± 0.19, and 4.0 ± 0.18 for the hour, day, week, and month conditions,

respectively. In-scanner behavioral measures significantly changed as a function of memory age (*d'*: $F_{(3,69)}=70.31$, $\eta^2 = 0.754$, $p < 0.001$; response time: $F_{(3,69)} = 26.27$, $\eta^2 = 0.533$, $p < 0.001$; confidence ratings: $F_{(3,69)} = 66.81$, $\eta^2 = 0.744$, $p < 0.001$). Participants obtained 199.6 ± 5.9 hits (Hour: 57.7 ± 0.7; Day: 56.0 ± 1.3; Week: 48.7 ± 2.4; Month: 37.3 ± 2.4) and 40.4 ± 5.9 misses (Hour: 2.3 ± 0.7; Day: 4.0 ± 1.3; Week: 11.3 ± 2.4; Month: 22.8 ± 2.4). On the surprise post-scan recognition memory test, participants exhibited a *d'* of 2.0 ± 0.2.

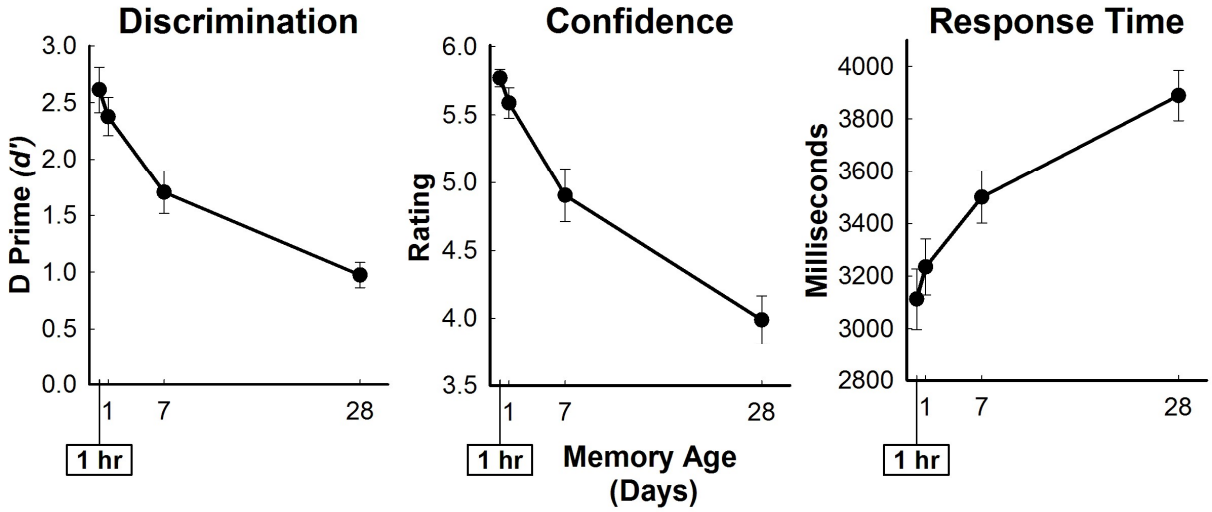

Figure 2.2: In-scanner behavioral measures of memory retrieval of three-word sentences. Measures of discrimination (d' [D Prime]) between old and new sentences, confidence ratings from 1 (definitely new) to 6 (definitely old) for targets, and response time in milliseconds for targets. Error bars show SEM.

Brain regions where activity changed as a function of memory age

The primary analysis detected a network of 30 brain regions within the prefrontal, temporal, parietal, and occipital cortices where activity was significantly associated with the age of the memory (Figure 2.3, Table 2.1). Relatively monotonic increases or decreases in activity were observed in all brain regions. Regions increasing in activity as a function of memory age were identified in the bilateral prefrontal cortex, left middle

temporal gyrus (MTG), and left superior parietal lobule (SPL). Regions decreasing in activity as a function of memory age were identified bilaterally in the prefrontal, temporal, parietal, and occipital cortices (Table 2.1).

Analysis of brain activity in hippocampal ROIs as a function of memory age

Brain activity in the bilateral hippocampal anatomical ROI significantly changed with memory age according to a power function (LME Estimate: 0.075; SE: 0.02; df: 46.5; $t=3.97$; $p < 0.001$) (Figure 2.4). Follow-up analyses to examine whether the effects of memory age were related to laterality or anterior/posterior portions of the hippocampus revealed similar findings. There were significant effects of memory age for the left, right, anterior, and posterior hippocampal ROIs (see Supplemental Table 7). Thus, activity in the entire hippocampus decreased as a function of memory age across one hour to one month. Note that a right posterior hippocampal cluster decreasing in activity as a function of memory age was observed in the whole-brain analysis described above when the cluster threshold was substantially more liberal ($p < 0.02$, $\alpha=0.05$; MNI center of mass: 18,-35,-15; volume = 696mm3.

Figure 2.3: Memory age network in which retrieval-related brain activity for three-word sentences changed as a function of memory age (A) Lateral and medial views of the network in which retrieval-related activity for sentences increased (warm colors) or decreased (cool colors) as memories aged from one hour to one month. Higher F values (cyan or yellow) indicate activity that more closely followed a power function. Clusters corrected at $p < 0.001$, $\alpha=0.05$. (B) Monotonic patterns of brain activity (beta coefficients) associated with memory age from selected regions shown in panel (A). ACC. Anterior Cingulate Cortex; IFG. Inferior Frontal Gyrus; IPL. Inferior Parietal Lobule; MFG. Middle Frontal Gyrus; MTG. Middle Temporal Gyrus; Occ Ctx. Occipital Cortex; OFG. Orbital Frontal Gyrus; PCC. Posterior Cingulate Cortex; SFG. Superior Frontal Gyrus; SPL. Superior Parietal Lobule; STS. Superior Temporal Sulcus; vmPFC. Ventral Medial Prefrontal Cortex.

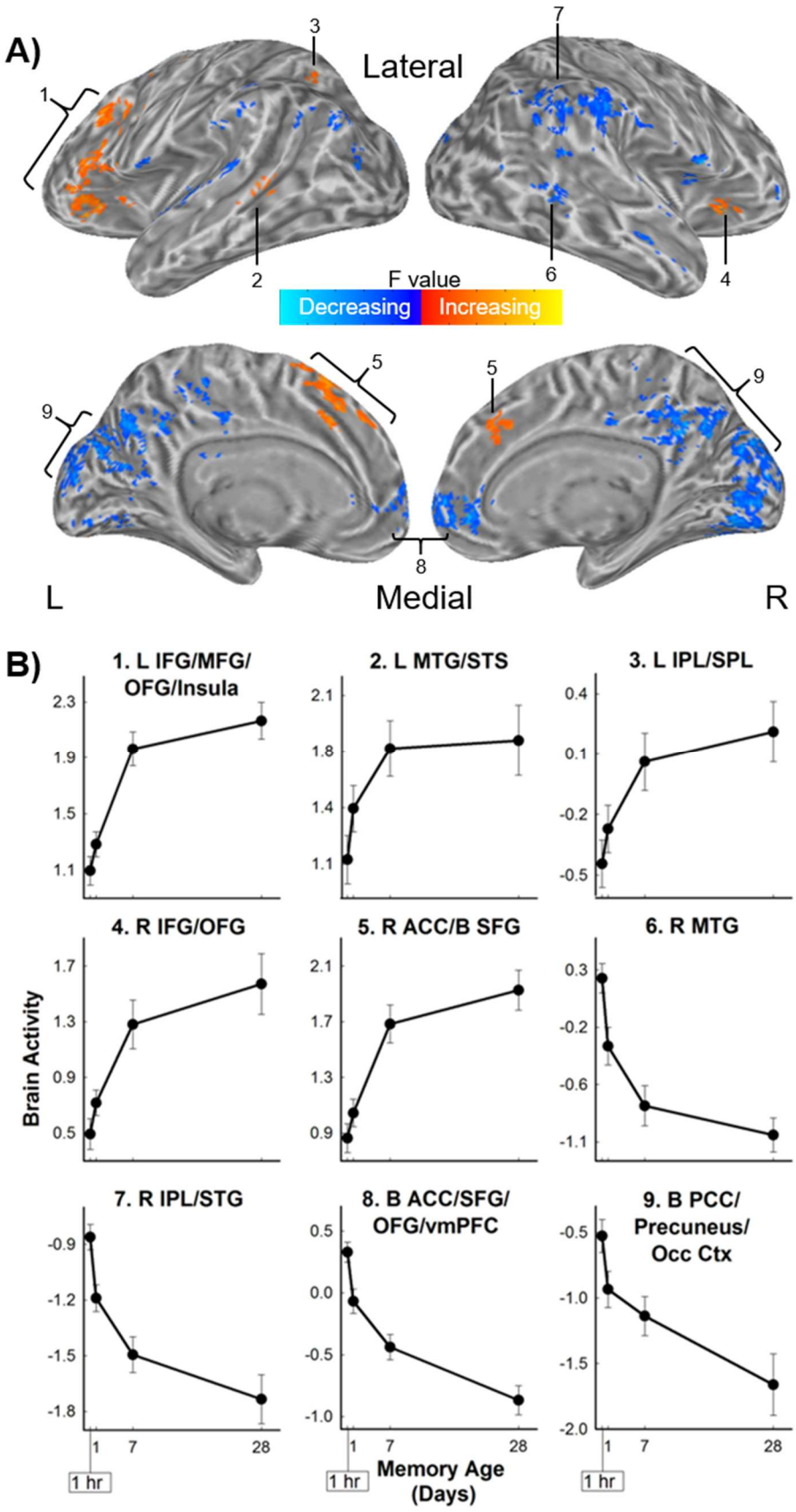
A)
Lateral
1
2
3
4
5
6
7
8
9
F value
Decreasing
Increasing
L
Medial
R
B)
1. L IFG/MFG/ OFG/Insula
2. L MTG/STS
3. L IPL/SPL
4. R IFG/OFG
5. R ACC/B SFG
6. R MTG
7. R IPL/STG
8. B ACC/SFG/ OFG/vmPFC
9. B PCC/ Precuneus/ Occ Ctx
Brain Activity
1 hr
1
7
28
Memory Age (Days)

Table 2.1: Brain regions where retrieval-related activity for three-word sentences was associated with the age of the memory. Activity in all clusters significantly changed across the four time periods according to a power function; voxel-wise threshold of $p < 0.001$, cluster-wise threshold of $p < 0.05$. For each monotonic pattern (M.P.) of activity across time periods [M.P., increasing (↑) or decreasing (↓)], clusters are listed from Anterior to posterior based on the MNI coordinate of the center of mass. Ant. Anterior; BA., Brodmann area; B, Bilateral; Ctx., Cortex; G., Gyrus; Inf., Inferior; L, Left; Lat., Lateral; Lob., Lobule; Mid., Middle; R, Right; Post., Posterior; S. Sulcus; Sup., Superior; Vol., Volume.

Brain Region	Vol (mm^3)	MNI X	MNI Y	MNI Z	B.A.	M.P.
Increasing activity with memory age						
Frontal						
R Inf. Frontal/Frontal Orbital G.	352	32	30	-1	12, 44, 47	↑
L Inf./Mid. Frontal/Insular/Frontal Orbital/Precentral G.	6536	-50	22	16	6, 12, 44, 45, 47	↑
R Cingulate G./B Sup. Frontal G.	3608	-3	22	47	8, 9, 32	↑
L Mid. Frontal G.	392	-29	-2	54	6	↑
Temporal						
L Posterior Sup. Temporal S./Mid. Temporal G.	176	-54	-44	3	21	↑
Parietal						
L Inf./Sup. Parietal Lob.	176	-32	-60	51	7, 39	↑
Occipital						
L Lat. Occipital Ctx.	352	-16	-92	-10	18	↑
Decreasing activity with memory age						
Frontal						
B Ant. Cingulate/Frontal Orbital/Sup./Med. Frontal G.	7832	3	55	1	10, 14, 32	↓
R Inf. Frontal G.	304	51	43	4	45	↓
R Mid./Sup. Frontal G.	216	28	34	50	8, 9, 46	↓
L Sup. Frontal G.	168	-25	29	57	8	↓
Temporal						
R Sup. Temporal/Precentral G.	720	62	5	4	4,6	↓
R Insular/Precentral G.	272	40	4	11	4,13,44	↓
R Mid. Temporal G.	160	62	2	-18	21	↓
L Sup. Temporal/Precentral G.	736	-62	-1	5	4,6	↓
L Sup. Temporal G.	248	-45	-2	-11	22	↓
R Insular G.	192	41	-5	-10	13	↓
L Sup. Temporal/Postcentral G.	424	-61	-16	8	41	↓
R Mid. Temporal G.	504	62	-17	-9	21	↓

Table 2.1 continued: Brain regions where retrieval-related activity for three-word sentences was associated with the age of the memory. Activity in all clusters significantly changed across the four time periods according to a power function; voxel-wise threshold of $p < 0.001$, cluster-wise threshold of $p < 0.05$. For each monotonic pattern (M.P.) of activity across time periods [M.P., increasing (↑) or decreasing (↓)], clusters are listed from Anterior to posterior based on the MNI coordinate of the center of mass. Ant. Anterior; BA., Brodmann area; B, Bilateral; Ctx., Cortex; G., Gyrus; Inf., Inferior; L, Left; Lat., Lateral; Lob., Lobule; Mid., Middle; R, Right; Post., Posterior; S. Sulcus; Sup., Superior; Vol., Volume.

	Vol	MNI				
Brain Region	(mm^3)	X	Y	Z	B.A.	M.P.
L Sup. Temporal G.	272	-41	-18	-2	22	↓
R Mid. Temporal G.	320	59	-63	8	37	↓
Parietal						
L Inf. Parietal Lob./Sup. Temporal G.	1584	-65	-34	26	22, 40-42	↓
R Paracentral Lob.	168	14	-40	49	1-3	↓
R Inf. Parietal Lob./Mid. Temporal G.	7896	60	-43	32	37, 39, 40	↓

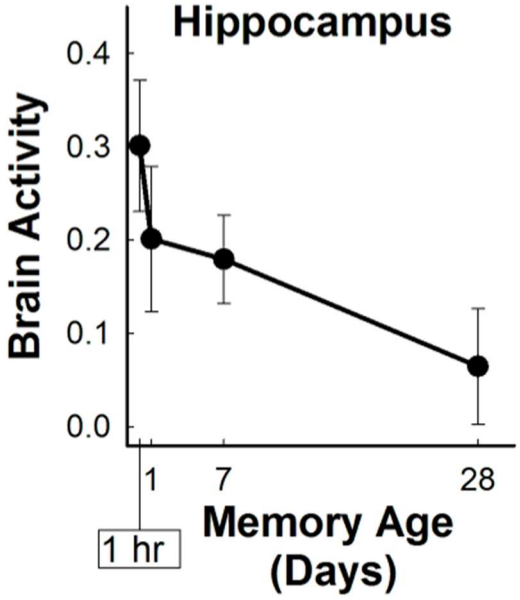

Figure 2.4: Hippocampal retrieval-related activity decreased for three-word sentences as a function of memory age. Bilateral hippocampal activity associated with the retrieval of target sentences significantly decreased as a function of memory age ($p < 0.001$).

