Age-related Neural Correlates of Multifeatural Encoding

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Abstract

Past research has demonstrated age-related structural and functional changes that contribute to declines in episodic memory performance. More specifically, there have been age-related functional connectivity changes to key regions including the medial temporal lobes and prefrontal cortex, as well as within the default mode network. Prior studies investigating age-related episodic encoding have either performed activation analyses, or have performed functional connectivity analyses but only regarding memory of a single association or single feature. Hence, age-related connectivity changes for memory of multiple features remain widely unstudied. Using a fMRI multidimensional source memory paradigm, this study sought to further understand the effect of aging on intra-item multifeatural encoding connectivity. Overall, results supported the hypothesis that young adults would display significantly more functional connectivity relative to older adults to the frontal and parietal lobes for multifeatural trials. A majority of these regions were also corroborated by a similar multifeatural *inter*-item encoding study by James et al. (2019). However, this study was limited by a small sample size and decreased statistical power. Future studies should seek to address these limitations, investigate reconnectivity at retrieval, and attempt to better differentiate between connectivity unique to multifeatural inter-item versus intra-item encoding.

Keywords: episodic memory, encoding, functional connectivity, aging

Everyday life relies on our ability to successfully encode and retrieve episodic memories. Remembering details such as where you parked your car, who you were with last Tuesday, what you cooked for dinner, etc., are all dependent on episodic memory. Past research has consistently documented that older adults do not perform as well as young adults on tests of episodic memory. (Anderson et al., 2008; Bastin and Van der Linden, 2003; Davidson and Glisky, 2002; Jacoby, 1999; Jennings and Jacoby, 1993; Naveh-Benjamin et al., 2009; Spencer and Raz, 1995; Yonelinas, 2002). Moreover, episodic memory changes are among the earliest behavioral markers of Alzheimer's disease, and severity of impairment on tests of episodic memory consistently predict the conversion from preclinical Alzheimer's disease to Alzheimer's disease (Borroni et al., 2006). Thus, to discern normal aging from very early Alzheimer's disease, it is crucial the scientific community have an understanding of episodic memory and its underlying neural mechanisms.

Mechanisms of Episodic Memory

A single episodic memory may incorporate countless features, all of which require encoding in order to form a holistic memory. A prominent model of memory suggests that episodic memories are mediated by two distinct components. This includes a strategic component that assists with the organization and elaboration of memory content, along with an associative component that forms cohesive representations of distinct memories (Shing et al., 2010). To be able to form a cohesive representation, individuals must be able to form mnemonic links between unrelated features of an event (Starns & Hicks, 2008; Tulving, 1983). Multiple features of the same memory maintain a level of dependency between them, but these feature are linked to form a complete memory trace of the original event. Thus, if one feature of a memory

is successfully retrieved, other features of the same memory are more likely to be successfully retrieved as well (Horner & Burgess, 2013).

Episodic memory relies critically on specific brain regions such as the medial temporal lobe (MTL) and the prefrontal cortex (PFC). The MTL has been deemed a "convergence zone" where feature/content is bound (i.e., the associative component of memory), while the PFC operates to strategically encode and organize mnemonic information (i.e., the strategic component of memory) (Shing et al., 2010). The hippocampus, located within the MTL, has been shown to directly influence episodic memory performance. Several experiments have linked increased hippocampal activity levels to successful encoding, as well as decreased hippocampal activity levels to declines in episodic memory performance (Davachi et al., 2003; Daselaar et al., 2003; Dennis, 2008; Mitchell et al., 2000, Ranganath et al., 2003). While these experiments reveal *what* neural regions are engaged during encoding (i.e., show a statistically significant relationship between the Bold Oxygen Level Dependent [BOLD] responses based on the cognitive task), they do not provide information as to *how* these regions are functionally connected over time during the encoding process.

In contrast, research studies using connectivity-based approaches afford the opportunity to examine neural regions for which the BOLD response is correlated over time, thus forming a functional neural network. For example, studies that utilize connectivity-based measures have shown that decoupling of certain brain regions functionally connected with the hippocampus is critical for successful encoding. These findings may be understood in the context of their relation to the default mode network (DMN). The DMN is a widespread network that is primarily active during resting wakefulness, introspection, and episodic memory (Foster et al., 2016; Gusnard & Raichle, 2001). Likewise, the DMN deactivates when a person is given a specific goal-related

cognitive task on which they must focus their attention (Perrson et al., 2007; Mazoyer et al. 2001; Shulman et al., 2007). In the context of episodic memory, the *hippocampal coupling hypothesis* describes the relationship between the hippocampus and the DMN as it relates to encoding and retrieval, stating that the hippocampus is coupled to the DMN during retrieval, but decouples from the DMN during encoding (Hujibers et al., 2011). During encoding, deactivation of the precuneus and posterior cingulate cortex, which are medial parietal cortex regions believed to be a part of the DMN, is associated with successful episodic memory performance (Daselaar et al., 2004; Otten & Rugg, 2001). Similar to these regions, deactivation of certain PFC regions (notably the right dorsolateral region) is linked to successful encoding, while activation of these regions impairs later memory performance (Daselaar et al., 2004; Otten & Rugg, 2001). The PFC plays a direct role in the executive control and spatial reallocation of attention, and experiments manipulating attention show subsequent effects on episodic memory performance (Stuss, 2011).

Age-related Changes and Episodic Memory Performance

Episodic memory deficits in older adults have been attributed to age-related reductions in cognitive resources, cognitive slowing, inhibitory deficits, and deficient binding processes (Craik & Byrd, 1982; Hasher et al., 2007; Naveh-Benjamin, 2000; Salthouse, 1996). The *associative deficit hypothesis* specifically asserts that older adults are less able to link or bind unrelated features into a cohesive memory representation (Naveh-Benjamin, 2000). This notion is supported by behavioral studies documenting that age-related episodic memory deficits are significantly larger for context (multifeatural) memory as compared to content (single feature) memory (Old & Navej-Benjamin, 2008).

Moreover, age-related changes within the PFC and MTL have repeatedly been shown to adversely impact memory performance. The PFC displays volumetric reductions in aging

(Coffey et al., 1998; Convit et al., 2001; Cowell et al., 1994; Gur et al., 2002; Raz et al., 1997), with the frontal lobes showing the steepest rate of age-related atrophy (Pfefferbaum et al., 1998; Raz et al., 2005; Resnick et al., 2003). The MTL also displays volumetric reductions in aging, and hippocampal atrophy has been specifically linked to impaired episodic memory (Perrson et al., 2006; Yonelinas et al., 2007). Consistent with these structural changes, age-related functional changes have been associated with impaired memory performance, particularly in the PFC. For example, a divided-attention study by Anderson and colleagues (2000) found that older adults had significantly less activity in PFC regions associated with successful encoding in young adults; however, older adults displayed activity in PFC regions where no activity in young adults was detected. Similar studies by Daselaar & Cabeza (2017) and Morcom et al. (2003) revealed diminished lateralization within the PFC for older adults, and Persson et al. (2006) found that episodic memory performance was correlated with greater overall frontal activation in older adults. Taken together, these findings suggest that the PFC regions utilized by older adults during encoding become less specific and more diffuse, leading to a reduction of functional specificity within the PFC (Daselaar & Cabeza, 2017).

More broadly, functional connectivity (FC) within the DMN has been shown to weaken with age. That is, older adults exhibiting weakened functional connections between the hippocampus and posterior cingulate cortex show worse episodic memory performance (Dunn et al., 2014). Similarly, reduced connections between the hippocampus and PFC have been proposed to underlie age-related binding difficulties, and are in part thought to be due to inhibitory dysfunction within the PFC (Nyberg, 2019). Moreover, older adults are proposed to inefficiently recruit regions due to lack of executive control processes and function within the PFC (Hasher et al., 2007). The lack of executive control processes and PFC function is thought to

be a main contributor to the reduced functional specificity of the PFC, the increased DMN activation during encoding, and overall worse memory performance that is seen in older adults.

