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The effect of age on relational encoding as revealed by hippocampal functional connectivity

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Abstract

The neural processes mediating cognition occur in networks distributed throughout the brain. The encoding and retrieval of relational memories, memories for multiple items or multifeatural events, is supported by a network of brain regions, particularly the hippocampus. The hippocampal coupling hypothesis suggests that the hippocampus is functionally connected with the default mode network (DMN) during retrieval, but during encoding, decouples from the DMN. Based on prior research suggesting that older adults are less able to modulate between brain network states, we tested the hypothesis that older adults' hippocampus would show functional connectivity with the DMN during relational encoding. The results suggest that, while the hippocampus is functionally connected to some regions of the DMN during relational encoding in both younger and older adults, older adults show additional DMN connectivity. Such age-related changes in network modulation appear not to be mediated by compensatory processes, but rather to reflect a form of neural inefficiency, most likely due to reduced inhibition.

1. INTRODUCTION

In recent years, the field of cognitive neuroscience has moved toward describing functional activity within the brain in terms of neural networks, as opposed to regional activations. While several networks supporting task-oriented cognitive processes have been described (Van den Heuvel & Hulshoff, 2010), one large-scale network, the default-mode network (DMN), has become the focus of a substantial amount of research (e.g., Ferreira & Busatto, 2013; Fox et al., 2005; Raichle et al., 2001). Correlated activity between brain regions within the DMN occurs when one's thoughts are internally driven (Andrews-Hanna, Smallwood, & Spreng, 2014a), such as during wakeful rest (Fox et al., 2005; Raichle et al., 2001), episodic retrieval and autobiographical memory (Addis, Wong, & Schacter, 2007; Andrews-Hanna, Saxe, & Yarkoni, 2014b), and during mind wandering or introspection (Mevel, Chételat, Eustache, & Desgranges, 2011). Neural components of the DMN include the posterior

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cingulate cortex (PCC)/precuneus, medial prefrontal cortex (MPFC), bilateral angular gyri, and the medial temporal lobes, including the hippocampus (for review see Andrews-Hanna et al., 2014a; Ferreira & Busatto, 2013; Mevel et al., 2011).

More recently, the hippocampal coupling hypothesis (HCH) proposes that the hippocampus is functionally connected with the DMN during episodic memory retrieval; however, it decouples from the DMN during episodic memory encoding (Huijbers, Pennartz, Cabeza, & Daselaar, 2011). The hippocampus contributes to the DMN primarily via its engagement in the retrieval of episodic memories, which is in line with its purported role in introspection or mind wandering (Mevel et al., 2011). Introspection requires mental time travel, theory of mind, and the construction of future and past events, all of which involve the hippocampally-mediated retrieval of episodes (Addis et al., 2007). The hippocampus is also posited to decouple from the DMN during encoding because of its role in the storage and processing of episodic memories, a largely externally oriented task (Huijbers et al., 2011).

The status of the DMN, as well as its relationship with other large-scale brain networks, has been the focus of several investigations of clinical samples, including Autism (Cherkassky, Kana, Keller, & Just, 2006; Courchesne & Pierce, 2005), Schizophrenia (Garrity et al., 2007), and others (Broyd et al., 2009). In addition to clinical populations, healthy aging has also been shown to lead to alterations in the strength of connections within neural networks (Geerligs, Maurits, Renken, & Lorist, 2014; Grady et al., 2010; Lustig et al., 2003; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Salami, Pudas, & Nyberg, 2014), the composition of networks (Andrews-Hanna et al., 2007; Geerligs et al., 2014; Grady et al., 2010; Lustig et al., 2003; Persson et al., 2007; Salami et al., 2014), and the modulation between network states (Grady et al., 2006; Grady et al., 2010; Salami et al.,2014; Sambataro et al., 2010; Sambataro et al., 2012). For example, Salami et al. (2014) examined the influence of age on hippocampal connectivity during relational encoding and separately during resting-state. To do so, they compared hippocampal functional connectivity to anterior and posterior DMN regions during rest, as well as connectivity between hippocampi during encoding. Their results showed that OAs exhibit reduced connectivity between the hippocampus and cortical portions of the DMN during rest and increased inter-hippocampal connectivity during task and rest. Their results also showed that the aberrant patterns of connectivity correlated with episodic memory performance. That is, as the hippocampus became less connected to the DMN and more connected to itself, memory performance declined. Further, Grady et al. (2010), using several different cognitive tasks, reported that OAs exhibited weaker MPFC connectivity to posterior DMN regions as compared to younger adults (YAs), suggesting that the strength of long-range connections decreases with age. Grady et al. (2010) also observed that OAs tended to deactivate several DMN regions, including the parahippocampal gyrus and precuneus, to a lesser extent than YAs during working memory tasks (i.e., OAs showed greater activity in DMN regions during task), indicating that OAs are less able to modulate between the two networks. Given that the HCH suggests that the hippocampus should be decoupled from the DMN during encoding, and that prior studies have demonstrated that OAs are less able to modulate between different networks, the primary goal of the current study was to examine whether OAs show evidence of less decoupling of the hippocampus from the DMN during a relational encoding task.