Secondary analyses to clarify the role of brain regions in the memory-age network

Two additional analyses were conducted to determine if the memory consolidation effects observed in the primary analysis were related to memory retrieval and not to additional confounding factors. First, we conducted an amplitude-modulated analysis to determine if the changes in brain activity observed in the memory age were influenced by the concomitant behavioral changes associated with memory age (see Figure 2.2). All of the brain regions associated with memory age in the primary analysis (see Table 2.1) were identified in the secondary analysis that minimized the effects of behavioral changes (Supplemental Table 8). There was substantial overlap in the voxels identified by the primary and secondary analyses of memory age (88%) (see Supplemental Figure 3) and no additional brain regions were identified. Generally, the memory age network and its patterns of activity remained unchanged and only varied based on the number of voxels identified in a particular brain region. The most notable differences were the identification of additional insular and lateral occipital voxels and the disappearance of middle temporal and prefrontal cortex voxels after minimizing the effects of memory age. Activity in the hippocampal ROI was almost identical after minimizing the effects of behavior, it still significantly changed as a function of memory age (LME Estimate: 0.07; SE: 0.02; df: 46; $t=3.65$ $p<0.001$), and this remained true for the left, right, and posterior ROIs. Therefore, the memory age network identified in the primary analysis did not appear to reflect concomitant changes in behavior associated with memory age.

Next, an analysis was conducted on the encoding-related activity associated with in-scanner foils to determine whether regions within the memory-age network overlapped with those involved in successful memory encoding (see Methods, Secondary analyses). Two clusters (left caudate and right middle/inferior frontal gyrus) were identified where

activity reflected successful encoding (Supplemental Table 9). Importantly, there was no voxel overlap between the memory-age network and this encoding network. Thus, the memory age network identified in the primary analysis reflected changes in retrieval associated with memory consolidation and not activity associated with encoding.

Brain regions where functional connectivity changed as a function of memory age

Analysis of vmPFC functional connectivity and hippocampal connectivity did not reveal any significant clusters where connectivity significantly changed with memory age ($p < 0.001$, $\alpha=0.05$). Exploratory analysis at a lower probability threshold ($p<0.02$, $\alpha=0.05$) did identify brain regions that exhibited changes in functional connectivity with either the hippocampus or vmPFC. For the vmPFC, connectivity increased with right vmPFC, right OFC (middle frontal and orbital gyri), and with the posterior parietal cortex bilaterally (4 clusters covering superior and inferior parietal lobules, precuneus, and sensorimotor areas). After minimizing the effects of behavior (amplitude-modulation analysis), vmPFC connectivity with the right posterior parietal cortex remained significant at the exploratory threshold (Table 2.2; Figure 2.5). For the hippocampus, functional connectivity decreased with the left and right vmPFC (orbital frontal gyrus, medial frontal gyrus, anterior cingulate gyrus) and increased with left cerebellum. After minimizing the effects of behavior (amplitude-modulation analysis), connectivity between the hippocampus and right vmPFC and the cerebellum remained significant at the exploratory threshold (Table 2.2; Figure 2.6).

To determine if there was overlap between the retrieval-related connectivity described above and encoding-related connectivity (subsequently remembered in-scanner foils vs. subsequently forgotten in-scanner foils), we assessed the overlap

between these two analyses using the same cluster threshold probability. When using the hippocampus as a seed region, no significant clusters were identified where connectivity reflected successful encoding (see Supplemental Table 10). When using the vmPFC as a seed region, four significant clusters in the left MFG, lateral temporal cortex (hippocampus, fusiform gyrus, MTG, STG, posterior STS), temporoparietal junction (posterior STG, IPL), and parietal cortex (bilateral precuneus, left PCC) were identified where connectivity was related to successful encoding (see Supplemental Table 11). There was no overlap between these clusters and the clusters identified by the memory age vmPFC-PPC connectivity results. Therefore, the functional connectivity results related to memory age and did not reflect encoding or changes in behavior.

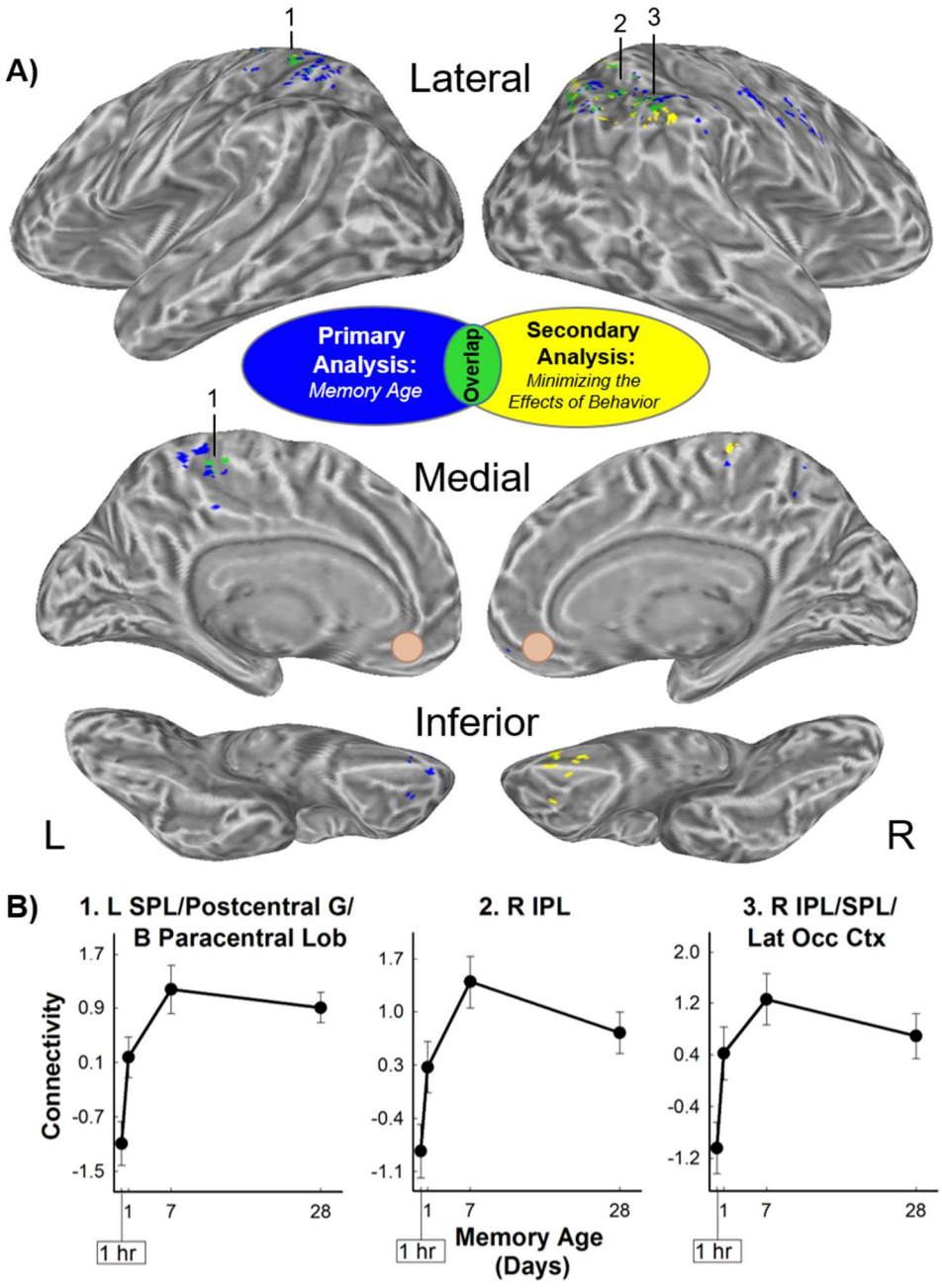

Figure 2.5: vmPFC retrieval-related functional connectivity increased for three-word sentences as a function of memory age. (A) Lateral, medial, and inferior views displaying clusters where retrieval-related functional connectivity associated with a vmPFC seed region (peach) increased as a function of memory age from one hour to one month. Clusters were corrected at $p < 0.02$, $\alpha=0.05$. Clusters are shown before (blue) and after (yellow) minimizing the effects of behavior (amplitude modulation). Three clusters (lime green) in the posterior parietal cortex (B) were common to both analyses (see also Table 2.2) and continued to show a monotonic increasing pattern of functional connectivity between the vmPFC. IPL., Inferior Parietal Lobule; Lat Occ Ctx., Lateral Occipital Cortex; OFG., Orbital Frontal Gyrus; SPL. Superior Parietal Lobule.

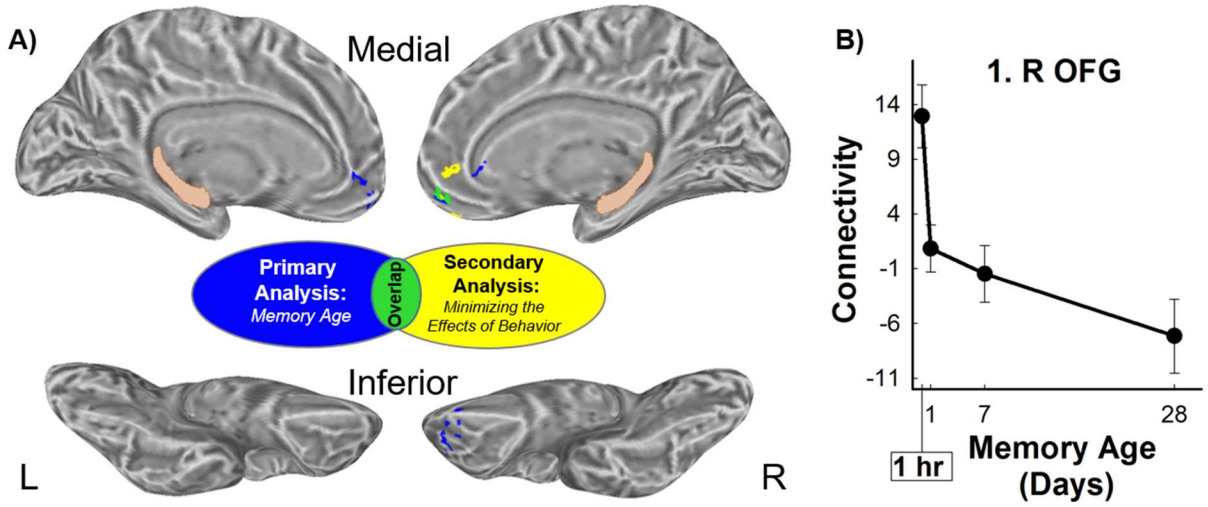

Figure 2.6: Hippocampal retrieval-related functional connectivity decreased for three-word sentences as a function of memory age. (A) Medial and inferior views displaying clusters where retrieval-related functional connectivity associated with a hippocampal seed region (peach) decreased as a function of memory age from one hour to one month. Clusters were corrected at $p < 0.02$, $\alpha=0.05$. Clusters are shown before (blue) and after (yellow) minimizing the effects of behavior (amplitude modulation). Only one cluster (lime green) in the OFG (part of vmPFC) (B) was common to both analyses (see also Table 2.2) and continued to show a monotonic decreasing pattern of functional connectivity between the hippocampus. OFG. Orbital Frontal Gyrus

Table 2.2: Brain regions where retrieval-related functional connectivity for three-word sentences was associated with the age of the memory. Functional connectivity significantly changed across the four time periods according to a power function (voxel-wise threshold of $p < 0.02$ [exploratory analysis], cluster-wise threshold of $p < 0.05$). AM (amplitude-modulated analysis) indicates that connectivity changed across time periods when the effect of concomitant changes in behavior were minimized. For each seed (ventromedial prefrontal cortex [vmPFC] or hippocampus), functional connectivity changed in a relatively monotonic pattern (M.P.) across time periods [M.P., increasing (↑) or decreasing (↓)]. A.M. Amplitude-modulated; Ant. Anterior; BA., Brodmann area; B, Bilateral; Ctx., Cortex; G., Gyrus; Inf., Inferior; L, Left; Lat., Lateral; Lob., Lobule; Mid., Middle; R, Right; Post., Posterior; S. Sulcus; Sup., Superior; Vol., Volume.

Brain Region	Vol (mm^3)	MNI X	MNI Y	MNI Z	B.A.	M.P.
vmPFC: non-AM Connectivity						
Frontal						
R Mid. Frontal/Frontal Orbital G.	1464	20	62	-17	10, 11	↑
R Pre/Postcentral G.	1176	55	-8	45	1-4, 6	↑
Parietal						
L Inf./Sup.Parietal/Paracentral Lob./Pre/Postcentral G./ B Precuneus	4264	-23	-43	59	1-5, 7, 40	↑
R Inf. Parietal Lob.	2104	50	-50	49	39, 40	↑
R Inf./Sup. Parietal Lob.	1768	31	-62	49	7, 39	↑
vmPFC: AM Connectivity						
Parietal						
B Paracentral Lob./L Postcentral G./Sup. Parietal Lob.	1088	-14	-38	58	1-3, 7	↑
R Inf. Parietal Lob.	1608	48	-52	45	39, 40	↑
R Inf./Sup Parietal Lob./Lateral Occipital Ctx.	1784	29	-64	53	7, 49	↑
Hippocampus: non-AM Connectivity						
Frontal						
L Cingulate G./Orbital G	1136	-14	50	-11	11,14, 32	↓
R Orbital G	1064	10	42	-11	11, 14	↓
Subcortical						
L Cerebellum	1336	-20	-78	-35	--	↑
Hippocampus: AM Connectivity						
Frontal						
R Orbital G	1600	11	43	-15	11, 14	↓
Subcortical						
L Cerebellum	1760	-22	-77	-33	--	↑

Discussion

We examined changes in retrieval-related brain activity and functional connectivity associated with the long-term memory consolidation of three-word sentences from one hour to one month. In-scanner behavioral measures of discriminability, confidence ratings, and response time significantly changed as a function of memory age. Primary analyses identified a widespread network of neocortical regions that demonstrated relatively monotonic increases or decreases in retrieval-related activity associated with memory age (Figure 2.3, Table 2.1). Hippocampal brain activity within an anatomical ROI significantly decreased as memories aged, regardless of whether we examined left, right, anterior, or posterior portions (Figure 2.4). Functional connectivity of the hippocampus or vmPFC did not significantly change as a function of memory age, although we observed patterns of changes consistent with memory consolidation at a less stringent cluster threshold (Figures 2.5 and 2.6, Table 2.2). Secondary analyses that examined if the primary retrieval-related brain activity and functional connectivity changes reflected confounding factors (changes in behavior with memory age or re-encoding of targets) revealed that our primary findings remained when these confounding factors were taken into account (Supplemental Figure 3; Supplemental Tables 7-11).