Studies of Age-related Multifeatural Encoding

Most of the aforementioned studies investigating these age-related changes have only considered encoding of single features or a single association; very few studies have been conducted that examine memory for more than one association. A recent study by James et al. (2019) is the only FC study to date to examine multifeatural encoding as it relates to aging. Motivated by Horner and Burgess' study (2013), they developed an experimental paradigm to 1) contrast neural recruitment in older and young adults and to 2) evaluate conditional dependence on pair memory, source memory, and context memory. For the study, participants were asked to judge the likelihood that a person with a given occupation would interact with a given object. Conditions without scene context versus conditions within a specific scene context were established in order to contrast two-element associations and three-element associations, respectively. Results showed conditional dependence between features, as well as comparable recruitment of the aPFC and MTL between age groups. Despite the fact that both age groups recruited these regions, this recruitment proved detrimental to older adult memory performance. The authors suggest that differential recruitment between young and old may be closely related to their ability to disregard irrelevant information, ultimately making it more difficult for older adults to bind key features. Hence, the potential reduced ability for older adults to disregard irrelevant information in this study support inhibitory dysfunction as well.

The Current Study

The aim of the current study is to examine the impact of age on multifeatural encoding. As with James et al. (2019), we utilized a connectivity-based approach to discern how different brain regions crucial to multifeatural encoding co-vary over time. However, while the study by James et al. (2019) examined inter-item associations (i.e., person, occupation, object), the current study investigated intra-item associations (i.e., word, location, color) by adapting a paradigm developed by Uncapher et al. (2006) in which words are presented on a screen in a particular color and at a particular location, with color and location varying independently. Additionally, I also matched task performance between young and old age groups. Matching behavioral performance between groups ensures that any neural differences observed are not solely due to task difficulty. Thus, the current study used a multidimensional encoding memory paradigm to investigate how the BOLD signal in brain regions co-vary over time during encoding in young and older adults for intra-item associations. At the neural level, I hypothesized that both young and older adults would show functional connectivity between several regions including prefrontal cortex, parietal, and medial temporal lobes. However, I hypothesized that the strength of that connectivity would be decreased in older adults, as compared to young adults, particularly during the multifeatural learning trials.

Methods

Participants

The sample consisted of fourteen young adults (9 females) and fourteen community dwelling older adults (8 females) who were paid for their participation. All subjects were right-handed, native English speakers, had normal or corrected-to-normal vision, were not colorblind, had no contraindications for fMRI, and reported no history of brain injury, neurological disorder,

or psychological illness. The older adult participants were screened for dementia with a neuropsychological test battery, including the Mini-Mental State Exam (Folstein et al., 1975), the AD8 (a screening test that assesses memory, orientation, executive functioning, and interest in activities; 2005, Washington University, St. Louis, MO), Shipley Vocabulary Test (Shipley, 1967), Digit Span Subtest from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981), and Immediate and Delayed Logical Memory subtests of the Wechsler Adult Memory Scale-Revised (Wechsler, 1987). Table 1 displays the demographics for the participants. All experimental procedures were approved by the Institutional Review Board at the University of North Carolina at Chapel Hill. All participants provided written informed consent.

Stimuli

Stimuli consisted of 288 nouns from the MRC Psycholinguistic Database (http://websites.psychology.uwa.edu.au/school/MRCDatabase/uwa_mrc.htm; Wilson, 1988). The nouns were 4-9 letters long, had a written Kucera-Francis (1967) frequency of 1-30 counts per million, and had a concreteness rating greater than 350 (actual range = 381 – 662). Eight of the words were used as primacy items (2 at the beginning of each of the 4 encoding lists used during scanning). Primacy items were omitted from all analyses. Color and location were randomly selected for these primacy items and they remained constant for all subjects. The remaining items were divided into 14 lists of 20 items each. All lists contained 10 animate items and 10 inanimate items. For both levels of animacy there were 5 items larger than a shoebox and 5 items smaller than a shoebox. This yielded four classes of 5 items each within a list (animate-small, inanimate-small, etc.). Twelve of the lists were used as experimental stimuli for the scanned portion of the study. The remaining 2 lists were used to create a pool from which the practice phase items were selected. For the practice items, 15 words were randomly chosen as

targets and 8 more were randomly chosen as lures.

The bank of items for the scanned portion of the study consisted of the remaining 12 lists. For each subject, 8 of these lists served as target/study items and the remaining 4 served as non-studied items (i.e., lures) that appeared only during the testing phase. The assignment of lists to run number and target or lure status was counterbalanced across subjects. The study phase of each run contained 40 items (i.e., 2 of the 20-item lists) that satisfied all combinations of color and location (plus the 2 primacy items). To ensure that color and location were not repeatedly associated with a given size-animacy combination, an item of each size-animacy combination appeared equally often in each color and location within subjects (but across runs). Moreover, all lists were inspected to ensure that obvious color-word combinations were avoided (e.g., red-apple, green-turtle, blue-bird, etc.). Participants were instructed to disregard the 8 items that appeared in black during the study phase, so these 8 items did not appear on the recognition test (resulting in a total of 32 target items). Items for a memory test consisted of the 32 chromatic items from the study episode (plus the 2 primacy items) and the 20 items from the list of lures. Finally, items were presented in random order as determined by the computer (using the algorithm Opt Seq. 2) for each test.

Behavioral Procedure

To ensure above chance performance, as well as to equate performance between the two age groups, we made several changes to the paradigm developed by Uncapher et al. (2006). The paradigm was broken into 4 small study-test runs. The study trials were lengthened from 3 seconds to 6 seconds, and the stimuli were present for the entire trial. The length of the retention interval between the study and test episodes was varied between age groups. Older adults were tested immediately upon completion of the encoding task, whereas young adults engaged in 4

minutes of math problems between each study episode and memory test. All subjects performed one of two orienting tasks on the encoding trials in order to direct attention to the word (i.e., the item). For the two orienting tasks, participants were either asked to decide if the study word was an animate or inanimate object, or decide if the study word was typically larger or smaller than a shoebox. During pilot testing, we found that older adults spent more time on this task than young adults, which reduced the time they had to study the features associated with each item. To help account for this disadvantage, the current study reminded older adults not to dwell too heavily on their orienting task decision and to spend no more than 2 to 3 seconds making their response. All participants performed a practice version of the task before entering the MRI scanner.

Participants were instructed that, for each study phase, each word would appear in 1 of 4 screen positions (top-left, top-right, bottom-left, and bottom-right). Most of the words would appear in a chromatic color (red, green, blue, or yellow) and some of the words would appear in black. For the chromatic words, participants were urged to remember the word, its color, and its location to the best of their ability. Conversely, the black words were only to be viewed and not remembered. In addition, participants were told that one of their tasks was to make a decision about the words based on some aspect of their meaning. For the chromatic words, the participants decided whether the word represented an item that is typically living (1 key) or non-living (2 key). For the black words, the participants decided whether or not the word represents an item that is typically bigger (1 key) or smaller (2 key) than a shoebox. (Uncapher et al. (2006) had previously found that the non-chromatic words were necessary for color memory performance above floor levels.) The words appeared one at a time and were accompanied by a prompt at the bottom of the screen reminding the participant what type of judgment (i.e.,

orienting task) was necessary and what the response options were.

All study trials lasted a total of 6 seconds; the word appeared for 5.5 seconds and then the screen was replaced with a fixation cross for 500 milliseconds (see Figure 1). For chromatic words, the participants were instructed to use the remaining time to encode the color and location. Finally, the participants were told that there would be some trials during which no word would appear (i.e., they would only see blank squares in which the words would normally appear). They were told that no response was needed in this case and to wait for the next word to appear.

Next, the participants were told that their memory for the chromatic words and their associated features would be tested. Some of the words on the test would be ones they had seen before ("old") and some would be ones they had not seen before ("new"). Words would appear one at a time with participants having 6 seconds to indicate whether they thought the word was "old" (1 key) or "new" (2 key). If a "new" response was made or no response was provided, the program moved on to the next test item. For words deemed old, participants were given up to 8 seconds to indicate its original color (i.e., red, green, blue or yellow) and another 8 seconds to indicate its original location (i.e., top-left, top-right, bottom-left, or bottom-right). Memory was always tested in this order (i.e., item, color, then location). Responses were collected with a 5-button MR-compatible response box. For both color and location, the respective key mappings for each feature dimension were always the 1, 2, 3, and 4 keys. Participants were told to provide their best guess if they were unsure about a word's features or old/new status. An example sequence of trials is shown in Figure 2. Note that the response options were always displayed during the test. Participants were given a 2-minute resting period between study phases.