Prior behavioral research centered on age-related memory differences has typically focused on relational or source memory, as this type of memory exhibits greater age-related reductions than memory for single items (for review, see Spencer & Raz, 1995; Old & Naveh-Benjamin, 2008). Relational encoding requires the binding of multiple items, or multiple features of an item, into a single memory trace for later recall. Prominent theories about relational encoding suggest that the "features" of the item are initially processed in the cortex, but are then bound into a single trace through processing via the hippocampus (Alvarez and Squire, 1994; Eichenbaum, 1992; Norman & O'Reilly, 2003). Encoding an array of features more closely mimics the type of episodic memory that occurs in day-to-day life. For example, it is less common that we need to remember lists of unrelated words; however, needing to remember on what parking garage level you parked your car, or the building, floor, and room number of a meeting (i.e., multiple features of a single event), is a comparatively more common mnemonic experience. As such, investigating the interaction between functional networks and relational memory processes offers important insights into the neural processing mechanisms that underlie memory changes due to aging.

Several studies have assessed functional connectivity associated with the encoding and retrieval of relational memories (e.g., Fornito, Harrison, Zalesky, & Simons, 2012; Ritchey, Yonelinas, & Ranganath, 2014); however, far fewer studies have specifically investigated hippocampal functional connectivity associated with age and relational memory (e.g., Grady, McIntosh, & Craik, 2003; Oh & Jaugst, 2013; Salami et al., 2014). The results of these studies primarily show increased connectivity with MTL regions and frontal regions during encoding; however, such studies also tend to find increased connectivity with regions of the parietal lobe, precuneus/cuneus, and between the left and right hippocampi (Grady, McIntosh, & Craik, 2003; Oh & Jaugst, 2013; Salami et al., 2014). While the results from these prior studies have been critical for building an understanding of how the hippocampus interacts with the rest of the brain to support mnemonic processes, only Salami et al. (2014) directly relate their results to established networks in the brain (e.g., the DMN). However, hippocampal connectivity to the DMN during the cognitive task was not assessed. Moreover, studies investigating functional networks that include the hippocampus have not used an encoding task to assess whether OAs show decoupling of the hippocampus from the DMN to a similar degree as YAs during encoding.

The current study also sought to address specific interpretational weaknesses that exist in the prior literature. To our knowledge, no prior study has matched all aspects of behavioral performance on the in-scanner cognitive task between OAs and YAs. Matching behavioral performance during a task enhances the ability to interpret neural differences (for a detailed discussion of these ideas see Morcom, Good, Frackowiak, & Rugg, 2003 and Snyder et al., 2011). In brief, the interpretation of neural differences when group differences in behavior exist may be hampered by differences in memory strength, memory quality, effort, motivation, uncertainty, or strategy. As such, we took several steps to equate performance on the memory tasks given to YAs and OAs. Additionally, we utilized a beta-series correlation analysis (Rissman, Gazzaley, & D'Esposito, 2004). One strength of this type of analysis is the ability to capture specific stages of a cognitive task. In the context of the current study, we isolated hippocampal functional connectivity associated with relational encoding as

compared to the semantic judgment used to orient participants to the to-be-encoded materials.

Based on prior research suggesting that OAs are less able to modulate between network states, and that OAs tend to perform worse on relational memory tasks, the current study sought to investigate whether connectivity between the hippocampus and other neural structures would be altered by age during a relational encoding task. More specifically, we tested the hypothesis that OAs, as compared to YAs, would exhibit greater hippocampal connectivity to regions associated with the DMN. Since the hippocampus is a critical component of memory encoding and retrieval, understanding how aging impacts hippocampal functional connectivity will improve our understanding of the potential causes of relational memory changes associated with age.

2. MATERIALS AND METHODS

2.1 PARTICIPANTS

Participants for this study included 14 YAs and 13 OAs who were right handed, native English speakers, had normal or corrected-to-normal vision, and no history of neurological or psychological illness. All participants provided written informed consent and were paid for their participation. Older adults were also screened for dementia with a neuropsychological test battery (see Table 1). Three YAs and 2 OAs were excluded from the analysis due to at-chance performance, perfect performance, or excessive motion. Experimental procedures were approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

2.2 STIMULI

To assess relational encoding, the current study utilized a paradigm similar to that of Uncapher, Otten, and Rugg (2006). In this paradigm, participants encode a word presented in one of four colors (red, green, blue, yellow) and in one of four locations (top left, top right, bottom left, bottom right) on a computer screen. Two hundred and eighty eight nouns, 4–9 letters long, were obtained from the MRC Psycholinguistic Database (http://websites.psychology.uwa.edu.au/school/MRCDatabase/uwa_mrc.htm; Wilson, 1988). Nouns had a written frequency of 1–30 counts per million and a concreteness rating greater than 350 (Kucera-Francis, 1967). Eight of the words were used as primacy items and not included in any analyses. The rest of the words were divided equally to create 4 categories, animate and smaller than a shoebox, animate and larger than a shoebox, inanimate and smaller than a shoebox, and inanimate and larger than a shoebox. Fourteen lists of 20 items (5 in each of the previously mentioned categories) were created. Two lists were used as a practice for each subject. Fifteen words were randomly chosen as targets and 8 as lures to match the target lure ratio during the actual experiment. Of the remaining 12 lists, each subject received 8 as study lists and 4 acted as lures for the memory test. Within each list, 4 of the items were not presented in color to act as “filler” items. This was done because the original study by Uncapher et al. (2006) found filler items were needed to improve performance of color memory. Essentially, when the only semantic judgment was animacy, and all of the words were presented in color, memory for the color feature was close to floor.