Changes in retrieval-related brain activity associated with long-term memory consolidation

Patterns of cortical brain activity as a function of memory age

SCT posits that as time passes after learning, long-term memories are initially dependent on the hippocampus and are slowly stabilized in the cortex until they can eventually be retrieved independently of the MTL (Marr, 1971; McClelland, McNaughton, O'Reilly, et al., 1992; McClelland et al., 1995; Squire & Alvarez, 1995). As memories

become established in the cortex over time, this process can be reflected as increases in fMRI brain activity as memories age. We identified a memory age network which exhibited increased brain activity associated with memory age within the prefrontal, temporal, posterior parietal, and lateral occipital cortices. Several regions of this network overlapped with regions previously identified as showing increasing activity with memory age for verbal memory, including the left PFC (left MFG, SFG, right ACC), left SPL, right STS, and bilateral IPL (Bosshardt, Degonda, et al., 2005; Bosshardt, Schmidt, et al., 2005). Voxel-wise overlap across studies examining changes in activity over time is difficult to ascertain due to the variation in experimental designs and memoranda studied. Nevertheless, at the level of brain regions, increases are consistently observed over relatively short time periods, ranging from 1 hour to several months in the prefrontal and parietal cortex (Davis et al., 2009; Gais et al., 2007; Sterpenich et al., 2009; Suchan et al., 2008; Takashima et al., 2009; Takashima et al., 2006; Yamashita et al., 2009). More specifically, a previous study of picture memory that used a similar design as the current study, identified the same regions showing increasing activity in bilateral MFG, SPL, precuneus, sensorimotor regions, and left insula and associative visual cortex (Tallman et al., 2022b).

Contrary to the predictions of systems consolidation theory, we also observed widespread decreases in brain activity across as a function of memory age. While it remains unclear exactly why certain cortical brain regions exhibit reduced in retrieval-related activity over time, this finding was observed in several studies of memory consolidation over shorter time periods, specifically within the prefrontal and parietal cortex (Bosshardt, Schmidt, et al., 2005; Harand et al., 2012; Takashima et al., 2017).

Consistent with our earlier study of picture memory across the same intervals (Tallman et al., 2022b), we observed decreases in the bilaterally in mPFC, MFG, PCC, PCC, IPL, precuneus, and left SFG.

Patterns of hippocampal brain activity as a function of memory age

The consensus for patterns of hippocampal brain activity associated with memory age over short time periods (e.g., hours to several months) is as sparse as the experimental designs, types of memoranda tested, and time intervals examined are variable. This variability poses difficulties in determining whether time-dependent changes support a specific memory consolidation theory and whether it is possible to detect time-dependent changes in recent and remote memory retrieval across short time intervals. Several studies found decreases in hippocampal activity associated with memory age, supporting SCT across intervals greater than ~60 days (Furman et al., 2012; Harand et al., 2012; Milton et al., 2011; Sterpenich et al., 2009; Takashima et al., 2006), between ~30 and ~40 days (Dandolo & Schwabe, 2018; Du et al., 2019; Smith et al., 2010), and less than ~30 days (Bosshardt, Schmidt, et al., 2005; Ritchey et al., 2015; Sekeres et al., 2018; Takashima et al., 2009). Like these other studies, the current study (28 day interval), also identified decreases in retrieval-related hippocampal activity, thus supporting the predictions of SCT.

MTT/TT predicts that the repeated retrieval of an episodic memory increases the number of memory traces within the hippocampus, thus increases in retrieval-related hippocampal activity are interpreted as support for this process. Other studies have observed increases in retrieval-related activity associated with memory age ranging across intervals of ~200 days (Vanasse et al., 2022), ~30 days (Bosshardt, Degonda, et al., 2005; Smith et al., 2010) and less than 2 days (Bosshardt, Schmidt, et al., 2005; Gais

et al., 2007). Even more studies found no change in retrieval-related hippocampal activity associated with memory age at intervals up to ~45 days (Davis et al., 2009; Du et al., 2019; Janzen et al., 2008; Stark & Squire, 2000; Suchan et al., 2008; Tallman et al., 2022b; Tompary & Davachi, 2017; Vilberg & Davachi, 2013). It is possible no change in retrieval-related hippocampal activity reflects the persistent hippocampal engagement in memory retrieval across all time periods, as predicted by MTT/TT. Alternatively, null results could be due a lack of statistical power to detect time-dependent changes in hippocampal activity.

When considering studies of verbal material, the picture is not much clearer. Like the findings reported here, three studies also reported decreases in hippocampal activity associated with memory age, supporting SCT (left hippocampus; Bosshardt, Degonda, et al., 2005; associative memory; Du et al., 2019; Ritchey et al., 2015). Conversely, three studies found increases in hippocampal activity associated with memory age, aligning with MTT/TT predictions (Bosshardt, Degonda, et al., 2005; right hippocampus; Bosshardt, Schmidt, et al., 2005; Gais et al., 2007). Two studies did not detect significant changes in hippocampal activity associated with memory age (Davis et al., 2009; item memory; Du et al., 2019). The current study provides evidence that hippocampal activity patterns consistent with SCT predictions can be observed for verbal material over short time intervals, although the overall consensus of hippocampal activation patterns across similar studies remains mixed.

Changes in retrieval-related functional connectivity associated with long-term memory consolidation

Patterns of cortico-cortical functional connectivity as a function of memory age

SCT predicts changing *connections* between brain regions, suggesting functional connectivity measures may be more apt for detecting long-term memory consolidation effects than brain activity measures. Specifically, SCT proposes that both existing and new cortico-cortical functional connections strengthen over time. The vmPFC is thought to be the "integration" hub, taking over memory consolidation functions from the hippocampus via communication with the rest of the cortex. This account suggests that vmPFC-cortical connectivity should increase with memory age. Exploratory analysis of vmPFC function connectivity was consistent with this prediction, showing increased connectivity with vmPFC/OFC and PPC with memory age. The finding that vmPFC-PPC connectivity increases with memory age, replicates the finding for picture memory across the same time intervals (Tallman et al., 2022b). These interactions between the vmPFC and PPC occur rapidly and are thought to establish memory traces in the PPC (Brodt et al., 2018; Brodt et al., 2016).

Patterns of hippocampal-cortical functional connectivity as a function of memory age

According to standard systems consolidation theory, bidirectional connections between the MTL and neocortex change as a function of memory age to reorganize memory traces, enabling the retrieval of long-term memories without the MTL (Marr, 1971; Squire & Alvarez, 1995). SCT predicts the connections between the MTL and neocortex weaken over time, possibly reflected as decreases in functional connectivity as a function of memory age. We identified such decreases in functional connectivity between the hippocampus and the vmPFC and OFC over a one-month period, albeit at an exploratory threshold. This finding is consistent with connectivity findings from previous studies of long-term memory consolidation across this time interval (Takashima et al., 2006; van Kesteren et al., 2010) and longer time intervals spanning years to

decades (Söderlund et al., 2012). Notably, in our prior study, we did not detect changes in hippocampal-vmPFC connectivity, but we did observe decreased functional connectivity between the hippocampus and specific brain regions, including the right medial frontal gyrus (MFG) and lateral temporal cortex (Tallman et al., 2022).

The vmPFC acts as mediator between hippocampus and cortex to integrate memories and stabilize them in the neocortex (Bontempi et al., 1999; Frankland & Bontempi, 2005; Nieuwenhuis & Takashima, 2011). Consequently, as the role of the vmPFC and its cortical connections strengthen over time, the role of the hippocampus and its cortical connections diminishes over time. Taken together, our functional connectivity findings demonstrate a simultaneous reorganization of the connections between the hippocampus, vmPFC, and cortex, supporting the predictions of systems consolidation theory.

Summary

In summary, we identified changes in retrieval-related brain activity and functional connectivity for three-word sentences from 1 hour to 1 month. Time-dependent increases and decreases in activation were observed in a widespread cortical memory age network. Hippocampal activity within an anatomical ROI significantly decreased with memory age. Cortico-cortical functional connectivity increased while hippocampal-cortical functional connectivity decreased as a function of memory age. These findings are consistent with the predictions of standard systems consolidation theory and suggest that long-term memory consolidation effects can be detected over short time intervals.

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Chapter 3 Human Brain Activity and Functional Connectivity Associated with News Event Memory Consolidation Across One Year to Thirty Years

Introduction

Theories of long-term memory consolidation such as systems consolidation theory (SCT) (Marr, 1971; McClelland, 2013; McClelland, McNaughton, & O'Reilly, 1992; Squire & Alvarez, 1995), multiple trace theory/transformation theory (MTT/TT) (Moscovitch et al., 2005; Nadel et al., 2000), and contextual binding theory (CBT) (Yonelinas et al., 2019) are in agreement that semantic memory retrieval eventually becomes independent of the hippocampus and established in the neocortex. Yet, the exact time course of these changes is unknown. Neuropsychological studies of patients with permanent damage to the hippocampus and other medial temporal lobe (MTL) structures exhibit the phenomenon of temporally-graded amnesia in which recent memories are disrupted but remote memories are preserved. These studies demonstrated the hippocampus and other MTL structures are not necessary for semantic memory retrieval, more specifically news event memory, years to decades after encoding (Bayley et al., 2006; J.R. Manns et al., 2003).

Functional magnetic resonance imaging (fMRI) studies in humans with an intact MTL suggest there is decreasing brain activity within the MTL for semantic memory retrieval across similar time frames using famous faces and names (Douville et al., 2005; Haist et al., 2001) and notable news events (Smith & Squire, 2009). In addition, increasing brain activity within neocortical brain areas was identified in the bilateral prefrontal cortex (inferior and middle frontal gyrus, insula), left superior temporal gyrus, bilateral temporopolar cortex, and right inferior parietal lobule (IPL) for news event memory (Smith & Squire, 2009). Therefore, evidence corresponding to theories of memory consolidation can be detected in the MTL and prefrontal, lateral temporal, and posterior parietal cortices

using fMRI. Although unexpected brain activity patterns for memory retrieval across the same time periods were detected, such as decreasing neocortical activity for famous name retrieval (Woodard et al., 2007) and news event memory retrieval (Smith & Squire, 2009). Thus, while fMRI is useful for examining changes in retrieval-related brain activity, it reveals inconsistent patterns with memory age, even for semantic memory.

Memory consolidation is dependent on changing connections between brain regions, therefore changes in retrieval-related functional connectivity may be a more appropriate measure to detect consolidation effects. No studies have examined task-based functional connectivity for semantic retrieval over this time period. Although several have examined retrieval-related functional connectivity changes for autobiographical memory and observed decreases in MTL connectivity with memory age (Gilmore et al., 2021; Söderlund et al., 2012) and is consistent with the predictions of SCT.

In general, few studies have examined functional brain changes associated with semantic memory consolidation. A previous approach was to use a block design rather than an event related design, which prevents the isolation of brain activity associated with individual memories (Haist et al., 2001). In addition, confounding factors such as changes in memory strength associated with the age of the memory due to forgetting were not addressed (Douville et al., 2005; Haist et al., 2001) or were accounted for by only analyzing correct trials, which disproportionately eliminates remote weaker memories from analysis (Smith & Squire, 2009). Within studies of different memory ages, the issue of re-encoding of targets can disproportionally affect remote memories compared to recent memories due to forgetting. In addition, recent greater than remote brain activity can also be observed due to differences in the vividness or detail of a memory as recent

memories are thought to be richer than remote memories (Gilboa et al., 2004; K. Niki & J. Luo, 2002). One study accounted for the confounds of encoding and richness by including the average score on encoding and richness measures as covariates in the group level analysis (Smith & Squire, 2009), although this approach does not account for confounds associated with brain activity for individual news events.

The present study uses a similar experimental design as Smith & Squire (2009) to examine retrieval-related changes in brain function associated with the recognition rather than recall of news event memory across 1-30 years. We used an updated form of the news events test, the retrograde memory news events test (RM-NET) which included additional questions from recent decades so that it can be administered in present day (Cawley-Bennett et al., 2022). News event memory retrieval was examined with eight memory age conditions across 1-30 years to achieve high temporal resolution with examining consolidation effects. Patterns of brain activity and functional connectivity associated with news event memory retrieval were measured. This study is unique in that we accounted for the confounds of behavioral changes and encoding associated with individual news events. We also examined the interaction between the age of the memory and functional connectivity between the hippocampus, ventromedial prefrontal cortex (vmPFC) and the rest of the brain. We predicted we would observe decreases in hippocampal brain activity and functional connectivity and increases in neocortical brain activity and vmPFC functional connectivity associated with the age of the memory.

Methods

Participants

The twenty-seven participants reported in Chapter 2 as well five additional healthy older adults were recruited from the San Diego community to complete the Retrograde-

Memory News Events Test (RM-NET) as reported in (Cawley-Bennett et al., 2022). Exclusion criteria were the same as reported in Chapter 2 (see Methods: Participants). Thirty-two participants (15 female; mean age = 72.6 yrs ± 1.2 yr; range = 65–91 yrs; mean education = 16.7 yrs ± 0.4 yr) underwent MRI scanning. One participant was excluded due to excessive motion during scanning. Thirty-one participants (14 female; mean age = 72yrs ± 1.1 yr; range = 65–91 yrs; mean education = 16.7 yrs ± 0.4 yr) were included in the reported statistical analyses for Chapter 3.

Retrograde Memory News Events Test (RM-NET) task design

News event questions and memory age conditions

Each news event was selected so that it had transient news coverage (e.g., South Korea impeaching their first female president) so each question could be associated with a distinct memory age. Enduring news events (e.g., what happened to the World Trade Center in New York City) were excluded. News event questions were selected for eight separate time periods to span memory ages from 1 year to 30 year prior to the memory test (2017-1988). The first 15 years were split into five separate 3-year time periods to create high temporal resolution for the recent memory age conditions. Studies of patients with permanent MTL damage suggest that memory retrieval of semantic memories becomes hippocampus-independent across this time frame (Bayley et al., 2006; Kapur & Brooks, 1999; J.R. Manns et al., 2003). The remote time periods (16-30 years) were split into three separate 5-year time periods. The final eight memory age conditions were 1-3 years, 4-6 years, 7-9 years, 10-12 years, 13-15 years, 16-20 years, 21-25 years, and 26-30 years. Twenty news event questions were selected for each memory age condition and there were 160 news event questions overall. Each participant was given the same

set of news event questions and the order of the news event questions was counter-balanced across participants.