Image Acquisition

The MRI data were collected at the University of North Carolina's Biomedical Research Imaging Center using a Siemens Magnetom Trio 3-T MR scanner (Siemens Medical Systems, Iselin, NJ) equipped with a three-axis gradient head coil to acquire both anatomical and functional images. All stimuli were back-projected onto a screen and viewed by the subject on an MR-compatible mirror above the subject's head. Subjects who normally wore glasses or contacts were fitted with MR-compatible glasses whose lenses matched their prescription. Responses were recorded with a 5-button MR-compatible response box using each subject's right hand. The anatomical images were collected with a high-resolution T1-weighted MPRAGE sequence and slices were acquired in an ascending manner (TR = 1900 msec, TE = 2.26 msec, voxel size = $1mm^3$, flip angle = 9°, 192 slices, acquisition time = 266 sec). The functional images were collected with a T2-weighted EPI sequence and slices were acquired in a bottom-up interleaved manner (TR = 3000 msec, TE = 23 msec, voxel size = $3mm^3$, flip angle = 9°). To fully volume the long axis of the hippocampi, slice acquisition was also oriented along the long axis of the hippocampi according to each subject's anatomical scan. The functional data were acquired in 4 runs, with the first 4 volumes in each run discarded to allow for stabilization of the magnetic fields. The trial sequences were generated using Opt Seq 2 (http://surfer.nmr.mgh.harvard.edu/optseq/). Using a set of user-defined constraints, this program generates a stimulus presentation schedule that helps a rapid-presentation event-related fMRI experiment achieve an optimal random design. Because scanning only took place during encoding, only the study phase sequences of each run were generated using Opt Seq 2. Trials which presented the grey squares containing no words were null events; all null events were a multiple of the TR (6 seconds).

Image Processing and Analysis

Data preprocessing and analyses were conducted with CONN (Whitfield-Gabrieli, & Nieto-Castanon, 2012; http://www.nitrc.org/projects/conn) and implemented in Matlab (Matlab Mathwork, Inc., Natick, MA). Participant trials were assigned to each condition (IO, IC, IL, ICL, or MISS) and analyzed through onset of the BOLD signal. Regions of interest as defined by Uncapher et al. (2006) were averaged and a task-modulation effects (gPPI) analysis was performed between ROIs and every other voxel in the brain. A statistical threshold of $p<.05$ for cluster and height threshold was applied in order to identify significant voxels. Significant voxels were reported using standard MNI space coordinates.

Results

Behavioral Results

To compare performance between young and old, I examined the proportion of correctly endorsed study items (hits) between groups. Behaviorally, no significant accuracy differences were observed in overall old/new recognition (Figure 3) or feature memory (Figure 4). Memory for multiple source features was also significantly greater than chance—ensuring the interpretability of the fMRI data. An analysis of performance broken down by test run showed that there was no main effect of test run and it did not interact with any variables, suggesting that participants complied with the task instructions and that there were no significant shifts in strategy for either group. In sum, all measures taken to promote the interpretability of the fMRI data were effective.

Imaging Results

A task modulation (gPPI) bivariate regression was performed to assess within subject differences. The analysis examined which voxels of the brain covaried over time with a given

ROI (the dorsal inferior frontal gyrus, intraparietal sulcus, precuneus, or hippocampus). Significant covariation between specific voxels and a given ROI denotes that the regions were functionally connected at the prespecified significance level. To assess FC differences between young and older adults, a positive contrast was performed across all conditions (height threshold $p<.05$; cluster threshold $p<.05$). The default height threshold of $p<.001$ was altered due to the small sample size and type of analysis used. Between group differences are reported below for each experimental condition. Experimental conditions were categorized according to what the participant recalled during the test phase and noted as either IO, IC, IL, ICL, or Miss (i.e., failing to identify a previously studied stimulus).

Trials where individuals were only able to recall the item itself (IO) showed no significant FC for young adults among the four ROIs. For older adults, I observed FC from the dorsal inferior frontal gyrus ROI to right intermediate frontal and left middle temporal regions (Table 2). That is, older adults showed greater FC between bilateral frontal regions, as well as FC with temporal lobe regions, than when compared to young adults.

Trials where individuals were able to recall the item and item color (IC) showed greater FC in young adults, as compared to older adults, between the dorsal inferior frontal gyrus ROI and right opercular, right premotor cortex, left primary sensory cortex, left ventral anterior cingulate, left temporopolar, and left primary motor cortex (Table 3). From the intraparietal sulcus ROI, young adults displayed FC to right parahippocampus. For the hippocampal ROI, young adults showed FC to the right anterior prefrontal cortex, left angular gyrus, right dorsal posterior cingulate, and left prefrontal regions. In contrast, older adults only displayed FC from the intraparietal sulcus ROI to the left superior parietal and right prefrontal regions, indicating

less FC relative to young adults in bilateral parietal and medial temporal connectivity. Moreover, the older adults showed no FC between the hippocampal ROI and other regions.

Trials where individuals were able to recall the item and item location (IL) showed FC in young adults between the dorsal inferior frontal gyrus ROI and the right caudate, right superior parietal, and left associative visual cortex (Table 4). Young adults showed additional FC between the intraparietal sulcus ROI and right fusiform, as well as between the precuneus ROI and right fusiform. Older adults showed FC between the dorsal inferior frontal ROI and left ventral posterior cingulate, left anterior prefrontal cortex, and left intermediate frontal, as well as between the intraparietal sulcus ROI and left dorsal posterior cingulate. Both young adults and older adults showed FC to the angular gyrus and middle temporal regions. For young adults, they demonstrated FC from the intraparietal sulcus ROI to left angular gyrus and right middle temporal regions. For older adults, they showed FC from the dorsal inferior frontal gyrus ROI to left angular gyrus, the right angular gyrus, and the left middle temporal regions.

During the multifeatural trials, individuals successfully recalled the item, item color, *and* item location (ICL). The ICL analysis revealed that young adults exhibited FC between the dorsal inferior frontal gyrus ROI and premotor cortex, left middle frontal, left associative visual cortex, and left superior parietal regions (Figure 5A). Young adults also displayed FC between the intraparietal sulcus ROI and right anterior prefrontal cortex, left angular gyrus, and left superior parietal regions (Table 5, Figure 5B). Conversely, older adults displayed greater FC between the hippocampal ROI and left primary sensory cortex, right fusiform gyrus, and left secondary visual cortex regions (Figure 5D). Both young and older adults demonstrated right associative visual cortex FC. Whereas older adults showed FC between the hippocampus ROI

and right associative visual cortex, young adults showed FC between the precuneus ROI and right associative visual cortex (Fig. 5C-D, Fig. 6A-D).

MISS trials represent participants incorrectly endorsing a studied item as "new." An analysis of these trials revealed that young adults exhibited FC from the intraparietal sulcus ROI to dorsolateral prefrontal cortex and left intermediate frontal regions. Young adults also exhibited FC from the hippocampal ROI to right dorsolateral prefrontal cortex and left dorsal anterior cingulate regions (Table 6). Older adults exhibited FC from the dorsal inferior frontal gyrus ROI to left angular gyrus and right supramarginal regions, as well as FC between the intraparietal sulcus ROI and right superior parietal region. From the precuneus ROI, older adults displayed FC to the right primary sensory cortex and left supramarginal regions. Both young and older adults displayed FC to the left angular gyrus, but the related ROI differed between age groups. For young adults, there was FC between the intraparietal sulcus ROI and the left angular gyrus. For older adults, there was similar FC between the intraparietal sulcus ROI and the left angular gyrus, but there was additional FC between the dorsal inferior frontal gyrus ROI and left angular gyrus.

Discussion

In the current study, I modified a paradigm developed by Uncapher et al. (2006) and matched behavioral performance between the two age groups. Results from Figures 3 and 4 displayed that there were no significant differences between either item recognition or feature memory, which indicates that behavioral performance was successfully equated. Unlike the current study that used a functional connectivity approach, Uncapher et al. (2006) conducted activation analyses of their data. Given this, I examined FC using the ROIs identified by the activation analysis of Uncapher et al. (2006).