The assignment of lists to each condition and run number was counterbalanced across subjects. Within a single study phase (2 lists), participants saw 40 words that equally represented each color and location. Across runs, color and location were also equally divided among the 4 categories of word types (i.e., animate and smaller than a shoebox, etc.). The memory test consisted of the 32 colored words and the 2 primacy items presented at study, as well as 20 items from the list of lures. Items on a test were presented in a random order.

2.3 PROCEDURE

Several strategies were implemented to aid in matching behavioral performance between the YA and OA groups. First, all participants were given 4 study-test runs in which each study-test run was made up of unique items. Each non-scanned test session occurred immediately after the corresponding scanned encoding run. Second, each item was presented for 6 seconds, in contrast to the 3-second rate used by Uncapher et al. (2006). Third, YAs were given 4 minutes of math problems between study and test whereas OAs were tested immediately after the study portion completed. To ensure participants maintained focus on the task, they were given two orienting tasks; participants either made animate/inanimate judgements or decided whether the item was larger than a shoebox. Older adults were coached not to dwell on the initial semantic judgment, but to make that decision quickly and then focus on encoding the material. During pilot testing, we observed that older adults spent more time on this task than young adults, impacting the time they had to study the features associated with each item. Since semantic judgments about a single word require different cognitive operations than does encoding a multifeatural event, we strove to ensure that both OAs and YAs spent similar amounts of time on each portion of the task.

Participants were instructed to encode each word along with its color and location to the best of their ability; however, they were told that they did not need to remember words presented in black. For words presented in color, participants made animacy judgments. For words presented in black, participants made size judgments. A reminder prompt for the judgment was presented on each trial at the bottom of the screen. Participants were also told that there would occasionally be screens where no words would be presented in the boxes and that no response was needed for these trials. All responses were collected with using a 5 button MR compatible response box (only the first two buttons were used for the encoding decisions). Trials lasted 6 seconds. The word was presented for 5.5 sec and displaced with a fixation cross for 500 msec.

At test, participants made “old”/”new” judgments to words presented one at a time for a maximum of 6 seconds. If participants indicated a word was “old,” they were then prompted to indicate in which color the word was presented and then in which location it was presented. A maximum of 8 seconds was given to make each color and location judgment. They were always asked in the same order, color then location, and the key corresponding to each option was indicated at the bottom of the screen (i.e., key 1 corresponds to red, etc.). If participants responded “new,” the next word was presented. Participants were told to make their best guess if they were unsure of the correct answer. A brief 2 minute break was given after each test phase.

While it is typical to collect resting state images before a task, we opted to collect resting state images after the task. The goal of this design was to reduce the delay between instruction and practice for the task and engagement in the in-scanner task. Although Groen, Sokolov, Jonas, Roebling, & Spitzer (2011) showed evidence that post-learning resting state data can be influenced by the preceding cognitive task, Grady et al. (2010) were able to extract the core components of the DMN even during fixations that were interspersed between tasks. This suggests that the key components of the DMN are robust even when collected after a task has been administered. For resting state data collection, participants were informed the task was over and that image collection would continue for approximately 5 minutes. They were given no specific instructions and presented with a blank screen for the duration of the scan.

2.4 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°). Slice acquisition was also oriented along the long axis of the hippocampi according to each subject's anatomical scan to improve signal from this region. The functional data were acquired in 4 sessions ranging from 190 to 192 volumes each. 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 stochastic design. Because scanning only took place during encoding, only the study phase sequences of each run were generated using Opt Seq 2. Null events were trials in which no words appeared on the screen; only the grey squares that, during encoding trials, contained words. All null events were a multiple of the TR (either 3 or 6 sec), with 50% of the null events lasting for 3 secs. Resting state images were collected with a T2-weighted EPI sequence and slices were acquired in a bottom-up interleaved manner (TR = 2000 msec, TE = 32 msec, voxel size = $4mm^3$, flip angle = 80°). Acquisition time was 5 minutes and 6 seconds.

2.5 IMAGE PROCESSING

Standard preprocessing procedures were used for both resting state and task based connectivity analyses. This included discarding the first two functional scans to allow for

scanner equilibrium, slice-time correction, rigid-body motion correction and unwarping, spatial normalization to the EPI template of the Montreal Neurological Institute (MNI) defined standardized brain space, and finally, images were smoothed with an 8mm FWHM Gaussian kernel. For task related functional scans a high-pass filter was used with a cutoff of 128. For resting state functional scans a band pass filter attenuated frequencies above .1 and below .01 Hz. We also segmented each participant's brain into white matter, cerebrospinal fluid (CSF), and grey matter, and used the white matter and CSF masks to extract an average signal from each volume across all scans in a functional run. The white matter and CSF signals were then used as regressors of no interest in the individual analysis to control for any signal coming from these regions. To ensure voxels used in the mask were within their respective tissue class, a binary mask was created from the segmented files using a cutoff of .95 (i.e., a 95% probability that the mask contains the correct tissue type).