RM-NET in-scanner test

During the in-scanner RM-NET, each news event was presented as a four-alternative forced choice question for 12.8 seconds (Figure 3.1A). Participants had the entire trial duration to read the news event question and complete the memory judgment using a button box (A [index finger], B [middle finger], C [ring finger], or D [pinky finger]). After each news event question, participants were prompted to give a confidence rating within 3.2 seconds (4 = definitely sure [index finger], 3 = probably sure [middle finger], 2 = somewhat sure [ring finger], or 1 = pure guess [pinky finger]). Even/odd digit trials (as described in Chapters 1 and 2) were jittered and presented in between the paired of one news event questions and its corresponding confidence judgment.

Surprise post test

A surprise post test was given immediately following MRI scanning to obtain three measures of interest associated with each of the 160 news event questions (Figure 3.1B). Participants had unlimited time to answer the three questions associated with each of the news events. First, a subsequent memory test was administered to measure anterograde episodic memory and to determine brain regions related to successful encoding during the in-scanner memory test. Participants were prompted to answer a three-alternative forced choice memory judgment about the topic of the news event question presented in the scanner. Second, participants gave a knowledge rating on a scale of 1-10 to indicate the amount of information they had related to each news event question. Lastly, participants responded yes or no if they had a personal memory related to the news event question. If they answered yes, questions from the Autobiographical Memory Interview

(AMI) were given to determine if there was an episodic memory associated with the news event question.

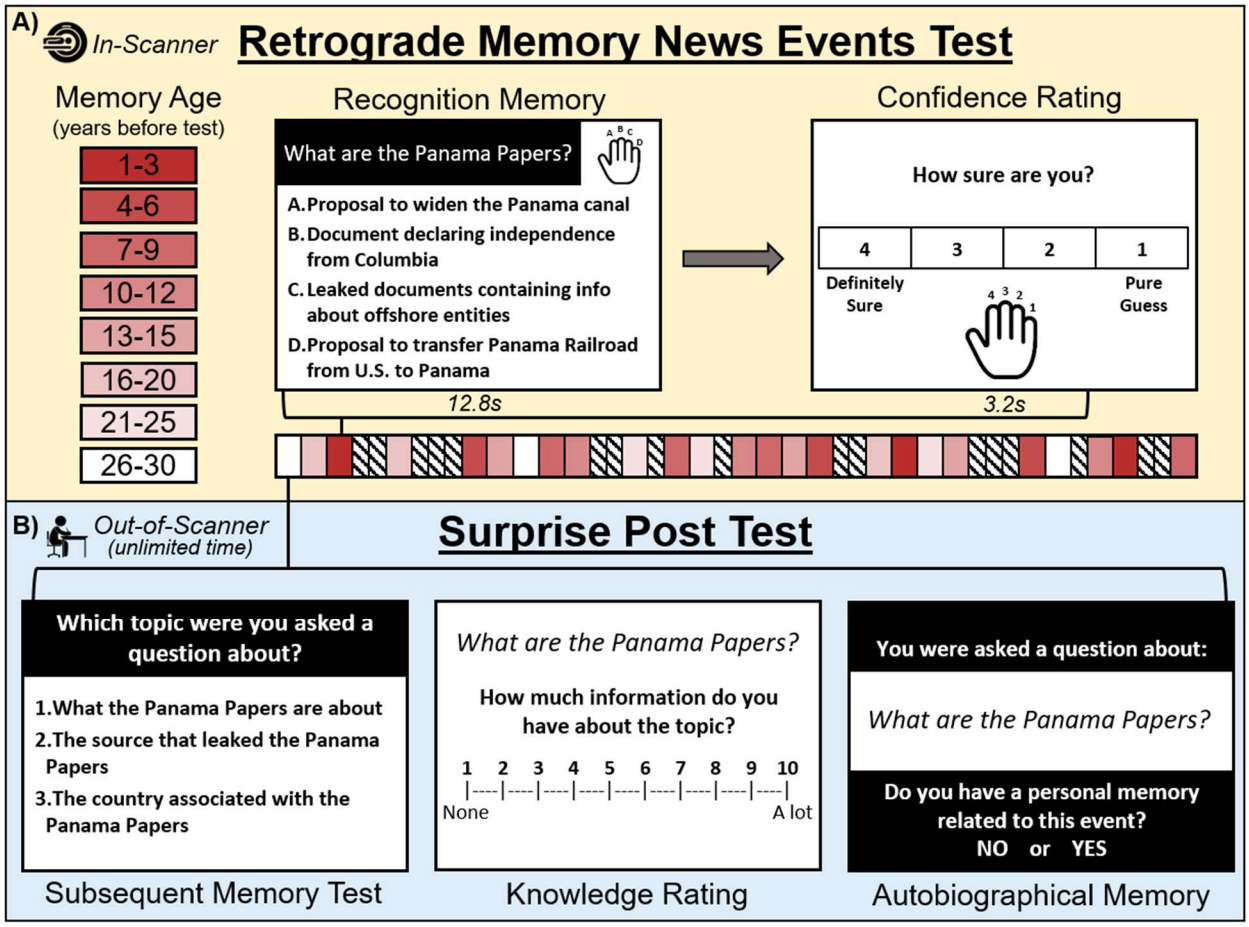


Figure 3.1: Retrograde Memory News Events Test (RM-NET) task design. (A) 160 News event questions from eight memory ages were selected with 20 questions per condition. The color gradient from red to white corresponds to recent memory ages (starting 1 year prior to test) to increasingly more remote time periods (ending 30 years prior to test), respectively. Participants completed a four-alternative forced choice recognition memory task to test news event memory while undergoing MRI scanning. Each news event question and the answer choices were presented simultaneously for 12.8 s during which participants entered their judgment. A confidence rating on a scale of 1-4 was presented directly after for 3.2s. Digit even/odd baseline trials were jittered and presented between the paired news event question and confidence rating judgments. (B) After MRI scanning, a surprise post test was given outside of the scanner to obtain subsequent memory for news event topics, the knowledge rating, and the presence of episodic memories associated with each news event question.

fMRI imaging protocol

Scanning was conducted on the same 3T General Electric MR750 Discovery MRI scanner at the Center for Functional MRI (University of California San Diego) with identical acquisition parameters as reported in Chapter 2 (see Methods, fMRI imaging protocol). Five functional runs were acquired and fieldmaps were collected before run 1 to correct functional runs 1-2 and before run 3 to correct functional runs 3-5.

Data Analysis

Data analysis was completed almost identically to Chapters 1 and 2 to allow for the identification of common changes in brain function across different memory ages. The analyses are summarized briefly below and highlight any differences between the chapters.

Behavioral data analysis

Measures of accuracy (percent correct), confidence, and response time for the in-scanner news events test were calculated by taking the mean across all targets for each memory age condition. For the surprise post test, the average accuracy (percent correct) on the subsequent memory test for news event topics, the average knowledge rating, and the count of autobiographical memories associated with each news event question were calculated. Means and SEM are reported. Significant changes across memory age conditions were tested using repeated measures ANOVA.

fMRI data preprocessing

The fMRI data reported in this chapter were preprocessed identically to the steps outlined in Chapter 2 using fMRIprep and AFNI (see Data Analysis: fMRI data preprocessing). After preprocessing, one participant was excluded as more than 10% of

their functional data were identified as motion outliers. The remaining subjects included in the statistical analyses (n=31) had on average 1.8% of their functional data censored due to motion artifacts. Anatomical hippocampal ROIs were created for each subject by segmenting the T1-weighted image using FSL FIRST as described in Chapter 2 (see Data Analysis, Region of interest analysis: Hippocampus).

General linear modeling

The general linear modeling approach was similar to the approach in Chapters 1 and 2 (see Data Analysis: General Linear Modeling). Multiple regression analyses were conducted using AFNI's *3dDeconvolve* and *3dREMLfit* to calculate beta coefficients representing the mean peak activation for vectors of interest relevant to each analysis (described below). Motion and anatomical signal confound regressors included in multiple regression analyses were selected using the aCompCor pipeline approach (Mascali et al., 2021). The hemodynamic response function was independently modeled for each news event trial using twenty-nine TENT functions spanning 0–22.4 seconds after the onset of the sentences. Peak activation from 5.6–12.8 seconds post-stimulus onset was isolated for analysis.

Whole-brain voxel-wise analysis of brain activity

Primary Analysis: Memory Age

The goal of this experiment was to identify patterns of retrieval-related brain activity that changed with memories from 1 year to 30 years old and were associated with long-term memory consolidation. To examine monotonic patterns over time, we tested for brain regions following a power law as in Chapters 1 and 2 (see Data Analysis: Whole-brain voxel-wise analysis of brain activity) as well as a linear function of interest associated with

long-term memory consolidation in the neocortex for news event memory (Smith & Squire, 2009). For each participant, a multiple regression was carried out with eight vectors, each one coding for the targets associated with a single memory age condition. The memory age conditions were news events which reached prominence from 1-3 years, 4-6 years, 7-9 years, 10-12 years, 13-15 years, 16-20 years, 21-25 years, or 26-30 years prior to test. Group-level LMEs were carried out to examine voxels where the beta coefficients changed across time periods according to the *a priori* functions of interest. Significant clusters were identified using a voxel-wise probability value of $p < 0.001$ and a cluster-wise probability of $p < 0.05$ (Woo et al., 2014). All cluster labels are reported in the tables using the brain region information from the Brainnetome atlas (Fan et al., 2016).

Secondary Analyses

The changes in brain activity from the primary analysis of memory age could reflect processes not related to memory retrieval, such as behavioral changes or encoding/re-encoding. Secondary analyses were completed to confirm the primary findings reflected memory retrieval.

Amplitude-modulated analysis: The same amplitude-modulated approach was conducted as Chapters 1 and 2 to obtain retrieval-related activity when the effects of the behavioral changes were minimized.

Re-encoding analysis: Similarly to Chapters 1 and 2, the differential level of re-encoding associated with the recent and remote time periods could appear as an increase in brain activity as the age of the memory increased. To obtain encoding-related brain regions, successful encoding was measured by testing subsequent memory for the topic of each news event question presented in the scanner during a surprise post test (see

Figure 3.1B). Successful encoding was assessed by a group-level contrast of the correctly answered post test topic questions versus incorrectly answered posttest topic questions (see Chapter 2, Data Analysis: Re-encoding). Out of the 160 news events presented in the scanner, there were on average 138 ± 2.6 subsequently remembered post test topic questions and 22 ± 4.6 subsequently forgotten post test topic questions per participant. Cluster significance testing was carried out at the same threshold as the primary analysis.

Whole-brain, voxel-wise analysis of functional connectivity

Generalized psychophysiological interaction (gPPI) analyses were carried out identically to Chapters 1 and 2. One gPPI analysis examined the interaction between the eight different news event memory age conditions (spanning across 1-30 years) and the functional connectivity between the bilateral hippocampus and the whole brain. A second gPPI analysis examined the interaction between the eight different news event memory age conditions and the functional connectivity between the bilateral vmPFC and the whole brain. The same LME approach as the primary analyses was used to calculate if hippocampal or vmPFC functional connectivity changed as a function of memory age according to the *a priori* functions of interest. The secondary analyses (amplitude-modulation and re-encoding) described for functional connectivity in Chapters 1 and 2 were also completed to validate the primary findings reflected retrieval-related connectivity.

Results

Behavioral Findings

The RM-NET was specifically designed to minimize changes in behavior, equate difficulty in news event questions across the recent and remote time periods, and eliminate confounds such as episodic memories or the amount of information associated with each news event question (Cawley-Bennett et al., 2022). As expected, retrograde memory accuracy (percent correct) and confidence ratings remained constant (retrograde memory accuracy: $F(_{7,210}) = 0.023$, $\eta^2 = 0.001$, $p = 0.88$; confidence ratings: $F(_{7,210}) = 0.000$, $\eta^2 = 0.000$, $p = 0.99$) while response times showed a marginally significant cubic change across time periods during the retrograde memory test in the scanner ($F(_{7,210}) = 4.42$, $\eta^2 = 0.128$, $p < 0.05$; Figure 3.2). Participants obtained retrograde memory percent correct scores of 69.5 ± 3.2, 74.0 ± 2.5, 67.7 ± 2.1, 71.0 ±, 2.4, 71.8 ± 2.6, 65.7 ± 2.8, 73.6 ± 3.1, and 70.1 ± 2.5, average response times (s) of 8.9 ± 0.2, 8.2 ± 0.2, 8.4 ± 0.2, 8.0 ±, 0.3, 8.3 ± 0.2, 8.1 ± 0.2, 7.7 ± 0.3, and 8.3 ± 0.2, and confidence ratings of 2.8 ± 0.1, 3.0 ± 0.1, 2.9 ± 0.1, 3.0 ± 0.1, 3.0 ± 0.1, 2.7 ± 0.1, 3.0 ± 0.1, and 2.9 ± 0.1, for the 1-3 years, 4-6 years, 7-9 years, 10-12 years, 13-15 years, 16-20 years, 21-25 years, and 26-30 years conditions, respectively.

Anterograde memory accuracy (percent correct), as measured during the post test subsequent memory test, significantly decreased as memory age increased ($F(_{7,210})=25.3$, $\eta^2 = 0.458$, $p < 0.001$) while knowledge ratings did not significant change with the age of the memory ($F(_{7,210})=0.053$, $\eta^2 = 0.002$, $p = 0.820$). Participants obtained anterograde memory percent correct scores of 89.6 ± 1.5, 92.4 ± 1.6, 85.1 ± 2.3, 85.0 ±, 2.1, 85.9 ± 2.0, 89.7 ± 1.9, 86.3 ± 1.9, and 80.9 ± 2.1 and identified knowledge ratings of

of 3.1 ± 0.3, 3.1 ± 0.3, 2.9 ± 0.3, 3.0 ± 0.3, 3.1 ±, 0.3, 3.0 ± 0.3, 3.1 ± 0.3, and 3.0 ± 0.3 for the 1-3 years, 4-6 years, 7-9 years, 10-12 years, 13-15 years, 16-20 years, 21-25 years, and 26-30 years conditions, respectively. Participants on average had 2 ± 0.1 episodic memories associated with any of the 160 news event questions and therefore were deemed negligible.