Multifeatural Connectivity Among Young and Older Adults

The primary aim of this study was to identify age-related differences in neural FC during multifeatural and single feature encoding. Successful multifeatural encoding, which more closely represents memory for everyday life, is mediated by binding processes that relate single event features into an integrative memory representation. For the analysis I used four ROIs that have been previously shown to be engaged during multifeatural encoding in young adults, including the dorsal inferior frontal gyrus, intraparietal sulcus, precuneus, and hippocampus (Uncapher et al., 2006). The findings support my hypothesis that both young and older adults would exhibit FC between the ROIs, prefrontal lobes, parietal lobes, and medial temporal lobes. The FC varied by condition, but the findings also support my hypothesis that young adults would display greater FC relative to older adults specifically during multifeatural trials. During multifeatural trials, young adults showed greater FC relative to older adults from the dorsal inferior frontal gyrus ROI to the frontal, parietal, and occipital lobes. Young adults also showed greater FC from the intraparietal sulcus ROI to frontal and parietal lobes. Moreover, young adults showed greater FC from the precuneus ROI to the occipital lobe.

In contrast, young adults did not display greater FC relative to older adults between any of the ROIs and other MTL regions for multifeatural trials. Young adults also did not display greater FC from the hippocampus ROI; rather, older adults displayed overall greater FC from the hippocampus ROI during multifeatural trials. I originally hypothesized that younger adults would have greater FC to MTL regions during multifeatural trials, but one possible way to account for this is that there have been numerous studies linking hippocampal hyperactivation in older adults to mild cognitive impairment and presymptomatic familial Alzheimer's disease (Nyberg, 2019). Hyperactivation does not necessarily imply hyperconnectivity, but it is certainly a possible cause

for the greater FC seen in older adults both from the hippocampus ROI and to other MTL regions during multifeatural trials. Furthermore, the roles of hippocampal hypoactivation and hyperactivation in multifeatural encoding are disputed among researchers, and they should be further investigated in order to better understand these results in the context of connectivity.

Differential PFC Connectivity

Age-related FC bilateralization of the PFC has been previously observed (Daselaar & Cabeza, 2017; Morcom et al., 2003). The current analysis yielded results consistent with these findings, as there was greater bilateral FC in prefrontal regions for older adults during the IO condition. In contrast, PFC connectivity remained lateralized in young adults during successful encoding. The only exception to this was during IC trials, in which young adults exhibited greater FC between the hippocampus and right aPFC, while also exhibiting greater FC between the hippocampus and left PFC. However, I hypothesize that this may be due to hypoconnectivity between the hippocampus and right PFC that has been previously documented in older adults for single feature associations (Nyberg, 2019). Thus, it may not be that young adults are demonstrating increased connectivity to the aPFC during this time; rather, young adults are demonstrating increased connectivity relative to hypoconnectivity in older adults. This could help explain the discrepancy found here, as this may not be an indication of true PFC bilateralization. Additionally, deactivation of the right dorsolateral PFC has been previously found to be associated with successful encoding in young adults (Daselaar et al., 2004; Otten & Rugg, 2001). Given this, it would be predicted that activation of this region would be associated with unsuccessful encoding as well. My findings support this theory, as the analysis showed greater FC in young adults relative to older adults to the right dorsolateral PFC from the intraparietal sulcus and hippocampus ROIs during MISS trials.

Ineffective Binding Among Older Adults

The associative deficit hypothesis describes how the ability to bind items into an integrative whole declines with age (Naveh-Benjamin 2000). In line with this hypothesis, James et al. (2019) reported decreased conditional dependency among older adults for their multifeatural FC study. That is, for older adults one feature was not dependent on the other for successful encoding, and vice versa. Decreased dependency suggests there is a lack of binding taking place for older adults during multifeatural encoding. Additionally, the ROIs chosen for the current study have been specifically associated with multifeatural trials, and the intraparietal sulcus ROI is thought to play a role in perceptual binding (Uncapher et al., 2006). Results from the current analysis revealed there was less FC in older adults from the dorsal inferior frontal gyrus, intraparietal sulcus, and precuneus ROIs compared to young adults. The decreased FC in older adults, especially from the intraparietal sulcus, may be indicative of a reduced ability to bind features into an integrative whole. Taken together, results of age-related multifeatural encoding studies continue to suggest binding capabilities are impaired among older adults.

FC Multifeatural Encoding Regions Across Studies

To date, only one other study has examined age-related FC changes during multifeatural encoding (James et al., 2019). In that study, the authors examined FC for inter-item (job-occupation-scene) associations. Performance was *not* matched for the two age groups. Two behavioral partial least squares analyses revealed a whole-brain functional encoding network, with specific regions being identified within an additional multifeatural functional encoding network. Specifically, the premotor cortex, left middle frontal, left associative visual, right associative visual, right aPFC, and right fusiform regions were found to be recruited within this network by both young and older adults during multifeatural encoding. These regions correspond

with the regions I observed as connected to the ROIs within the current study during multifeatural trials. Notably, five of the seven identified regions for the YA>OA contrast in the current study's multifeatural trials correspond with regions from the study by James et al. (2019) (see Table 5). The premotor cortex, left middle frontal, left associative visual, right associative visual, and right anterior prefrontal cortex regions identified within the James et al. (2019) study displayed greater FC to the ROIs among young adults in the current study. These findings support the idea that FC, particularly among multifeatural encoding, decreases in age.

Differential Recruitment Within the Same Functional Network

James et al. (2019) observed that older adults exhibit the same functionally connected regions as those of young adults during multifeatural trials despite having worse memory performance. If older adults had incorporated alternative regions into their functional network compared to young adults, this would suggest that older adults possessed weakened FC to the regions that are typically associated with successful young adult multifeatural encoding. Yet, the older adults recruited the same regions as young adults, suggesting that older adults differentially engage these regions instead.

The current analysis is able to offer more support to the idea of differential recruitment, as I was able to demonstrate that the same regions identified in the James et al. (2019) study as "differentially recruited" were "differentially connected" between young and old in the current study. That is, there were significant differences in FC between young and older adults for these same "differentially recruited" regions.. Although differential recruitment implies differential connectivity, the current study was able to identify *explicit* differential connectivity that coincided with some of the James et al. (2019) differentially recruited regions.

Furthermore, there were several instances in which both young and older adults displayed heightened FC to the same region for the **same** trials, but from a *different* ROI. For instance, both young and older adults displayed greater FC to the right associative visual cortex during ICL trials. However, young adults exhibited greater FC between the precuneus ROI and right associative visual cortex relative to older adults, and older adults exhibited greater FC between the hippocampus ROI and right associative visual cortex relative to young adults. Similarly, both young and older adults displayed greater FC to the left angular gyrus and right middle temporal for IL trials. However, young adults displayed greater FC relative to older adults from the intraparietal sulcus ROI to the left angular gyrus and right middle temporal, and older adults displayed greater FC relative to young adults from the dorsal inferior frontal gyrus ROI to the left angular gyrus and right middle temporal. These instances offer further support to the idea that older adults employ differential recruitment within the same functional network as young adults.

Among young adults for the multifeatural trials, there was also an instance where multiple ROIs displayed significant FC to the same region relative to the older adults. Young adults exhibited FC to the left superior parietal region from both the dorsal inferior frontal gyrus and intraparietal sulcus ROIs. Significant FC to the same region, from multiple ROIs, indicates that the left superior parietal region may play a significant role within the multifeatural encoding network that is impacted by age.

Limitations and Future Directions

While the results of the current analysis seem to be promising given the fact that they coincide closely with those of James et al. (2019), it should be noted that the statistical threshold was lowered to $p<.05$ due to the small sample size. Moving forward it would be helpful to have a

larger sample to use a statistical threshold of $p < .001$. Additionally, the current study assessed FC at encoding, but did not consider FC at retrieval. Future studies should examine whether or not the same functional connections required for successful encoding are re-engaged/re-connected during successful retrieval. Moreover, if these regions are found to be reconnected during retrieval, whether or not they remain more connected for one age group over the other should be verified. Lastly, directly comparing inter-item vs. intra-item within the same sample should be further investigated. There could be differences between inter-item and intra-item that further clarify FC processes that occur during multifeatural encoding. This could in part explain certain discrepancies that exist between the results of the current study and those observed by James et al. (2019). Furthermore, examining FC for inter-item and intra-item within the same sample helps to more visibly establish what is common to all multifeatural encoding versus what is unique to inter- or intra-associations. Ultimately, future studies targeting multifeatural encoding can continue to work towards delineating healthy aging from diseased aging, which can help to more promptly and reliably clinically diagnose those with Alzheimer's disease and other age-related memory afflictions.