2.6 TASK ANALYSIS

Due to the nature of the encoding task, participants were engaged in the semantic judgment (e.g., animacy or size) during the first half of the encoding trial, after which they focused on encoding all of the features of the item. Based on the similar reaction times between the two groups and the fact that almost all reaction times to the semantic judgment occurred before the first 3 seconds of the encoding trial, each trial type was modeled as a stick function starting 3 seconds after the initial presentation of the stimulus. This approach afforded the opportunity to more accurately model relational encoding processes, as opposed to processes associated with making the semantic judgments. To assess whole brain functional connectivity we implemented a beta-series correlation analysis (Rissman, Gazzaley, & D'Esposito, 2004). In this analysis, each event is modeled as an individual regressor within the general linear model (i.e., beta value) and then sorted into the appropriate trial types (i.e., beta series). The degree to which two voxels' beta series correlate within a certain trial type is the degree to which they are functionally connected. We implemented this strategy within Statistical Parametric Mapping 8 (SPM 8, Wellcome Department of Cognitive Neurology, London) operating within Matlab (Matlab Mathwork, Inc., Natick, MA).

For the beta series correlation analysis a seed region was chosen that has been shown to be equivalently activated by both OAs and YAs during a similar encoding task (Morcom et al., 2003). A 6mm sphere (chosen because it fit within the confines of the hippocampus) centered in the anterior portion of the left hippocampus (Talairach coordinates: xyz, -30, -15, -15) was used as the seed of interest. At the fixed effects level, each trial was modeled as an individual regressor within the GLM framework along with several regressors of no interest. Regressors of no interest included six parameters for motion, one parameter for white matter signal and one for CSF signal. Due to the low number of misses, incorrect trials were also modeled but not included in the final analysis. The beta estimate for each correct trial was then sorted into either item only (IO; i.e., only the word was remembered but no other details), item and color (IC; i.e., both the word and the color in which it was presented were remembered, but not the location), item and location (IL; i.e., both the word and the location were remembered but not the color), or item, color, and location (ICL; i.e., the item and both of its features were remembered). A correlation was then calculated for each condition between the hippocampal ROI and every other voxel in the brain. For statistical

interpretation, correlation values were transformed to *z* scores using an arc-hyperbolic tangent transform (Fisher, 1921) divided by its known standard deviation ($1/\sqrt{N-3}$), N being the number of data points in the correlation).

Each participant's condition specific *z*-maps were then entered into a second level analysis. Unless otherwise noted, significance thresholds were determined using a cluster-wise approach for correction of multiple comparisons. Monte Carlo simulations (10,000 iterations) conducted within AFNI's 3dClustSim were used to determine a combined voxel wise and cluster extent threshold to produce an α of .05. To explore overall group similarities in whole brain hippocampal functional connectivity, we conducted a conjunction analysis collapsing across all levels of trial type. A one sample t-test was conducted for OAs ($p < .005$ uncorrected, cluster extent $k = 158$). The results of this test were used as an inclusive mask for the same one sample t-test in YAs ($p < .005$, cluster extent $k = 80$). For group differences, a 2 (Group: OA and YA) x 4 (Trial type: IO, IC, IL, ICL) full factorial analysis of variance (ANOVA) conducted in SPM 8 was used to assess whole brain hippocampal functional connectivity. Group was a between- subjects factor that assumed independence bot not equal variance. Trial type was a within- subjects factor that did not assume independence of measurements or equal variance ($p < .005$ uncorrected, cluster extent $k = 158$). For all analyses, peak voxels were identified using the Talairach atlas. Regions within clusters were identified using the Talairach Daemon atlas within the WFU Pickatlas (Lancaster, Summerln, Rainey, Freitas, & Fox, 1997; Lancaster et al., 2000; Madjian, Laurienti, Kraft, & Burdette, 2003; Maldjian, Laurienti, & Burdette, 2004).

2.7 RESTING STATE ANALYSIS

The analysis of resting state data was conducted using the CONN functional connectivity toolbox (Whitfield-Gabrieli, & Nieto-Castanon, 2012; http://www.nitrc.org/projects/conn). For the resting state data we included the additional steps of despiking and included a linear detrending term in the model. Again, white matter signal, CSF signal, and motion parameters were entered as regressors of no interest in the analysis. The entire time series was modeled as a single block with a boxcar function that began with the first scan. The posterior cingulate cortex (PCC) was used as a seed to obtain a default mode network for each group (Fox et al., 2005). At the fixed effects level a semi-partial correlation was calculated between each voxel in the brain and the PCC. A default mode network mask was created for each group and within all participants using a threshold for significant voxels of $p < .005$ (uncorrected). Cluster thresholds were determined for each result using an FDR-correction (YAs $k = 174$; OAs $k = 143$; OA > YA $k = 321$; YA > OA $k = 274$; all participants $k = 185$).

3. RESULTS

3.1 BEHAVIORAL RESULTS

3.1.1. OLD/NEW RECOGNITION—Due to the nature of the recognition test, the target items greatly outnumbered the lures. It is recommended in these conditions to use proportion correct instead of hits-minus-false-alarms (Macmillan & Creelman, 2005). Proportion correct was computed by taking the sum of hits and correct rejections and dividing by the

number of test trials. Primacy items were omitted from this calculation. An average of this value was computed from all 4 runs of each participant. A comparison of recognition performance between the old and young found no significant difference, $t(20) = 1.537$, $p = .14$ (See Table 1). Therefore item recognition did not differ between young and old. Hit rates exceeded false alarm rates for both age groups. For older adults, hit and false alarm rates were .83(.09) and .03(.04), respectively. For young adults, hit and false alarm rates were .77(.10) and .03(.02), respectively.