Brain regions where activity changed as a function of memory age

The primary analysis detected a memory age network of 15 brain regions, four changing as a power function within the frontal, parietal, and occipital cortices and 11 changing linearly within the frontal, temporal, and parietal cortices cortices (Figure 3.3, Table 3.1). Relatively monotonic increases or decreases in activity were observed in all brain regions. Regions increasing in activity with the age of the memory were identified in the right prefrontal cortex (inferior, middle, orbital frontal, and precentral gyrus), inferior temporal gyrus, and inferior parietal lobule. Regions decreasing in activity with the age of the memory were identified in the left prefrontal cortex (inferior and orbital frontal gyrus), lateral temporal cortex (middle, superior, inferior temporal gyrus and posterior superior temporal sulcus), parietal cortex (posterior cingulate cortex, precuneus, inferior parietal lobule), and right medioventral occipital cortex (Table 3.1).

Analysis of brain activity in hippocampal ROIs as a function of memory age

Brain activity in the bilateral hippocampal anatomical ROI did not significantly change with memory age (Figure 3.4; $F_{(7,210)}=1.70$, $\eta^2 = 0.331$, $p = 0.158$) or for amplitude-modulated brain activity where the effects of behavior were minimized ($F_{(7,210)}=0.95$, $\eta^2 = 0.032$, $p =0.337$). Follow-up analyses to examine whether the effects

of memory age were related to laterality or anterior/posterior portions of the hippocampus were also not significant.

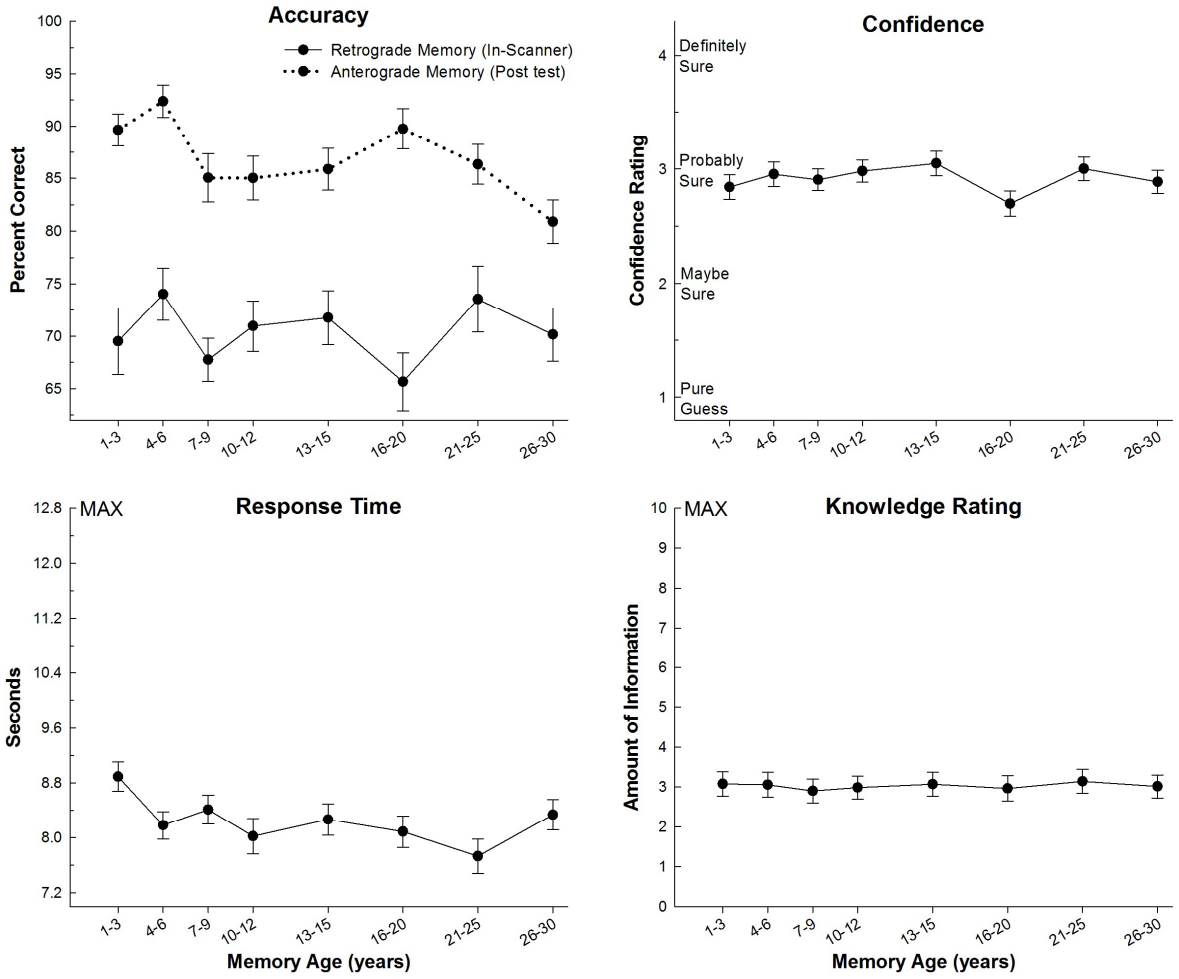


Figure 3.2: Behavioral measures of memory retrieval associated with news event memory. (A) Average accuracy scores for retrograde memory test of news events in the scanner (solid line) and the post test anterograde memory test of the news event topic questions as presented in the scanner. (B) Average confidence ratings from 1 (pure guess) to 4 (definitely sure) given for news event questions during scanning C) Average response times for news event questions during scanning (D) Average knowledge ratings collected during the post test associated with each news event question. Error bars show SEM.

Figure 3.3: Memory age network in which retrieval-related brain activity for news events changed as a function of memory age. (A) Lateral and medial views of the network in which retrieval-related activity for news events increased (warm colors) or decreased (cool colors) as memories aged from one hour to one month. Higher F values (cyan or yellow) indicate activity that more closely followed a power or linear function. Clusters corrected at $p < 0.001$, $\alpha=0.05$. (B) Monotonic patterns of brain activity (beta coefficients) associated with memory age from selected regions shown in panel (A). ACC. Anterior Cingulate Cortex; IFG. Inferior Frontal Gyrus; IPL. Inferior Parietal Lobule; MFG. Middle Frontal Gyrus; MTG. Middle Temporal Gyrus; Occ Ctx. Occipital Cortex; OFG. Orbital Frontal Gyrus; PCC. Posterior Cingulate Cortex; SFG. Superior Frontal Gyrus; SPL. Superior Parietal Lobule; STS. Superior Temporal Sulcus; vmPFC. Ventral Medial Prefrontal Cortex.

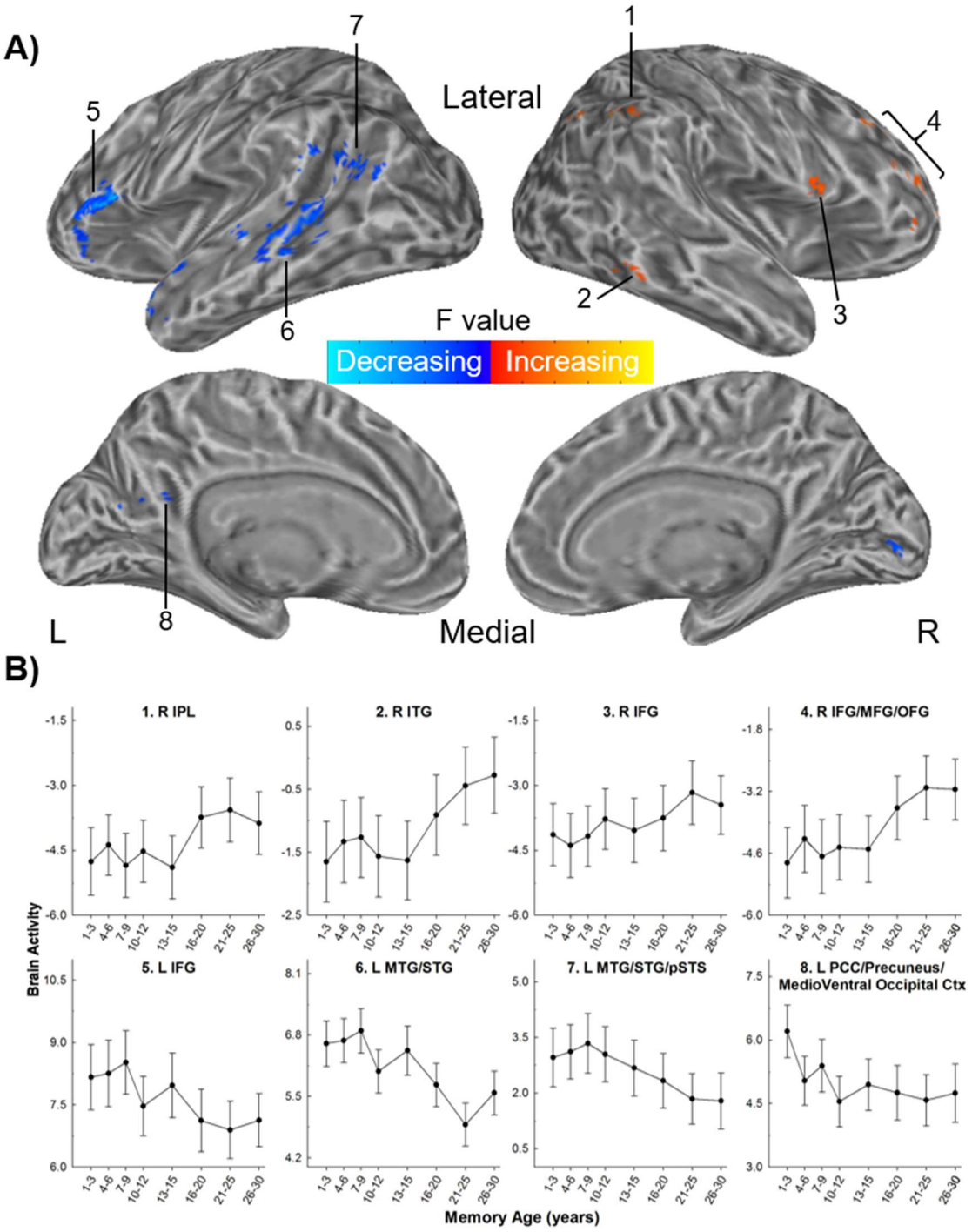

A)
Lateral
1
2
3
4
5
6
7
F value
Decreasing
Increasing
L
8
Medial
R
B)
1. R IPL
2. R ITG
3. R IFG
4. R IFG/MFG/OFG
5. L IFG
6. L MTG/STG
7. L MTG/STG/pSTS
8. L PCC/Precuneus/
MedioVentral Occipital Ctx
Brain Activity
Memory Age (years)
1-3
4-6
7-9
10-12
13-15
16-20
21-25
26-30

Table 3.1: Brain regions where retrieval-related activity for news events was associated with the age of the memory. Activity in all clusters significantly changed across the eight time periods according to a power or linear function; voxel-wise threshold of $p < 0.001$, cluster-wise threshold of $p < 0.05$. For each monotonic pattern (M.P.) of activity across time periods [M.P., increasing (↑) or decreasing (↓)], clusters are listed from Anterior to posterior based on the MNI coordinate of the center of mass. [a] indicates regions that exhibited activity changes following both a power and linear function. Ant. Anterior; BA., Brodmann area; B, Bilateral; Ctx., Cortex; G., Gyrus; Inf., Inferior; L, Left; Lat., Lateral; Lob., Lobule; Mid., Middle; R, Right; Post., Posterior; S. Sulcus; Sup., Superior; Vol., Volume.

Brain Region	Vol (mm^3)	MNI X	MNI Y	MNI Z	B.A.	M.P.
Activity changing with memory age following a Power Function						
Frontal						
L Inf. Frontal G. [a]	256	-56	20	17	44-45	↓
Parietal						
L Post. Cingulate G./Precuneus/ MedioVentral Occipital Ctx.	216	-9	-59	18	31	↓
R Inf. Parietal Lob.[a]	256	51	-60	50	39-40	↑
Occipital						
R MedioVentral Occipital Ctx.	224	12	-90	3	18	↓
Activity changing with memory age following a Linear Function						
Frontal						
R Inf./Mid./Orbital Frontal G.	1808	45	54	10	9-10, 12, 45-47	↑
R Mid. Frontal G.	392	42	38	32	8-9, 46	↑
L Inf./Orbital Frontal G. [a]	2280	-56	26	10	12,44-45,47	↓
R Inf. Frontal/Precentral G.	152	53	9	6	4, 6, 44	↑
Temporal						
L Mid./Sup. Temporal G.	808	-54	7	-20	21-22,38	↓
L Mid./Sup. Temporal G./ Post. Sup. Temporal Sulcus	1960	-60	-43	3	21-22,37	↓
R Inf. Temporal G.	216	61	-49	-13	20, 37	↑
Parietal						
R Inf. Parietal Lob. [a]	144	48	-45	43	40	↑
R Inf. Parietal Lob. [a]	296	51	-55	50	39-40	↑
L Inf. Parietal Lob.	1344	-53	-59	25	39-40	↓
R Inf. Parietal Lob. [a]	184	38	-70	53	39	↑

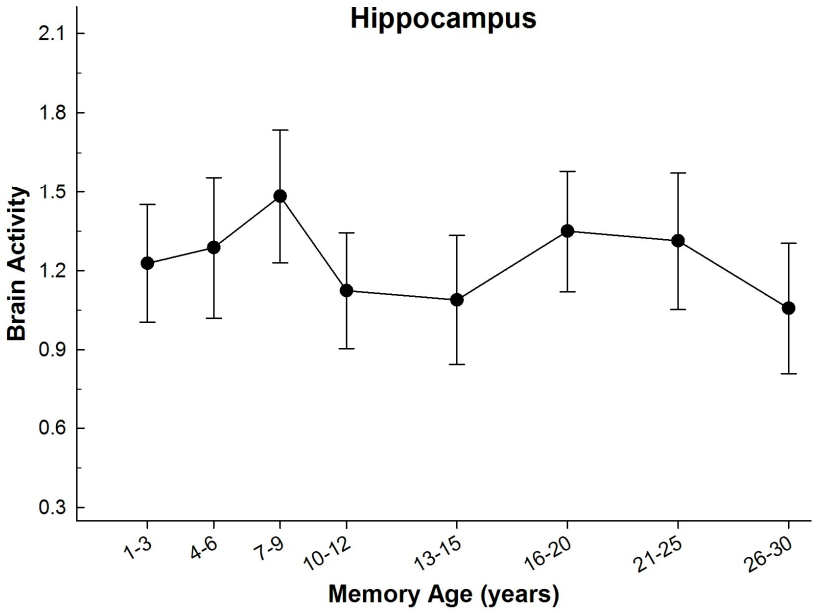


Figure 3.4: Hippocampal retrieval-related activity for news events did not significantly change with the age of the memory.