References

Anderson, N. D., Iidaka, T., Cabeza, R., Kapur, S., Mcintosh, A. R., & Craik, F. I. (2000). The Effects of Divided Attention on Encoding- and Retrieval-Related Brain Activity: A PET Study of Young and Older Adults. *Journal of Cognitive Neuroscience, 12*(5), 775-792. doi:10.1162/089892900562598

Andrea E. Cavanna, Michael R. Trimble, The precuneus: a review of its functional anatomy and behavioural correlates, *Brain*, Volume 129, Issue 3, March 2006, Pages 564–583, https://doi.org/10.1093/brain/awl004

Borroni, B., Anchisi, D., Paghera, B., Vicini, B., Kerrouche, N., Garibotto, V., . . . Perani, D. (2006). Combined 99mtc-ecd SPECT and neuropsychological studies In MCI for the assessment of conversion to ad. *Neurobiology of Aging, 27*(1), 24-31. doi:10.1016/j.neurobiolaging.2004.12.010

Craik, F. I., & Byrd, M. (1982). Aging and cognitive deficits. *Aging and Cognitive Processes,* 191-211. doi:10.1007/978-1-4684-4178-9_11

Coffey, J. F., Lucke, J. A., Saxton, G., Ratcliff, L. J., Unitas, B., Billing, B., & Byran, R. N. (1998). Sex differences in brain imaging. *Archives of Neurology, 55*, 169-179.

Convit, A., Wolf, O. T., de Leon, M. J., Patalinjug, M., Kandil, E., Caraos, C., Scherer, A., Saint Louis, L. S., &, Cancro, R. (2001).Volumetric analysis of the prefrontal regions: Findings in aging and schizophrenia. *Psychiatry Research, 107*, 61-73.

Cowell, P. E., Turetsky, B. T., Gur, R. C., Grossman, R. I., Shtasel, D. L., & Gur, R. E. (1994). Sex differences in aging of the human frontal and temporal lobe. *Journal of Neuroscience, 14*, 4748-4755.

Daselaar, S. & Cabeza, R. (2017). Age-Related Changes in Hemispheric Organization. *Cognitive neuroscience of aging: Linking cognitive and cerebral aging* (pp. 326-347). New York, NY: Oxford university press. doi:10.1093/acprof:oso/9780195156744.003.0014

Daselaar, S., Prince, S., & Cabeza, R. (2004). When less means more: Deactivations during encoding that predict subsequent memory. *NeuroImage, 23*(3), 921-927. doi:10.1016/j.neuroimage.2004.07.031

Dennis, N. A., Kim, H., & Cabeza R. (2008). Age-related differences in brain activity during true and false memory retrieval. *Journal of Cognitive Neuroscience, 20*(8), 1390-402.

Dunn, C. J., Duffy, S. L., Hickie, I. B., Lagopoulos, J., Lewis, S. J., Naismith, S. L., & Shine, J. M. (2014). Deficits in episodic memory retrieval reveal impaired default mode network connectivity in amnestic mild cognitive impairment. *NeuroImage: Clinical, 4*, 473-480. doi:10.1016/j.nicl.2014.02.010

Foster, C. M., Picklesimer, M. E., Mulligan, N. W., & Giovanello, K. S. (2016). The effect of age on relational encoding as revealed by hippocampal FC. *Neurobiology of Learning and Memory, 134*, 5-14. doi:10.1016/j.nlm.2016.07.026

Gur, R. C., Gunning-Dixon, F., Bilker, W. B., and Gur, R. E. (2002). Sex differences in temporolimbic and frontal brain volumes of healthy adults. *Cerebral Cortex, 12*, 998-1003.

Gusnard, D., Raichle, M. Searching for a baseline: Functional imaging and the resting human brain. *Nat Rev Neurosci* **2,** 685–694 (2001). https://doi.org/10.1038/35094500

Hasher, L., Lustig, C., & Zacks, R. (2007). Inhibitory mechanisms and the control of attention. *Variation in Working Memory,* 227-249. doi:10.1093/acprof:oso/9780195168648.003.0009

Horner, A. J., & Burgess, N. (2013). The associative structure of memory for multi-element events. *Journal of Experimental Psychology: General, 142*(4), 1370-1383. doi:10.1037/a0033626

Huijbers, W., Pennartz, C. M., Cabeza, R., & Daselaar, S. M. (2011). The Hippocampus Is Coupled with the Default Network during Memory Retrieval but Not during Memory Encoding. *PLoS ONE, 6*(4). doi:10.1371/journal.pone.0017463

Iidaka T, Sadato N, Yamada H, Murata T, Omori M, & Yonekura Y. (2001). An fMRI study of the functional neuroanatomy of picture encoding in young and older adults. *Brain Research: Cognitive Brain Research, 11*, 1-11.

James, T., Rajah, M. N., & Duarte, A. (2019). Multielement Episodic Encoding in Young and Older Adults. *Journal of Cognitive Neuroscience, 31*(6), 837-854. doi:10.1162/jocn_a_01384

Kim, S. Y. and Giovanello, K. S. (2011). The effects of attention on age-related memory deficits: fMRI evidence from a novel attentional manipulation. *Journal of Cognitive Neuroscience, 23*, 3637-56.

Mazoyer, B., Zago, L., Mellet, E., Bricogne, S., Etard, O., Houdé, O., . . . Tzourio-Mazoyer, N. (2001). Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Research Bulletin, 54*(3), 287-298. doi:10.1016/s0361-9230(00)00437-8

Miller, S. L., Celone, K., Depeau, K., Diamond, E., Dickerson, B. C., Rentz, D., . . . Sperling, R. A. (2008). Age-related memory impairment associated with loss of parietal deactivation but preserved hippocampal activation. *Proceedings of the National Academy of Sciences, 105*(6), 2181-2186. doi:10.1073/pnas.0706818105

Mitchell, K. J., Johnson, M. K., Raye, C. L., & D'Esposito, M. (2000). FMRI evidence of age-related hippocampal dysfunction in feature binding in working memory. *Brain Research: Cognitive Brain Research, 10*, 197-206

Morcom, A. M., Good, C. D., Frackowiak, R. S., & Rugg, M. D. (2003). Age effects on the neural correlates of successful memory encoding. *Brain, 126*(1), 213-229. doi:10.1093/brain/awg020

Naveh-Benjamin, M. (2000). Adult age differences in memory performance: Tests of an associative deficit hypothesis. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 26*(5), 1170-1187. doi:10.1037/0278-7393.26.5.1170

Naveh-Benjamin, M., Craik, F. I., Perretta, J. G., & Tonev, S. T. (2000). The effects of divided attention on encoding and retrieval processes: The resiliency of retrieval processes. *The Quarterly Journal of Experimental Psychology A, 53*(3), 609-625. doi:10.1080/027249800410454

Naveh-Benjamin, M., Guez, J., & Sorek, S. (2007). The effects of divided attention on encoding processes in memory: Mapping the locus of interference. *Canadian Journal of Experimental Psychology/Revue canadienne de psychologie expérimentale, 61*(1), 1–12. https://doi.org/10.1037/cjep2007001

Nyberg, L., Andersson, M., Lundquist, A., Salami, A., & Wåhlin, A. (2019). Frontal contribution to hippocampal hyperactivity during memory encoding in aging. *Frontiers in Molecular Neuroscience, 12*. doi:10.3389/fnmol.2019.00229

Otten, L. J., & Rugg, M. D. (2001). When more means less: Neural activity related to unsuccessful memory encoding. *Current Biology, 11*(19), 1528-1530. doi:10.1016/s0960-9822(01)00454-7

Persson, J., Lustig, C., Nelson, J. K., & Reuter-Lorenz, P. A. (2007). Age Differences in Deactivation: A Link to Cognitive Control? *Journal of Cognitive Neuroscience, 19*(6), 1021-1032. doi:10.1162/jocn.2007.19.6.1021

Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L.G., Ingvar, M., & Buckner, R. L. (2006). Structure-function correlates of cognitive decline in aging. *Cerebral Cortex, 16*, 907-15.