3.1.2. FEATURE MEMORY—The analysis of feature memory was based on the proportions of hit types: Item-Only (IO), Item and Color (IC), Item and Location (IL), or Item-Color-Location (ICL). Feature memory was analyzed with a 2x4 (Age by Hit Type) mixed factorial ANOVA (see Table 1). There was no main effect of Age ($F < 1$) and no Age by Hit Type interaction, $F(1.77, 35.41) = 2.005$, MSE = .048, $p = .154$. There was a significant main effect of Hit Type, $F(1.77, 35.41) = 8.254$, MSE = .199, $p = .002$, $\eta_p^2 = .292$. A test of the least significant difference revealed that the proportion of IC hits was the lowest of the hit types, followed by IO hits. Highest were the proportions of IL and ICL hits; and these did not significantly differ. Therefore, feature memory did not differ between young and old.

3.2 CONNECTIVITY RESULTS

3.2.1 CONJUNCTION ANALYSIS–TASK-BASED CONNECTIVITY—The conjunction analysis revealed a widespread set of regions that were functionally connected to the hippocampus, including the bilateral hippocampus (in the conjunction contrast the seed region is correlated with itself; however, a large cluster extending throughout both hippocampi was significant), bilateral parahippocampal gyrus, bilateral middle temporal gyrus, bilateral superior temporal gyrus, left inferior temporal gyrus, bilateral fusiform gyrus, bilateral insula, bilateral Precuneus, left posterior cingulate, and left inferior parietal lobule (see Fig. 1 and Table 2).

3.2.2 ANOVA–TASK-BASED CONNECTIVITY—The results of the 2 x 4 ANOVA revealed a main effect of age on hippocampal functional connectivity, but no main effect of trial type and no significant interaction between age and trial type. To follow up on the main effect of age, we contrasted YAs greater than OAs and OAs greater than YAs to investigate how hippocampal connectivity was altered by age (see Fig. 2). Young adults showed greater hippocampal connectivity in two clusters: one cluster contained the putamen and caudate, and the other contained portions of the precentral gyrus and right middle frontal gyrus. Older adults also showed several clusters with greater hippocampal functional connectivity including the right precuneus, bilateral posterior cingulate, bilateral cuneus, and bilateral middle and superior temporal gyrus (see Table 2).

3.2.3 DEFAULT MODE NETWORK—The resting state analysis revealed 7 clusters that were significantly correlated with the PCC in YAs. One was centered in the PCC, two were centered within the MPFC, two occurred bilaterally along the middle temporal gyrus, and two were centered bilaterally in the angular gyrus (see Fig. 3). For OAs, 6 clusters were significantly correlated with the PCC including one large cluster that contained the PCC,

bilateral angular and supramarginal gyri, and the left middle temporal gyrus. Another cluster centered in the anterior cingulate gyrus, two centered bilaterally in the posterior middle temporal gyrus, and two centered in the middle/superior frontal and frontal pole. We also included all participants as a single group to calculate a "canonical" DMN. In this case, all the core components of the DMN were found including the PCC/precuneus, bilateral angular gyrus, medial prefrontal cortex, and hippocampus (see Fig 3). The canonical DMN was used as a mask to investigate whether group differences in task based activation occurred within the DMN.

To examine age-related changes in DMN, two contrasts were calculated, one for YAs greater than OAs and one for OAs greater than YAs. YAs showed significantly greater correlations to the PCC primarily in the MPFC; however, they also showed greater connectivity within the left temporal pole and the left middle frontal gyrus. OAs showed significantly greater connectivity in a cluster that included the bilateral anterior cingulate gyrus and bilateral superior frontal gyrus, as well as bilaterally in the supramarginal gyrus, bilaterally in the middle frontal gyrus, and in the right insula.

3.2.4 TASK-BASED CONNECTIVITY vs. DEFAULT MODE NETWORK—To assess whether OAs were more likely to show hippocampal functional connectivity with the DMN as compared to YAs, we masked the results of each task-based group effect (i.e., YA > OA and OA > YA) with the canonical DMN. Neither group revealed significant clusters within the DMN using a threshold of $p < .005$ (uncorrected) and cluster extents calculated with 3dClustSim. Older adults, however, exhibited several regions in the task-based group contrast that are typically related to the DMN. To investigate this result further, we used a stringent, but slightly relaxed threshold ($p < .005$, cluster extent $k = 10$; for more information, see Lieberman & Cunningham, 2009) and found several regions only within the OAs' DMN that were functionally connected to the hippocampus during task. These clusters included the left precuneus and right cuneus, as well as the left middle temporal gyrus, and right superior temporal gyrus (see Fig. 2 and Table 2). The same analysis was also conducted using the DMNs defined by each group and the same pattern of results were found.

3.2.5 CORRELATIONS WITH BEHAVIOR—Several approaches were taken to understand how changes in hippocampal connectivity relate to behavior. First, we used a mask created from the canonical DMN to calculate an average z score within the mask for each individual during the task. We then took an average across trial types and correlated each individual's average z score with their old/new recognition accuracy. No significant relationship was found between task-based hippocampal connectivity within regions in the DMN and old/new recognition accuracy, $r(20) = -.11$, $p = .63$. To further examine possible relationships between task based hippocampal connectivity in each group's DMN activity, we correlated each individual's average z score by trial type with the percent correct for each trial type. Again, no significant correlations were found, all p's > .1.