Secondary analyses to clarify the role of brain regions in the memory-age network

Secondary analyses were conducted to determine if the changes in brain activity associated with memory age identified in the primary analysis were related to retrieval and not confounding factors. We examined the amplitude-modulated activity which minimized any potential effects of concomitant behavioral changes during the in-scanner retrograde memory test (see Figure 3.2). All of the brain regions associated with the age of the memory in the primary analysis (see Table 3.1) were identified in the secondary analysis that minimized the effects of behavioral changes (Supplemental Table 12). There was substantial overlap in the voxels identified by the primary and secondary analyses of memory age (77%) (Supplemental Figure 4) and no additional brain regions were identified. The memory age network identified in the primary analysis remained unchanged and only varied based on the number of voxels identified in a particular brain

region. The most notable differences were the identification of additional anterior temporal cortex voxels and the disappearance of posterior cingulate/retrosplenial cortex voxels after minimizing the effects of memory age. Activity in the hippocampal ROI was almost identical after minimizing the effects of behavior and still did not significantly change with the age of the memory.

Next, an analysis was conducted on the encoding-related activity associated with correctly answered post test topic questions versus incorrectly answered post test topic questions to determine whether regions within the memory-age network overlapped with those involved in successful memory encoding (see Methods, Secondary analyses). No clusters were identified where activity reflected successful encoding at the primary analysis cluster threshold. One cluster was identified in the left inferior parietal lobule at a substantially more liberal cluster threshold ($p < 0.02$, $a=0.05$; center of mass MNI: -51, -67, 34; volume=190mm^3) and did not overlap with the retrieval-related activity. Thus, the memory age network identified in the primary analysis reflected changes in retrieval associated with memory consolidation and not activity associated behavioral changes or encoding.

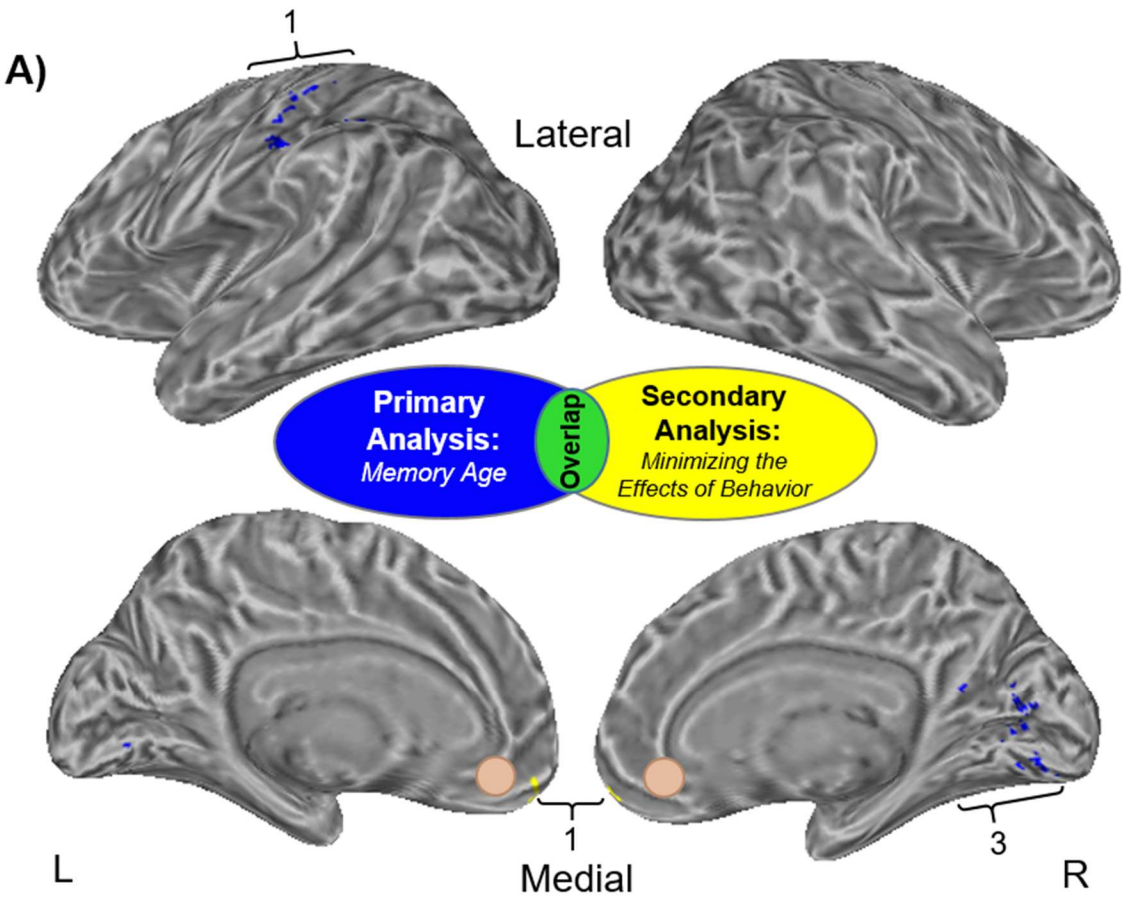
Brain regions where functional connectivity changed as a function of memory age

Analysis of vmPFC functional connectivity and hippocampal connectivity did not reveal any significant clusters where connectivity significantly changed with memory age ($p < 0.001$, $\alpha=0.05$). Exploratory analysis at a lower probability threshold ($p<0.02$, $\alpha=0.05$) did identify brain regions that exhibited changes in functional connectivity with either the hippocampus or vmPFC. For the vmPFC, connectivity decreased with right posterior parietal cortex (posterior cingulate and precuneus) and occipital cortex following a power

function. vmPFC connectivity increased with the left inferior parietal lobule, postcentral gyrus, and right cerebellum linearly (Table 3.2). After minimizing the effects of behavior (amplitude-modulation analysis), only vmPFC connectivity decreasing with the bilateral prefrontal cortex (superior and orbital frontal gyrus) was significant (Figure 3.5, Table 3.2). For the hippocampus, functional connectivity increased with the left middle frontal gyrus and the bilateral superior frontal gyrus following a power function. Hippocampal connectivity increased linearly with the prefrontal (right middle frontal gyrus, bilateral superior and inferior frontal gyrus, left insula, and left sensorimotor areas), temporal (bilateral superior temporal gyrus, left posterior superior temporal sulcus), and parietal (bilateral inferior parietal and right paracentral lobules) cortices. After minimizing the effects of behavior, no hippocampal functional connectivity clusters remained significant (Figure 3.6, Table 3.3).

To determine if there was overlap between the retrieval-related connectivity described above and successful encoding-related connectivity, we assessed the overlap between these two analyses using the same exploratory cluster threshold probability. No clusters were identified where connectivity reflected successful encoding for either the vmPFC or hippocampal functional connectivity analyses. Therefore, the functional connectivity results related to memory age and did not reflect encoding but were possibly influenced by changes in behavior.

Figure 3.5: vmPFC retrieval-related functional connectivity changed for news events with the age of the memory. (A) Lateral and medial views displaying clusters where retrieval-related functional connectivity associated with a vmPFC seed region (peach) changed with the age of the memory across one year to thirty years. Clusters were corrected at $p < 0.02$, $\alpha=0.05$. Clusters are shown before (blue) and after (yellow) minimizing the effects of behavior (amplitude modulation) (see Table 3.2). B, Bilateral; IPL, Inferior Parietal Lobule; L, Left; OFG, Orbital Frontal Gyrus; PCC, Posterior Cingulate Cortex; R, Right.


A)
1
Lateral
Primary Analysis: Memory Age
Overlap
Secondary Analysis: Minimizing the Effects of Behavior
1
3
L
Medial
R

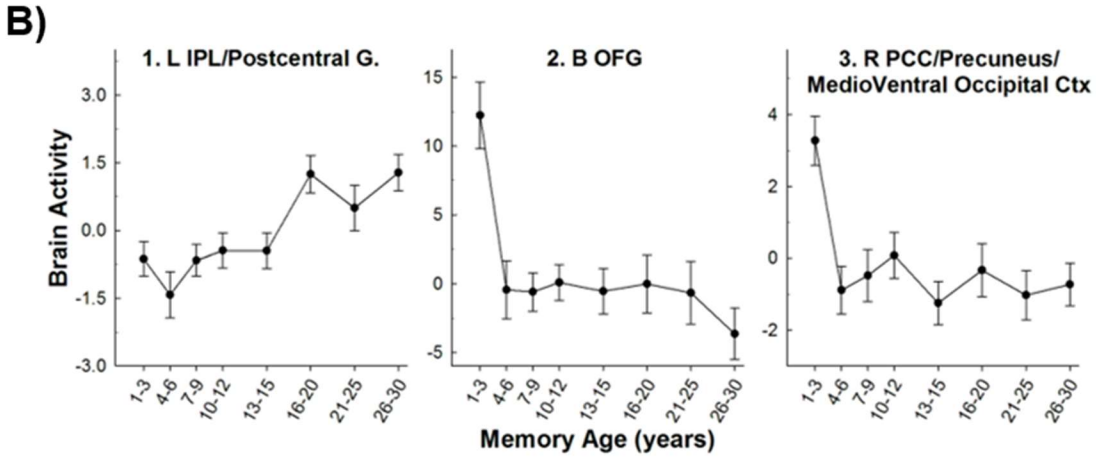

B)
1. L IPL/Postcentral G.
2. B OFG
3. R PCC/Precuneus/ MedioVentral Occipital Ctx
Brain Activity
3.0
1.5
0.0
-1.5
-3.0
15
10
5
0
-5
4
2
0
-2
1-3
4-6
7-9
10-12
13-15
16-20
21-25
26-30
Memory Age (years)

Figure 3.6: Hippocampal retrieval-related functional connectivity increased for news events with the age of the memory. (A) Lateral and medial views displaying clusters where retrieval-related functional connectivity associated with a hippocampal seed region (peach) increased as a function of memory age from one year to thirty years. Clusters were corrected at $p < 0.02$, $\alpha=0.05$. Clusters are shown before (blue) minimizing the effects of behavior using amplitude modulation. No clusters remained after amplitude modulation and thus no connectivity clusters associated with only amplitude-modulated activity (yellow) or overlap between the primary and secondary analyses (green) are present in the figure (see Table 3.3). B, Bilateral; Ctx, Cortex; IFG, Inferior Frontal Gyrus; IPL, Inferior Parietal Lobule; MFG, Middle Frontal Gyrus; OFG, Orbital Frontal Gyrus; pSTS, Posterior Superior Temporal Sulcus; SFG, Superior Frontal Gyrus; STG, Superior Temporal Gyrus.

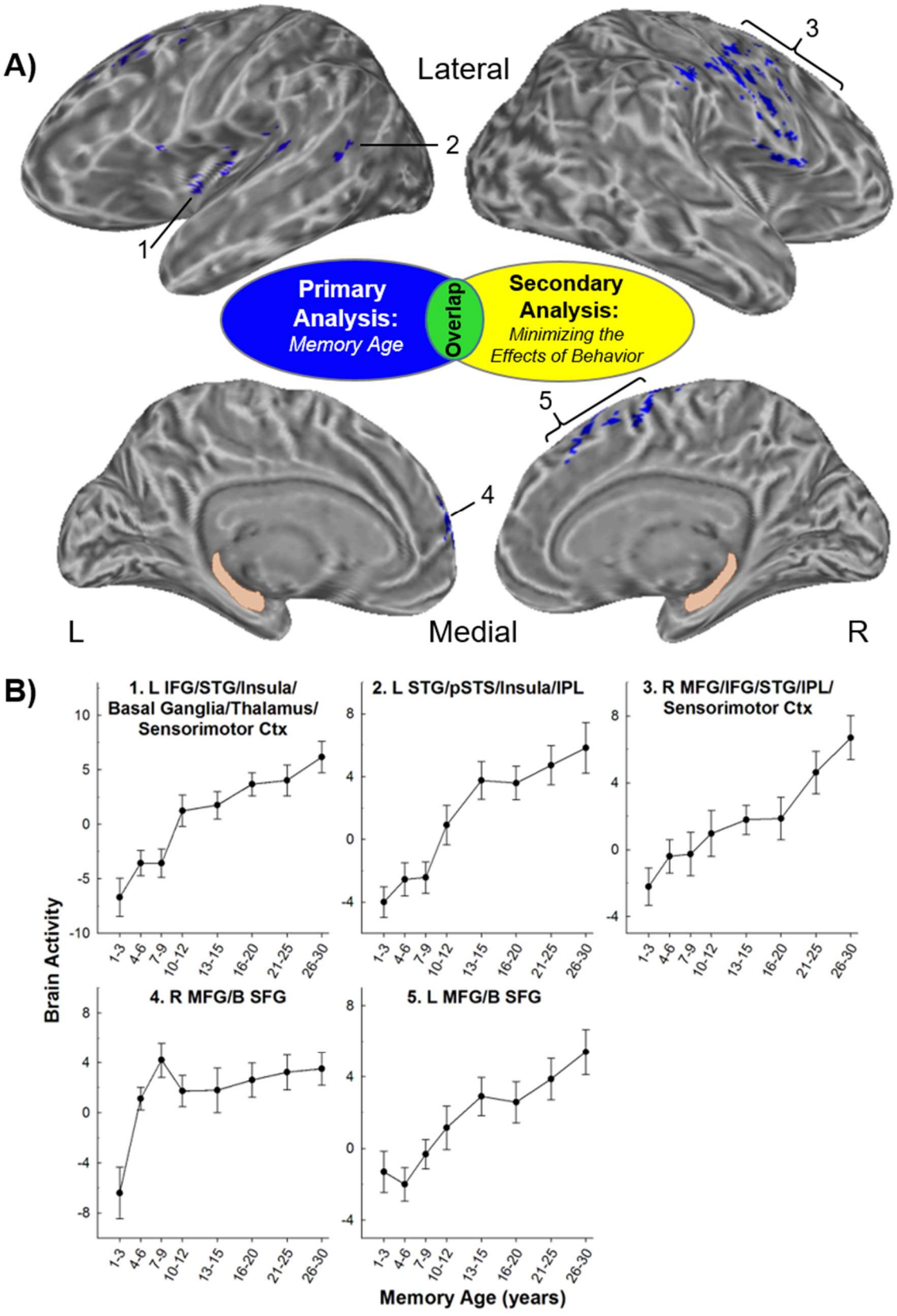

A)
Lateral
1
2
3
Primary Analysis: Memory Age
Overlap
Secondary Analysis: Minimizing the Effects of Behavior
4
5
L
Medial
R
B)
1. L IFG/STG/Insula/ Basal Ganglia/Thalamus/ Sensorimotor Ctx
2. L STG/pSTS/Insula/IPL
3. R MFG/IFG/STG/IPL/ Sensorimotor Ctx
4. R MFG/B SFG
5. L MFG/B SFG
Brain Activity
Memory Age (years)
1-3
4-6
7-9
10-12
13-15
16-20
21-25
26-30

Table 3.2: Brain regions where retrieval-related vmPFC functional connectivity for news events was associated with the age of the memory. Connectivity in all clusters changed across the eight time periods according to a power or linear function; voxel-wise threshold of $p < 0.02$, cluster-wise threshold of $a = 0.05$. For each monotonic pattern (M.P.) of activity across time periods [M.P., increasing (↑) or decreasing (↓)], clusters are listed from anterior to posterior based on the MNI coordinate of the center of mass. Ant. Anterior; BA., Brodmann area; B, Bilateral; Ctx., Cortex; G., Gyrus; Inf., Inferior; L, Left; Lat., Lateral; Lob., Lobule; Mid., Middle; R, Right; Post., Posterior; S. Sulcus; Sup., Superior; Vol., Volume.