Pfefferbaum, A., Sullivan, E.V., Rosenbloom, M.J., Mathalon, D.H., & Lim, K.O. (1998). A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. *Archives of General Psychiatry, 55*, 905-12.

Raz, N., Gunning-Dixon, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., Loken, W. J., Thornton, E. A. & Acker, J. D. (1997). Selective aging of the human cerebral cortex

observed in vivo: Differential vulnerability of the prefrontal gray matter. *Cerebral Cortex, 7,* 268-282

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., ... & Acker, J. D. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cerebral cortex, 15*(11), 1676-1689.

Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., & Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *Journal of Neuroscience, 23,* 3295-301.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review, 103*(3), 403-428. doi:10.1037/0033-295x.103.3.403

Shing, Y. L., Werkle-Bergner, M., Brehmer, Y., Müller, V., Li, S., & Lindenberger, U. (2010). Episodic memory across the lifespan: The contributions of associative and strategic components. *Neuroscience & Biobehavioral Reviews, 34*(7), 1080-1091. doi:10.1016/j.neubiorev.2009.11.002

Shulman, G. L., Corbetta, M., Buckner, R. L., Fiez, J. A., Miezin, F. M., Raichle, M. E., & Petersen, S. E. (1997). Common Blood Flow Changes across Visual Tasks: I. Increases in Subcortical Structures and Cerebellum but Not in Nonvisual Cortex. *Journal of Cognitive Neuroscience, 9*(5), 624-647. doi:10.1162/jocn.1997.9.5.624

Stuss, D. (2011). Functions of the Frontal Lobes: Relation to Executive Functions. *Journal of the International Neuropsychological Society, 17*(5), 759-765. doi:10.1017/S1355617711000695

Sun, F. W., Stepanovic, M. R., Andreano, J., Barrett, L. F., Touroutoglou, A., & Dickerson, B. C. (2016). Youthful Brains in Older Adults: Preserved Neuroanatomy in the Default Mode and Salience Networks Contributes to Youthful Memory in Superaging. *Journal of Neuroscience, 36*(37), 9659-9668. doi:10.1523/jneurosci.1492-16.2016

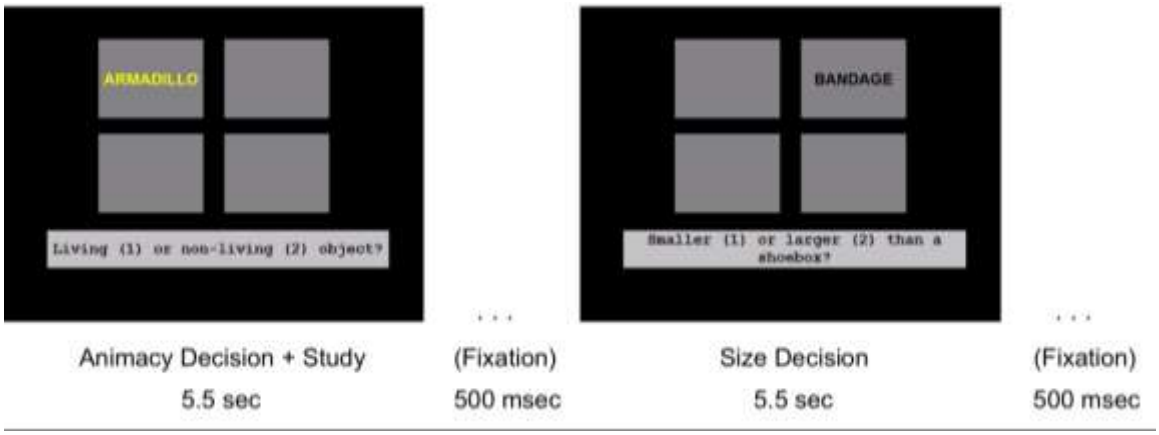
Uncapher, M. R., Otten, L. J., & Rugg, M. D. (2006). Episodic Encoding Is More than the Sum of Its Parts: An fMRI Investigation of Multifeatural Contextual Encoding. *Neuron, 52*(3), 547-556. doi:10.1016/j.neuron.2006.08.011

Wang, L., Negreira, A., LaViolette, P., Bakkour, A., Sperling, R. A., & Dickerson, B. C. (2010). Intrinsic interhemispheric hippocampal FC predicts individual differences in memory performance ability. *Hippocampus, 20*(3), 345–351. https://doi.org/10.1002/hipo.20771

Yonelinas, A. P., Widaman, K., Mungas, D., Reed, B., Weiner, M.W., & Chui, H.C. (2007). Memory in the aging brain: Doubly dissociating the contribution of the hippocampus and entorhinal cortex. *Hippocampus 17*, 1134-40.

Figure 1.

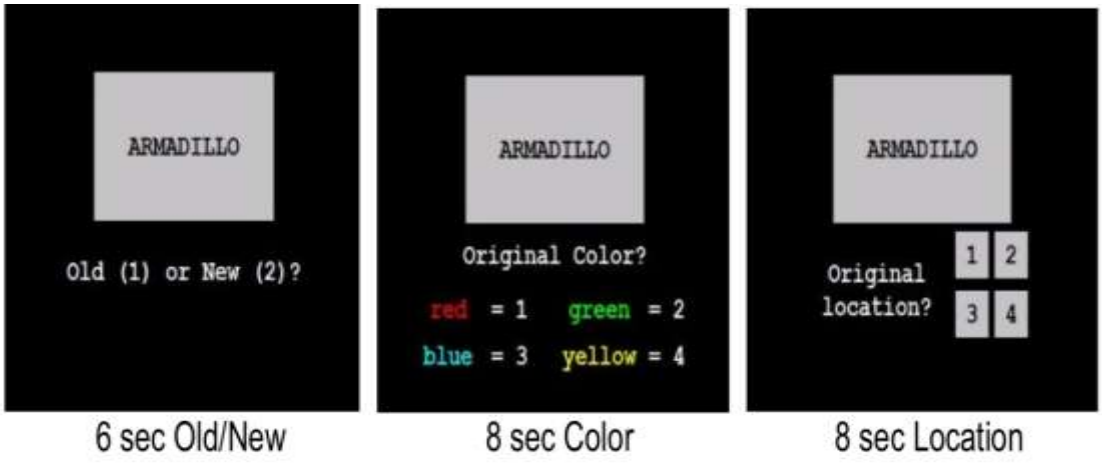
Paradigm for Encoding Trials



Note. Example encoding trials. Animacy decisions were used for colored words. Size decisions were used for black words. Fixation (not depicted) was a white cross-hair in the middle of a black screen.

Figure 2

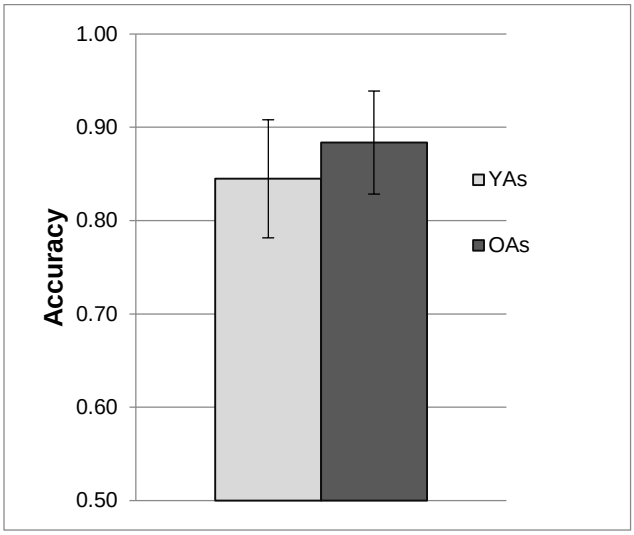
Paradigm for Testing Trials



Note. An example test sequence for an item that is deemed “old”

Figure 3

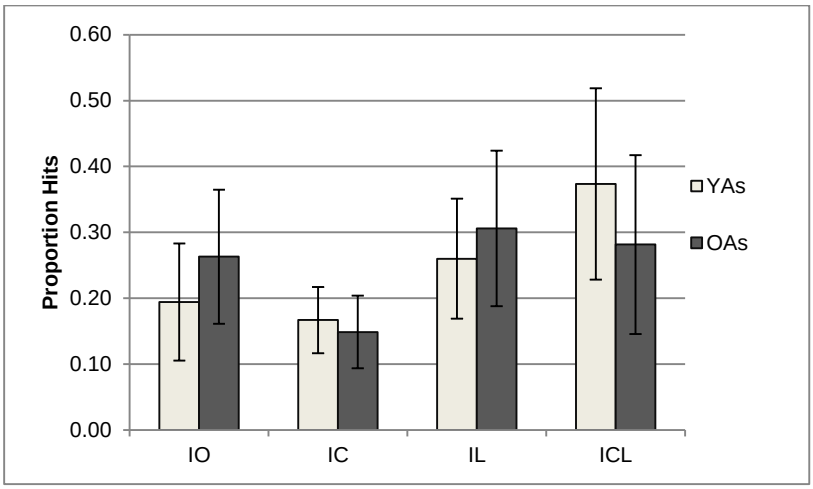
Old/New Recognition Accuracy



Note. Error bars reflect +/- 1 standard deviation. Results are based on a measure of proportion correct.