A similar logic was used to investigate relationships between regions in OAs' DMN connectivity that were uniquely connected to the hippocampus. A mask was created of these regions and average z scores were obtained from these masks both across all trial types and

within each trial type. No significant correlations were observed between old/new recognition accuracy and average *z* scores collapsed across trial type, $r(9) = .25$, $p = .46$. Again, no significant correlations were obtained within each trial type; however, the strongest relationship found was between the ICL number correct and average *z* scores, $r(9) = -.47$, $p = .14$.

4. DISCUSSION

The primary goal of the study was to determine whether OAs show differential hippocampal connectivity to the DMN during relational encoding. According to the HCH, the hippocampus is functionally connected to the DMN during rest because it supports retrieval; however, during encoding, the hippocampus decouples from the DMN to support externally driven encoding processes (Huijbers et al., 2011). Our results suggest that OAs exhibit increased hippocampal connectivity to the DMN during relational encoding. Another goal of the study was to equate performance between OAs and YAs. Using a delay for YAs and training OAs on the importance of encoding the materials instead of focusing on the semantic decision, we were able to match both groups on all aspects of behavior during the task. We also used a seed region that has been shown to be equally activated by both groups during a very similar task. This choice was made to reduce potential biases in the analysis that may come from choosing a seed region which is already differentially utilized by each group. Therefore, changes in hippocampal functional connectivity are not due to effort, strength or quality of the memory trace, or hypothesized differences in the seed region, but instead are due to core changes in mnemonic encoding processes carried out in the brain.

During encoding, both groups exhibited hippocampal connectivity to a widespread set of regions. Several of these connected regions match well with a prior activation study using a similar paradigm, including the bilateral hippocampus/parahippocampal gyrus, bilateral middle temporal gyrus, left superior temporal gyrus, left inferior temporal gyrus, left fusiform gyrus and right insula (Morcom et al., 2003). Several meta-analyses of encoding effects have also found similar regions of activation including the medial temporal lobes, superior/middle temporal gyri, and fusiform gyrus (Cabeza & Nyberg, 2000; Kim, 2011). The fact that both OAs and YAs maintained a robust network of regions functionally connected to the hippocampus during encoding suggests that, to a large extent, a relational encoding network exists that is unaltered by age under conditions of equivalent behavioral performance between young and older adults.

The lack of a significant main effect of trial type and interaction between trial type and age in the imaging data suggests that OAs and YAs were consistently engaged in encoding the materials throughout the task. In the literature it is often found that as task difficulty increases, DMN activity decreases (e.g., McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Persson et al., 2007). If memory success were related to effort on individual trials, then we would expect a main effect of trial type or interaction with trial type and age as the DMN was modulated across different levels of feature encoding.

Several regions typically associated with the DMN were functionally connected with the hippocampus during encoding, including the precuneus and left posterior cingulate (Mevel

et al., 2011). These regions are thought to be hub regions for the DMN and have been shown to exhibit subsequent forgetting effects (i.e., increased activity for later forgotten items; Kim, 2011). It is difficult to specify why these regions are functionally connected to the hippocampus during relational encoding; however, these hub regions of the DMN may be important for some aspects of encoding. For example, it is likely that as a potential encoding strategy, participants retrieved either semantic or episodic memories to aid in encoding. While no specific instructions were given as to an encoding strategy, participants have been found to spontaneously employ elaborative strategies to aid in encoding (McDaniel & Kearney, 1984). It has also been shown when using a paradigm that requires a many-to-one mapping, in this case items (words) to repeated features (color and location), OAs and YAs do not differ in mediator-based encoding strategies which includes interactive imagery (Kuhlman & Touron, 2012).

Forming images may have been particularly useful in the current paradigm as a way to incorporate all aspects of the stimulus into a single mnemonic event. Addis et al. (2007) have shown that the posterior cingulate, precuneus, and left hippocampus are important for the construction of imaginative episodes. Further, while Kim (2011) found subsequent forgetting effects in the precuneus, the precuneus was also shown to be active during associative pictorial memory. Activation studies may generally be hampered from finding similar results as spontaneous strategy use, while somewhat consistent within individuals, often changes throughout the course of a study (McDaniel & Kearney, 1984). Therefore, simply looking at which parts of the brain are most active at encoding may average out this activity (however, see Uncapher et al. (2006) for a similar result). Since we used the left hippocampus as a seed to investigate functional connectivity, we are at a distinct advantage to find correlated activity in these regions.

Despite both OAs and YAs exhibiting a similar functionally connected network during encoding, there were distinct group differences. Younger adults demonstrated unique hippocampal connectivity to two clusters. One such connection included the putamen and caudate, while the other included the right middle frontal gyrus and precentral gyrus. The latter connection is typically associated with the dorsal attention network and likely represents YAs' ability to efficiently recruit neural regions associated with externally oriented and goal-directed behavior (Fox et al., 2005; Grady et al., 2010). The caudate and putamen have also been implicated in learning and memory and maintain strong anatomical connections to the hippocampus, as well as anterior portions of the frontal lobe. Activity in basal ganglia regions is typically related to statistical learning (Seger & Cincotta, 2005). For the present study, it is important to note that neither of these clusters fell within the YAs' group-defined DMN, suggesting that YAs are able to modulate efficiently between task and resting states (Grady et al., 2006; Grady et al., 2010; Sambataro et al., 2010; Sambataro et al., 2012).