	Vol	MNI				
Brain Region	(mm^3)	X	Y	Z	B.A.	M.P.
Functional connectivity changing with memory age following a Power Function						
R Post. Cingulate G./ MedioVentral Occipital Ctx./ Precuneus	1032	10	-73	7	18,31	↓
Functional connectivity changing with memory age following a Linear Function						
Parietal						
L Inf. Parietal Lob./Postcentral G.	1256	-49	-34	50	2,39-40	↑
Subcortical						
R Cerebellum	1801	31	-78	-51	-	↑
Amplitude-modulated functional connectivity changing with memory age following a Power Function						
B Sup./Orbital Frontal G.	152	3	-12	-70	9, 12	↓

Table 3.3 Brain regions where hippocampal retrieval-related functional connectivity for news events was associated with the age of the memory. Connectivity in all clusters changed across the eight time periods according to a power or linear function; voxel-wise threshold of $p < 0.02$, cluster-wise threshold of $a = 0.05$. For each monotonic pattern (M.P.) of activity across time periods [M.P., increasing (↑) or decreasing (↓)], clusters are listed from Anterior to posterior based on the MNI coordinate of the center of mass. [a] indicates regions that exhibited activity changes following both a power and linear function. Ant. Anterior; BA., Brodmann area; B, Bilateral; Ctx., Cortex; G., Gyrus; Inf., Inferior; L, Left; Lat., Lateral; Lob., Lobule; Mid., Middle; R, Right; Post., Posterior; S. Sulcus; Sup., Superior; Vol., Volume.

	Vol	MNI				
Brain Region	(mm^3)	X	Y	Z	B.A.	M.P.
Functional connectivity changing with memory age following a Power Function						
Frontal						
L Mid. Frontal G./ B Sup. Frontal G. [a]	1216	-12	59	13	9-10,46	↑
L Mid./Sup. Frontal G. [a]	2280	-30	17	42	6,8,9,46	↑
Functional connectivity changing with memory age following a Linear Function						
Frontal						
R Mid. Frontal G., B Sup. Frontal G. [a]	1904	13	18	54	6, 8	↑
L Inf. Frontal/Insula/ Precentral/Postcentral/ Sup. Temporal G./ BasalGanglia/Thalamus	1504	-35	-6	3	1-4, 44	↑
R Mid./Inf. Frontal/ Precentral/Postcentral/ Sup. Temporal G./ Inf. Parietal Lob.	5240	55	-8	36	1- 4, 6, 40, 44	↑
R Paracentral Lob./ Sup. Frontal/Precentral G.	1384	10	-9	67	4,6	↑
Temporal/Parietal						
L Insular/Sup. Temporal G./ Inf. Parietal Lob/ Post. Sup. Temporal S.	1216	-40	-40	11	39-42	↑

Discussion

We examined changes in retrieval-related brain activity and functional connectivity of news events learned 1 year to 30 years in healthy older adults. The RM-NET test was designed to minimize changes in behavior that might pose as confounds when detecting

changes in brain activity with memory age. In-scanner behavioral measures of confidence, accuracy, and the post-test measure of knowledge ratings associated with news events did not significantly change with memory age. Response times collected during the in-scanner RM-NET test and accuracy on the subsequent memory post test significantly changed over time (Figure 3.2). We identified an extensive neocortical brain network both increasing and decreasing in brain activity with the age of the memory (Figure 3.3, Table 3.1). Brain activity within hippocampal anatomical ROIs (bilateral, left, right, anterior, and posterior) did not significantly change with memory age (Figure 3.4). Task-based functional connectivity analyses of the hippocampus and vmPFC also did not significantly change with memory age. Exploratory analyses conducted at a less stringent cluster threshold revealed functional connectivity changes between vmPFC, hippocampus, and the rest of the brain that were mostly inconsistent with memory consolidation theories (Figures 3.5 and 3.6, Tables 3.2 and 3.3). Secondary analyses examined if the changes in brain function were related to retrieval and not additional confounds (i.e., the re-encoding of targets or changes in behavior with memory age). Retrieval-related changes in brain activity were not influenced by these confounding factors although the observed changes in functional connectivity at the exploratory level were influenced by changes in behavior.

Changes in retrieval-related brain activity associated with long-term memory consolidation

Patterns of cortical brain activity changing with the age of the memory

Theories of long-term memory consolidation such as SCT (Marr, 1971; McClelland, McNaughton, & O'Reilly, 1992; Squire & Alvarez, 1995), MTT/TT (Moscovitch et al., 2005; Nadel et al., 2000), and CBT (Yonelinas et al., 2019) are in agreement that semantic

memory will eventually be retrieved independently of the hippocampus after the memory is established in the cortex. Using fMRI, we can examine if retrieval-related brain activity in the neocortex increases with the age of the memory. We identified an extensive neocortical network changing with the age of the news event memory according to power and linear functions. Brain regions overlapping with the semantic memory network (Binder et al., 2009; Dede & Smith, 2016) were identified, in particular the right dorsomedial prefrontal cortex (middle frontal gyrus, BA 8), bilateral IFG (BA 47), left anterior temporal cortex (middle and superior temporal gyrus, BA 21-22, 38), bilateral retrosplenial/posterior cingulate cortex (BA 31), and bilateral regions near the temporoparietal junction (BA 37,39,40). We also observed a laterality effect in which right hemispheric brain activity increased with the age of the memory while left hemispheric brain activity decreased with the age of the memory.

Few studies have identified neocortical changes with memory age for semantic memory retrieval over the course of years to decades, although we identified several regions changing in a consistent pattern. We identified decreasing activity with memory age in the MTG, a result found in a study of famous face retrieval (Woodard et al., 2007). Although consistent with fMRI studies, this result is theoretically incongruent; damage to the lateral temporal cortex in patients results in deficits in both recent and remote semantic memory (Irish et al., 2012; Kapur et al., 1994). It would be predicted that as semantic memories age, brain regions in the lateral cortex would increase in activity. Within our study, we identified the right inferior temporal gyrus (ITG) as the only lateral temporal cortex region increasing with news event memory age. Smith et al. (2009) demonstrated increasing activity in the left MTG, but only at exploratory p value. At a

more stringent p value they identified decreasing left STG activity, which we also identified in addition to decreasing activity in left MTG. Our results in lateral temporal cortex are relatively consistent with previous studies of semantic memory consolidation using fMRI. Yet, our study and others are not completely consistent with the theoretical prediction that lateral temporal cortex would increase in brain activity associated with memory age.

In addition to the lateral temporal cortex, we also found increasing activity within the right dmPFC (middle frontal gyrus, BA 8) and right IFG (BA 47) which was not observed in previous studies of semantic memory retrieval associated with memory age, although these regions are located within the semantic memory network (Binder et al., 2009; Dede & Smith, 2016). We also observed increasing brain activity associated with memory age within the right IPL, located in posterior parietal cortex (PPC), which is an area we identified in Chapters 1 and 2 to increase in activity with memory age over 1 hour to 1 month and was also identified as increasing in activity from 1 year to 30 years in Smith et al., (2009). The IPL is associated with memory retrieval success (Gilmore et al., 2015) and the PPC, in general, helps to establish engrams within the neocortex (Brodt et al., 2018; Brodt et al., 2016). Additionally, we identified other neocortical areas (left IFG, MFG, OFG, and IPL) which exhibited patterns of decreasing neocortical activity. One study which examined neocortical changes associated with famous name retrieval also identified brain regions decreasing in activity (posterior cingulate cortex, left middle temporal regions, right MFG, and right fusiform) which did not overlap with our findings (Woodard et al., 2007). Overall, we identified changes in retrieval-related brain activity with memory age that were consistent with regions in the semantic memory network.

Patterns of hippocampal brain activity associated with the age of the memory

Studies of patients with permanent hippocampal or MTL damage demonstrate that the hippocampus is not necessary for the retrieval of remote semantic memory years to decades old, as evidenced by temporally-graded retrograde amnesia (Bayley et al., 2006; J.R. Manns et al., 2003). fMRI studies of retrieval of famous faces and news events demonstrated a decreasing dependence on the MTL for remote memory retrieval across a similar time frame as brain activity in these structures decreased with the age of the memory (Douville et al., 2005; Haist et al., 2001; Smith & Squire, 2009). In this study, we would predict that retrieval-related hippocampal activity would decrease with the age of news event memory. We did not detect any changes in retrieval-related hippocampal brain activity with memory age, either at the whole-brain functional level or within anatomical hippocampal ROIs (bilateral, left, right, anterior, and posterior). This finding is unexpected as most memory consolidation theories are in agreement that semantic memory becomes hippocampus-independent.

These inconsistencies in fMRI results that contradict strong theoretical predictions highlight the limitations of generalizing fMRI studies to support one memory consolidation theory or the other. The failure to detect a significant effect does not mean the effect is not present (see Chapter 1: Introduction for further discussion) and this could be due to low statistical power or issues with obtaining clear MTL signal during MRI acquisition. In particular, this study was carried out in older adults where the hippocampus is commonly atrophied (Du et al., 2006) which increases the difficulty in obtaining MRI signal and completing accurate registration to group templates for fMRI analysis.

This study was unique in that it was designed to minimize confounds so that the only difference between the news event memories was the age of the memory. In this way,

changes in accuracy, confidence, richness (knowledge rating), or encoding could not be the driving effect for observed changes in brain function associated with memory age. Additionally, we implemented secondary statistical analyses to minimize the effects of confidence and response time associated with each news event question. This is the first study to thoroughly account for these confounds simultaneously. It is possible that hippocampal activity could be associated with changes in these confounds rather than the age of the memory (e.g., vividness and richness is more associated with recent than remote memory; Gilboa et al., 2004).

Changes in retrieval-related functional connectivity associated with long-term memory consolidation

According to SCT, bidirectional connections between the MTL and neocortex change with the age of the memory so that remote declarative memories become completely independent of the hippocampus and dependent on the neocortex for memory retrieval (Squire & Alvarez, 1995). Task-based functional connectivity is a more direct measure than brain activity to assess retrieval-related changes associated with the age of the memory. We did not detect any significant functional connectivity changes between our two seed regions of interest (hippocampus and vmPFC) and the rest of the brain with the age of the memory. Although, we did observe changes in functional connectivity at a less stringent cluster threshold ($p=0.02$, $a=0.05$).

We would expect to observe increases in functional connectivity between neocortical regions as memories become established in the cortex. We chose the vmPFC as a neocortical seed region because the vmPFC is thought to act as a mediator between the fast-acting hippocampus and the gradual learning of rest of the neocortex (Frankland

& Bontempi, 2005; Nieuwenhuis & Takashima, 2011). Functional connectivity between the vmPFC and the left IPL, postcentral gyrus, and right cerebellum increased with the age of the memory. Changes in the functional connectivity between the vmPFC and the PPC was observed in studies of memory retrieval over short time periods of 1 day (Brodt et al., 2018; Brodt et al., 2016) or 1 month (Tallman et al., 2022b). After minimizing the effects of behavior in our secondary analysis, this pattern was no longer significant and only decreasing functional connectivity between the vmPFC and bilateral superior and orbital frontal gyrus remained, suggesting the vmPFC disengaged with other subregions in the PFC over time.

We would expect to observe decreases in functional connectivity between the hippocampus and neocortex as semantic memories become independent of the hippocampus for retrieval. The exploratory analysis of hippocampal connectivity revealed increased functional connectivity between the hippocampus and the prefrontal, temporal, and parietal cortices with the age of the memory. After minimizing the effects of behavior, all of these relationships were no longer significant. While this is the first study of connectivity in news event memory over long time periods, studies of autobiographical memory find decreases in hippocampal-neocortical functional connectivity (with prefrontal, temporal cortex, and parietal cortex: Gilmore et al., 2021; with prefrontal cortex: Söderlund et al., 2012). Our observed increases in hippocampal-neocortical functional connectivity are inconsistent with theoretical predictions of memory consolidation theories as well as the functional connectivity studies of episodic memory and they were no longer significant after minimizing the effects of behavior.

Summary

In summary, we identified changes in retrieval-related brain activity and functional connectivity for news events associated with memories 1 year to 30 years old. An extensive neocortical network was identified which monotonically increased or decreased in brain activity according to several a priori patterns of interest. Brain activity within a hippocampal anatomical ROI did not significantly change with memory age. Functional connectivity between the vmPFC and neocortex both increased and decreased with the age of the memory while connectivity between the hippocampus and neocortex increased as a function of memory age. These effects were no longer significant after minimizing the effects of behavior. The observed changes in neocortical brain activity were consistent with systems consolidation theory. The lack of a significant change in hippocampal activity could be interpreted as support for MTT/TT although it's possible there was not enough statistical power to detect such an effect. Lastly, the functional connectivity results did not survive statistical correction and the patterns observed at an exploratory level did not correspond to a consistent theory of memory consolidation and disappeared after minimizing the effects of behavior.

Acknowledgements

Chapter 3, in part, is currently being prepared for submission for publication of the material. Tallman, Catherine W.; Wixted, John T.; Smith, Christine N. The dissertation author was the primary researcher and author of this material.

DISCUSSION

Theories of memory consolidation were informed from neuropsychological studies of patients with permanent hippocampal or medial temporal lobe (MTL) damage exhibiting retrograde amnesia. In these studies, patients exhibited temporally-graded retrograde amnesia in which they were able to retrieve memories from the remote but not recent past for both semantic (Bayley et al., 2006; J.R. Manns et al., 2003) and autobiographical (Kirwan, Bayley, Galván, et al., 2008; Kopelman & Bright, 2012) memories. Although, ungraded amnesia is also observed in which retrograde memory was impaired for both the recent and remote past (Steinvorth et al., 2005)

Functional magnetic resonance imaging (fMRI) provides the unique opportunity to study changes in memory retrieval across different memory ages and within adults with normal cognition. Changes in brain function as measured by fMRI are a useful proxy to examine the phenomenon of memory consolidation. Although careful consideration must be taken during the experimental design and interpretation of results when considering a specific pattern of brain changes to be support of one memory consolidation theory over the other. In conjunction, decreases in MTL activation or MTL-neocortical connectivity and increases in neocortical or cortico-cortical connectivity are taken as support for systems consolidation theory (Squire & Alvarez, 1995). In contrast, any increases in MTL activity or MTL-neocortical connectivity, and the failure to detect MTL changes are taken in support for alternate theories, such as MTT/TT, which suggest episodic memories are always dependent on the hippocampus for retrieval (Moscovitch et al., 2005).