Figure 4

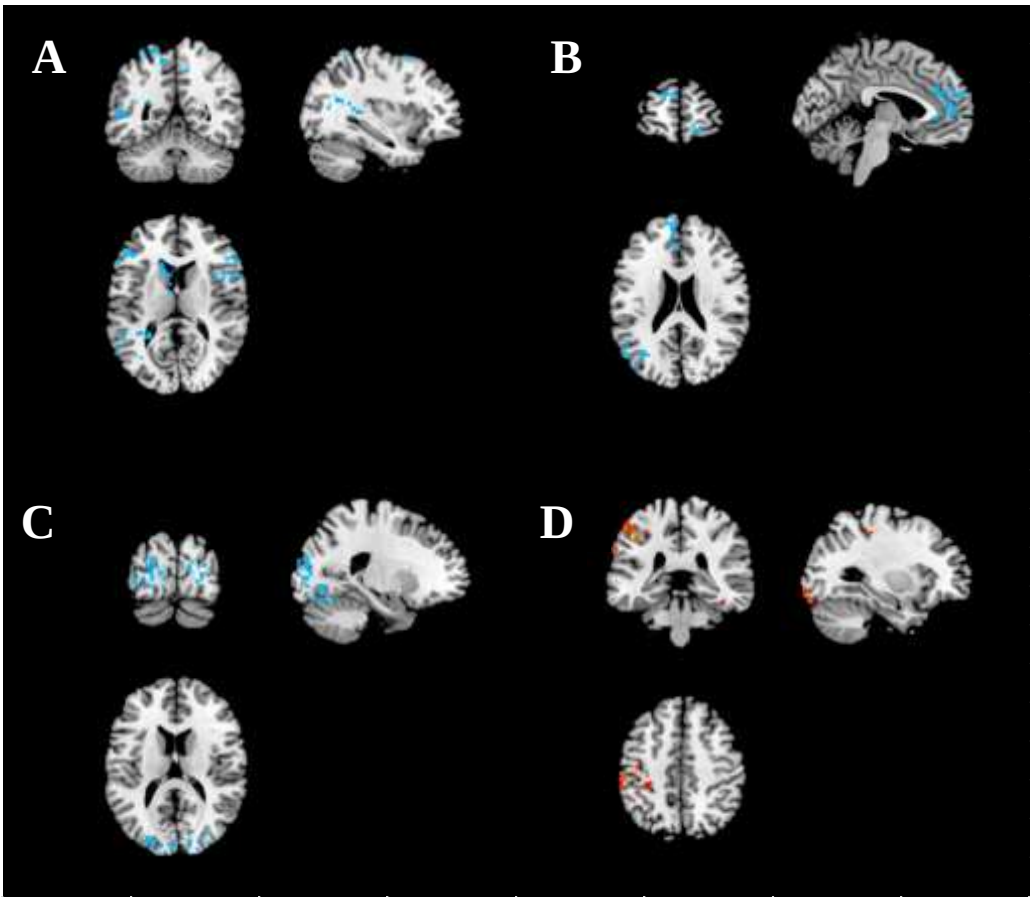
Proportion of Hit Types



Note. Error bars reflect +/- 1 standard deviation. IO = Item-Only, IC = Item+Color, IL = Item+Location, ICL = Item+Color+Location. Because these are proportions of all hits, the proportions add up to 1.00 for each subject. Therefore, more hits in one category necessitates less hits in another.

Figure 5

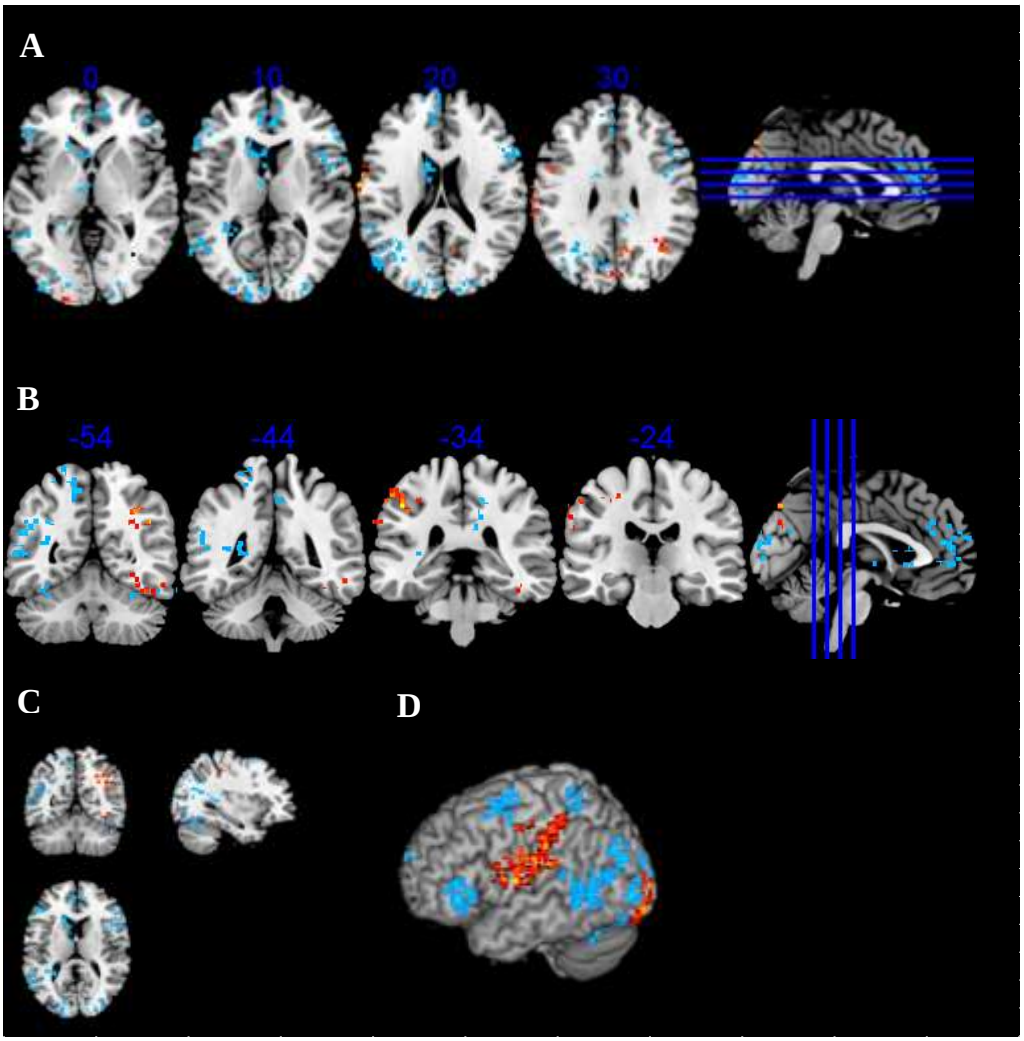
ROI to Voxel Connectivity for ICL Trials



*Note***.** ICL= item+color+location. Blue represents regions where young adult connectivity was significantly greater than older adult connectivity. Red represents regions where older adult connectivity was significantly greater than young adult connectivity. **A**) ICL connectivity from dorsal inferior frontal gyrus **B**) ICL connectivity from intraparietal sulcus **C**) ICL connectivity from precuneus **D**) ICL connectivity from the hippocampus (height threshold= $p<.05$; cluster threshold= $p<.05$)

Figure 6

Composite ROI to Voxel Connectivity for ICL Trials



*Note***.** ICL= item+color+location. Blue represents regions where young adult connectivity was significantly greater than older adult connectivity. Red represents regions where older adult connectivity was significantly greater than young adult connectivity. Connectivity displayed is ICL connectivity from each ROI overlaid on top of one another. **A)** Axial view of composite ICL connectivity from all ROIs **B)** Coronal view of composite ICL connectivity from all ROIs **C)** Axial, coronal, and sagittal view of composite ICL connectivity from all ROIs **D)** 3D view of composite left hemisphere ICL connectivity from all ROIs (height threshold= $p<.05$; cluster threshold= $p<.05$)

Table 1.