Older adults also showed several clusters with greater hippocampal functional connectivity including the right precuneus, bilateral posterior cingulate, bilateral cuneus, and bilateral middle and superior temporal gyrus. In line with past research, we suggest that these additional connections within OAs' DMN represent an inability to efficiently modulate between network states (Grady et al., 2006; Grady et al., 2010; Sambataro et al., 2010;

Sambataro et al., 2012). It will be important for future research to elucidate exactly why OAs show altered modulation between network states; however, it has been proposed that altered modulation may be due to compensatory processes associated with reductions in binding, reduced inhibitory processes in these regions, or a failure to divert attention away from internal states (Lustig et al., 2003; Persson et al., 2007). If altered network modulation in OAs was compensatory, positive correlations between behavioral performance and increased DMN connectivity would be expected. If altered network modulation in OAs was related to reduced inhibitory processes or due to attentional differences, negative correlations would be expected. Despite the fact that no significant behavioral correlations were found, the additional DMN recruitment is not likely due to attentional differences at encoding for two reasons. First, one strength of a beta-series correlation analysis is the ability to model and capture distinct stages of a cognitive operation (Rissman et al., 2004). Older adults' greater hippocampal connectivity to the DMN was observed during the moment of encoding and while attention was focused on the presented materials. Secondly, OAs' greater connectivity to the DMN occurred in the absence of behavioral differences. This result suggests that the two groups were attending to the goals of the task to a similar extent. Therefore, it is unlikely that the increased DMN activity was caused by an internally focused state.

Based on our findings, it is difficult to determine whether the increased DMN connectivity in OAs represents a compensatory process or whether it is a form of neural inefficiency reflecting reduced inhibitory processes. Younger adults exhibit connectivity to key regions of the dorsal attention network while OAs do not, and OAs exhibit increased connectivity to DMN regions where YAs do not. It is possible that OAs' increased DMN connectivity compensates for the reduced connectivity to the dorsal attention network; however, it is also possible that increased DMN connectivity impairs the ability to recruit the dorsal attention network. The inability to support one of these options is a limitation in the current study, but prior work has provided evidence that increased activity in OAs' DMN connectivity during tasks tends to relate to worse performance (Grady et al., 2010; Persson et al., 2007). The altered modulation between network states in OAs is, therefore, likely caused by reduced inhibitory processes or some other form of neural inefficiency.

Although we have concluded that OAs exhibit greater hippocampal connectivity to the DMN during encoding in the absence of behavioral differences, there are several limitations to the current study. First, this study used a relatively small sample size. Despite the small sample size, we were able to replicate several findings that have been consistently found in the literature. For example, our conjunction analysis revealed regions functionally connected to the hippocampus that have been reported in prior research including the medial and lateral temporal lobes, fusiform gyrus, and insula (Cabeza & Nyberg, 2000; Kim, 2011; Morcom et al., 2003). The analysis also revealed the key regions reported in prior studies examining the DMN. Second, in the behavioral data we observed no group differences in accuracy or reaction time; however, we did find a main effect of trial type. Taken together, these results suggest that the sample used in the current study was sufficient; however, it will be important for future research to establish the precise mechanisms mediating the altered hippocampal decoupling that occurs with age. Similarly, the lack of correlations between behavior and connectivity measures may be due to the relatively small sample size. Third,

resting state data was acquired after the memory task. The ordering of these tasks has been shown to have an impact on connectivity of the DMN (Groen et al., 2011). We adopted this methodology as a strategy to reduce the time between training and performance on the task. While we cannot separate out the effects of the prior task on the resting state data in the current analysis, we do not believe that collecting the resting state data before the task would alter the conclusions drawn from the study. We believe this to be the case because the regions uniquely connected to the hippocampus in OAs are not only regions within their self-defined DMN, but also regions that are well established as key components of the DMN.

In conclusion, the current study investigated whether hippocampal connectivity is altered by age during a relational encoding task and tested the hypothesis that OAs, as compared to YAs, exhibit greater hippocampal connectivity to regions typically associated with the DMN. Moreover, the current study addressed several interpretational weaknesses that exist in the prior literature, including matching of behavioral performance between age groups, definition of functional networks, and utilization of an event-related approach to task-based functional connectivity. The main findings support the hypothesis that OAs, due to altered network modulation, exhibit hippocampal functional connectivity to regions within their DMN during relational encoding. In line with the hippocampal coupling hypothesis, we also found that YAs are able to efficiently modulate between networks states (Huijbers et al., 2011). This study provides novel information on the nature of connectivity changes that occur with age; however, it will be important for future research to determine the precise mechanisms mediating the imbalance and how these changes impact behavior.

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Highlights

- This study investigated the hippocampal coupling hypothesis (HCH) in aging.
- The hippocampus is a core component of the default mode network (DMN).
- The HCH predicts hippocampal decoupling from the DMN during encoding.
- Our results revealed that older adults' exhibit reduced decoupling during encoding.
- Such age-related changes in decoupling likely reflect reductions in inhibitory processes with age.