Many studies have tried to characterize changes in the functional roles of the hippocampus and neocortex in retrieval associated with memory consolidation across

different types of memoranda and time periods ranging from as short as 15 minutes to 1 day (e.g., Takashima et al., 2009) and as long as 1 year to 30 years (e.g., Smith & Squire, 2009). Additionally, many of these studies suffer from three major weaknesses by examining only one recent and one remote time point, not appropriately accounting for behavioral changes, or not considering the differential re-encoding of targets across recent and remote conditions. Direct overlap between studies of the observed brain changes associated with memory consolidation has not been tested while simultaneously addressing these confounds.

The overarching goal of this dissertation was to identify common functional brain networks associated with long-term memory consolidation. Several studies were conducted that used different types of memoranda and tested retrieval at different intervals between the most recent and most remote task conditions (i.e., 1 hour to 1 month or 1 year to 30 years). Each chapter was dedicated to one fMRI study which examined changes in retrieval-related brain activity, hippocampal functional connectivity, and vmPFC functional connectivity. We also addressed common experimental confounds that can influence patterns observed with memory age when studying long-term memory consolidation with fMRI. Within each experiment we examined patterns of changes across multiple time points, statistically minimized the effects of behavior associated with each trial, and assessed encoding-related activity.

In Chapter 1, we examined changes in brain function associated with memory consolidation of natural scenes across 1 hour to 1 month in younger adults with normal cognition. We found a widespread neocortical network which exhibited monotonic increases and decreases in brain activity with memory age. Hippocampal brain activity

did not decrease with the age of the memory although hippocampal functional connectivity with the parahippocampal cortex and fusiform gyrus decreased with the age of the memory. Functional connectivity between the vmPFC and posterior parietal cortex (PPC) increased with the age of the memory. Taken together, these findings indicate changes in functional brain networks consistent with systems consolidation can be detected as early as 1 hour to 1 month.

In Chapter 2, we examined changes in brain function associated with memory consolidation of three-word sentences across 1 hour to 1 month in healthy older adults with normal cognition. We found a widespread neocortical network which exhibited monotonic increases and decreases in brain activity with memory age. Hippocampal brain activity decreased with the age of the memory. Significant functional connectivity changes were not detected. Exploratory analyses revealed decreases in hippocampal-vmPFC connectivity and increases in vmPFC-PPC. Taken together, these findings indicate changes in functional brain networks consistent with systems consolidation can be detected as early as 1 hour to 1 month.

In Chapter 3, we examined changes in brain function associated with memory consolidation of news events across 1 year to 30 years in the same older adults as Chapter 2. We found a widespread neocortical network which exhibited monotonic increases and decreases in brain activity with memory age. Hippocampal brain activity did not significantly change with the age of the memory. Significant functional connectivity changes were not detected. Exploratory analyses revealed increases in hippocampal-prefrontal, temporal, and parietal connectivity, increases in vmPFC-PPC connectivity, and decreases in vmPFC-posterior cingulate cortex connectivity. After minimizing the effects

of behavior, these exploratory connectivity findings were no longer significant. The patterns of hippocampal brain activity and functional connectivity are inconsistent with common theories of memory consolidation. Several of the neocortical brain function patterns are consistent with theories of memory consolidation.

Functional Brain Network Associated with Long-Term Memory Consolidation Across One Hour to One Month

The studies from both Chapters 1 and 2 examined changes in retrieval-related brain function across 1 hour to 1 month, although with different memoranda (natural scenes versus three-word sentences) and a different study sample (younger adults versus older adults). Only changes in retrieval-related brain activity networks demonstrated directly overlapping regions. A conjunction map was created to determine if a common functional brain activity network arose from memory consolidation studies over short time periods.

The conjunction map of significant changes in brain activity revealed overlap between the left superior temporal gyrus (STG), bilateral posterior parietal cortex (PPC)/retrosplenial cortex (RSC), anterior cingulate cortex (ACC), and right vmPFC (Figure 0.1; cyan). The pattern of activity between these regions in the two studies was consistent: the left STG, bilateral PPC/RSC, and right vmPFC decreased and bilateral ACC increased with the age of the memory. More specifically, the patterns observed in the RSC/PPC and ACC are consistent with lesion and neuroimaging evidence in support of memory consolidation. The bilateral RSC/PPC is thought to be associated with a “recency” effect as lesions to the RSC impair recent episodic memory (Valenstein et al., 1987). In addition, this region is found to decrease in brain activity with the age of episodic memories years to decades old (K Niki & J Luo, 2002) . Conversely, the bilateral ACC is

thought to be associated with remote memory retrieval as lesions to the ACC result in deficits in remote memory but not recent memory (Maviel et al., 2004; Takehara et al., 2003). There was no direct overlap between the whole-brain MTL brain activation findings and the hippocampal-neocortical functional connectivity findings for Chapters 1 and 2. Yet, a general decrease in hippocampus function with memory age was observed across the two chapters as there were decreases in hippocampal brain activity for the retrieval of three-word sentences and decreases in hippocampal-neocortical functional connectivity for the retrieval of natural scenes. Thus, we were able to identify a hippocampal, medial prefrontal, PPC, and lateral temporal cortex network changing over short time intervals that supported the predictions of SCT.

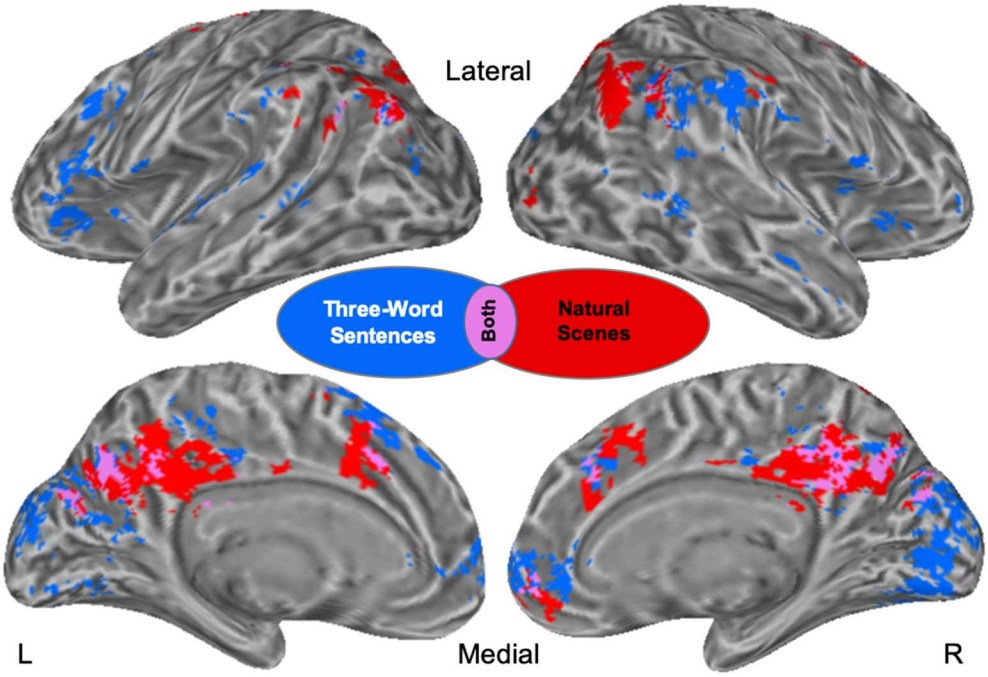


Figure D.1: Comparison of retrieval-related brain activity changes over short time periods and different memoranda. Lateral and medial views displaying clusters where retrieval-related brain activity changed with memory age for three-word sentences (Chapter 2, blue), natural scenes (Chapter 1, red) and voxels which were significant in both studies (violet).

Functional Brain Network Associated with Long-Term Memory Consolidation of Similar Memoranda Across Different Time Periods

The studies from both Chapters 2 and 3 examined changes in retrieval-related brain function in older adults with normal cognition for similar memoranda (three-word sentences versus news events) and across different time periods (1 hour to 1 month versus 1 year to 30 years). Only changes in retrieval-related brain activity networks demonstrated directly overlapping regions. A conjunction map was created to determine if a common functional brain activity network arose from memory consolidation studies over short time periods.

The conjunction map of significant changes in brain activity revealed direct overlap between the left middle temporal gyrus (MTG), inferior frontal gyrus (IFG), and occipital cortex (Figure 0.2; cyan). The overlap of the left MTG and IFG revealed increases in brain activity across 1 hour to 1 month for three-word sentences and decreases in activity across 1 year to 30 years. The overlap of the occipital cortex demonstrated decreases in activity with the age of the memory for both studies. Generally, the pattern of increasing MTG and IFG activity for the retrieval of the three-word sentences aligns more with the predictions of memory consolidation theories. Increases in MTG and IFG would be expected as they are both nodes in the semantic memory network (Binder et al., 2009; Dede & Smith, 2016). There was no overlap between the hippocampal brain activity or functional connectivity results over short and long time periods. We were able to identify a prefrontal, lateral temporal, and occipital cortex network changing over short and long time intervals for similar “fact-like” memoranda.

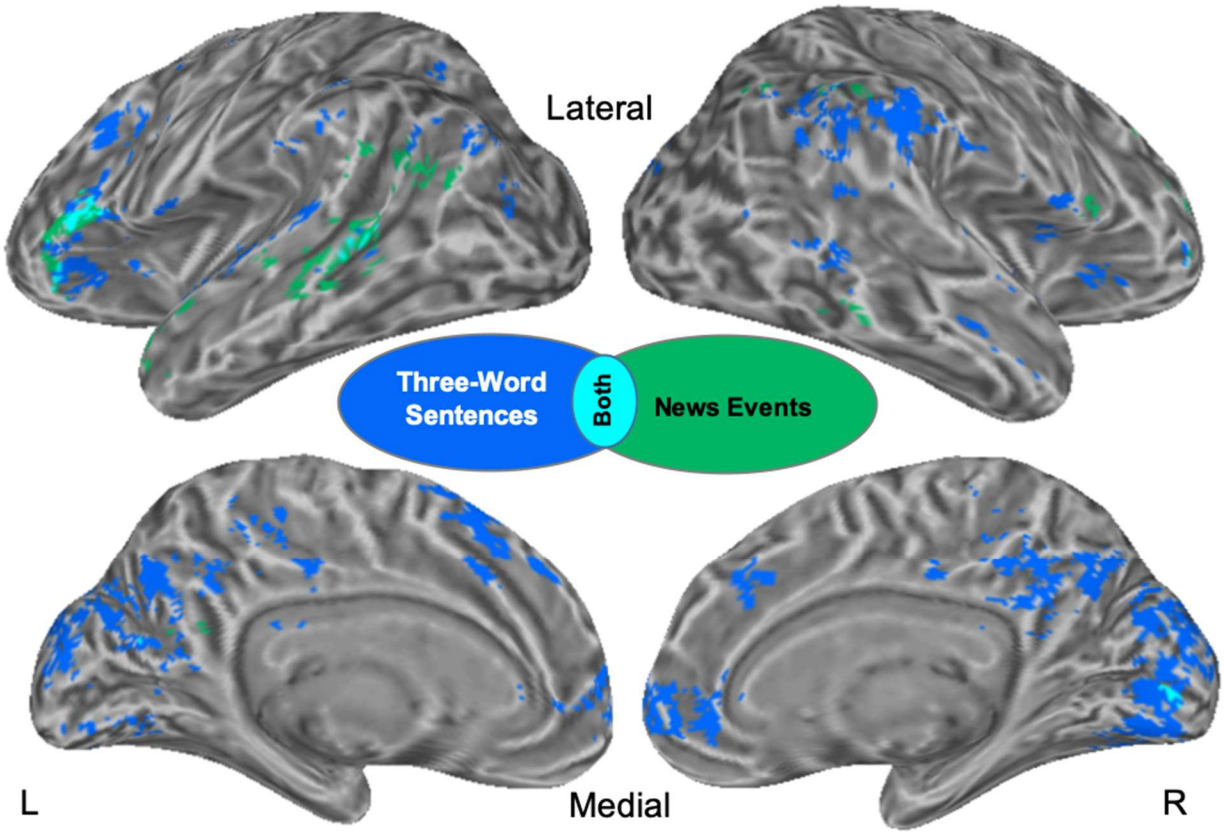


Figure D.2: Comparison of retrieval-related brain activity changes over short and long time period for similar memoranda. Lateral and medial views displaying clusters where retrieval-related brain activity changed with memory age for three-word sentences (Chapter 2, blue), news events (Chapter 1, dark green) and voxels which were significant in both studies (cyan).

Limitations and Future Directions

One limitation of examining the functional relationships between brain regions using the generalized psychophysiological interaction (gPPI) approach is the inherent assumption that the hemodynamic response function (HRF) is similar across brain regions. An alternative approach that does not assume the shape of the HRF would be to use finite-impulse-response basis functions in conjunction with constrained-principle components analysis to elucidate functional connectivity networks (Metzak et al., 2011).

Additionally, our methodological approach was to test for specific patterns of change in the brain (i.e., power, linear). It's also possible that brain changes associated with memory consolidation are changing as a different nonlinear function. Utilizing Multilevel Smoothing-Spline (MSS) Modeling (AFNI's 3dMSS; Chen et al., 2021) would be an alternative way to characterize these nonlinear changes without an *a priori* function.

CONCLUSION

This dissertation aimed to identify functional brain networks associated with long-term memory consolidation while accounting for common experimental confounds. Three fMRI studies examined changes in retrieval-related brain function with memory ages spanning 1 hour to 30 years and for different types of memoranda. Chapters 1 and 2 examined memory consolidation from 1 hour to 1 month for different memoranda. The changes in retrieval-related brain function from both chapters were aligned with the predictions of systems consolidation theory. We were able to identify a hippocampal, medial prefrontal, PPC, and lateral temporal cortex network changing over short time intervals. Chapters 2 and 3 examined memory consolidation from 1 hour to 1 month and 1 year to 30 years for similar memoranda. The changes in retrieval-related brain function showed consistent regional overlap in prefrontal, lateral temporal, and occipital cortices although with inconsistent patterns with memory age.

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