Participant Demographics

Group	Age	YoE	MMSE	Shipley	Digit span	LM Imm .	LM delay
YAs	21.29 (2.21)	14.60 (1.14)	29.6 (.7)	29.2 (5.4)	16.3 (2.4)	17.4 (3.2)	16.0 (2.5)
OAs	73.94 (7.02)	17.90 (1.64)	29.5 (.9)	34.7 (4.2)	16.7 (3.3)	16.2 (2.7)	15.4 (2.2)

Note. Means and standard deviations (in parentheses) for the young adult and older adult groups. YAs = Young Adults. OAs = Older Adults. YoE = Years of Education. MMSE = Mini-mental Status Exam. Shipley = Shipley Vocabulary Test. Digit Span = Digit Span subtest from the Wechsler Adult Intelligence Scale – Revised. LM Imm. = Logical Memory Immediate Recall subtest from the Wechsler Memory Scale – Revised. LM Delay = Logical Memory Delayed Recall from the Wechsler Memory Scale – Revised.

Table 2.

Differential ROI to Voxel Connectivity for IO Trials

Contrast	ROI	Anatomical region	X	Y	Z	Cluster size	pFWE
OA>YA	Dorsal Inferior Frontal Gyrus	left middle temporal	-58	-36	-2	220	0.0299
		right intermediate frontal (frontal eye fields)	22	20	50	246	0.0129

Note: IO= item only. YA= young adults. OA= older adults. ROI= region of interest. Cluster size refers to the number of significantly connected voxels found within a specified region. MNI Coordinates, cluster sizes of peak activations, and pFWE values are given for IO encoding connectivity between ROIs and voxel regions resulting from between-group contrasts of young and old.

Table 3.

Differential ROI to Voxel Connectivity for IC Trials

Contrast	ROI	Anatomical region	X	Y	Z	Cluster size	pFWE
YA>OA	Dorsal Inferior Frontal Gyrus	right opercular	42	22	18	780	<.0001
		right premotor cortex	0	-18	68	654	<.0001
		left primary sensory cortex	-42	-20	34	336	0.0006
		left ventral anterior cingulate	-8	-16	40	258	0.0068
		left temporopolar	-36	22	-30	216	0.027
		left primary motor cortex	-16	-32	70	192	0.0612
	Intraparietal Sulcus	left opercular	-44	8	16	282	0.0031
		right parahippocampus	34	-32	-16	187	0.0717
	Hippocampus	right aPFC	0	60	26	324	0.0008
		left angular	-52	-54	22	203	0.0393
		right dorsal posterior cingulate	6	-68	22	184	0.0759
		left prefrontal (orbitofrontal)	-2	54	-18	163	0.1579
OA>YA	Intraparietal Sulcus	left superior parietal	-28	-60	60	1124	<.0001
		right prefrontal (orbitofrontal)	6	42	-22	201	0.0443

Note: IC= item+color. YA= young adults. OA= older adults. ROI= region of interest. Cluster size refers to the number of significantly connected voxels found within a specified region. MNI Coordinates, cluster sizes of peak activations, and pFWE values are given for IC encoding connectivity between ROIs and voxel regions resulting from between-group contrasts of young and old.

Table 4.

Differential ROI to Voxel Connectivity for IL Trials

Contrast	ROI	Anatomical region	X	Y	Z	Cluster size	pFWE
YA>OA	Dorsal Inferior Frontal Gyrus	right caudate	10	20	6	359	0.0003
		right superior parietal	24	-70	46	344	0.0005
		left associative visual cortex	-58	-66	2	171	0.1302
	Intraparietal Sulcus	left angular	-50	-61	-12	300	0.0017
		right fusiform	26	-50	-14	289	0.0023
		right middle temporal	66	-30	-10	284	0.0027
	Precuneus	right fusiform	30	-64	-18	387	0.0002
OA>YA	Dorsal Inferior Frontal Gyrus	left angular	-36	-72	40	366	0.0003
		right angular	44	-48	32	227	0.0194
		left ventral posterior cingulate	-4	-56	12	203	0.0435
		left aPFC	-10	52	18	199	0.0499
		left middle temporal	-62	-32	-2	173	0.1216
		left intermediate frontal (frontal eye fields)	-22	22	44	158	0.2822
	Intraparietal Sulcus	left dorsal posterior cingulate	-14	-38	44	249	0.0084

Note: IL= item+location YA= young adults. OA= older adults. ROI= region of interest. Cluster size refers to the number of significantly connected voxels found within a specified region. MNI Coordinates, cluster sizes of peak activations, and pFWE values are given for IL encoding connectivity between ROIs and voxel regions resulting from between-group contrasts of young and old.

Table 5.

Differential ROI to Voxel Connectivity for ICL Trials

Contrast	ROI	Anatomical region	X	Y	Z	Cluster size	pFWE
YA>OA	Dorsal Inferior Frontal Gyrus	right premotor cortex +	42	0	32	470	<.0001
		left middle frontal +	-54	34	14	187	0.0693
		left associative visual cortex +	-14	-70	26	170	0.1253
		left premotor cortex +	-8	-6	62	164	0.1543
		left superior parietal	-6	-56	64	162	0.1653
	Intraparietal Sulcus	right aPFC +	14	60	-8	500	<.0001
		left superior parietal	-22	-66	40	263	0.0057
		left angular	-52	-54	24	228	0.0179
	Precuneus	right associative visual cortex +	24	-72	-16	262	0.0056
OA>YA	Hippocampus	left primary sensory cortex	-44	-18	50	542	<.0001
		right fusiform gyrus +	44	-48	-22	186	0.0698
		right associative visual cortex +	16	-64	34	185	0.0723
		left secondary visual cortex	-22	-92	-20	166	0.1405

Note: ICL= item+color+location. YA= young adults. OA= older adults. ROI= region of interest. Cluster size refers to the number of significantly connected voxels found within a specified region. MNI Coordinates, cluster sizes of peak activations, and pFWE values are given for ICL encoding connectivity between ROIs and voxel regions resulting from between-group contrasts of young and old.

+ denotes regions that coincide with the multifeatural encoding regions identified by James et al. (2019)

Table 6.

Differential ROI to Voxel Connectivity for MISS Trials

Contrast	ROI	Anatomical region	X	Y	Z	Cluster size	pFWE
YA>OA	Intraparietal Sulcus	left angular	-38	-74	40	164	0.1705
		right dorsolateral PFC	40	34	28	195	0.0593
		left intermediate frontal (frontal eye fields)	-4	38	32	605	<.0001
		left dorsolateral PFC	-34	28	38	162	0.1824
	Hippocampus	right dorsolateral PFC	4	62	28	338	0.0007
		left dorsal anterior cingulate	-2	44	14	266	0.0059
OA>YA	Dorsal Inferior Frontal Gyrus	left angular	-62	-46	30	295	0.0023
		right supramarginal	54	-28	18	429	0.0001
	Intraparietal Sulcus	right superior parietal	8	-48	68	248	0.0102
		left angular	-48	-42	36	171	0.1345
	Precuneus	right primary sensory cortex	6	-40	68	642	<.0001
		left supramarginal	-48	-42	48	200	0.0536

Note: YA= young adults. OA= older adults. ROI= region of interest. Cluster size refers to the number of significantly connected voxels found within a specified region. MNI Coordinates, cluster sizes of peak activations, and pFWE values are given for MISS encoding connectivity between ROIs and voxel regions resulting from between-group contrasts of young and old.