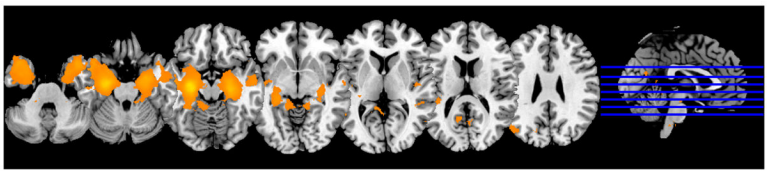

Figure 1.

Regions functionally connected to the hippocampus to the same extent in both older and younger adults. Note that the left hippocampal seed is correlated with itself in this contrast. These large clusters included regions in the bilateral hippocampus, bilateral temporal gyrus, bilateral precuneus, and left posterior cingulate. ($p < .005$ uncorrected, cluster extent $k = 80$)

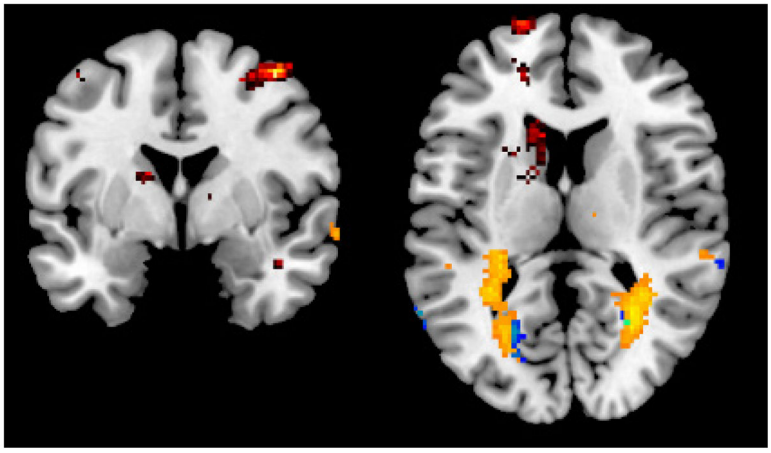

Figure 2.

Results from the main effect of age. Red = A contrast of younger greater than older adults. Regions include the putamen, caudate, and middle and precentral gyrus ($p < .005$ uncorrected, cluster extent $k = 158$). Yellow = A contrast of older greater than younger adults. Regions include posterior cingulate, parahippocampal gyrus, hippocampus, and caudate tail ($p < .005$ uncorrected, cluster extent $k = 158$). Blue = Regions within the default mode network identified using all participants that exhibit greater hippocampal connectivity in older adults as compared to younger adults. Regions include the precuneus, cuneus, and middle and superior temporal gyrus ($p < .005$ uncorrected, cluster extent $k = 10$).

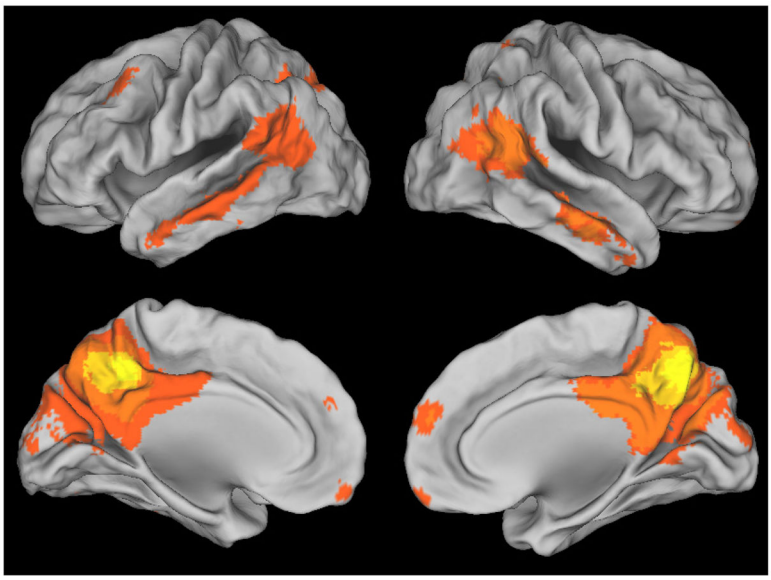

Figure 3.
The default mode network identified using all participants ($p < .005$ uncorrected, FDR-corrected cluster extent $k = 185$) and by using the posterior cingulate cortex as a seed (Fox et al., 2005).

Table 1

Participant characteristics

	Young Adults	Older Adults
N	11	11
Age	21.29 (2.21)	73.94 (7.02)
Education	14.60 (1.14)	17.90 (1.64)
MMSE	29.6 (.7)	29.5 (.9)
Shipley	29.2 (5.4)	34.7 (4.2)
Digit Span	16.3 (2.4)	16.7 (3.3)
LM Immediate	17.4 (3.2)	16.2 (2.7)
LM Delay	16.0 (2.5)	15.4 (2.2)
Recognition		
Old/New Accuracy	.84 (.06)	.88 (.06)
Proportion of hit types		
IO	.19 (.09)	.26 (.10)
IC	.17 (.05)	.15 (.06)
IL	.26 (.09)	.31 (.12)
ICL	.37 (.09)	.28 (.13)
Reaction Time		
IO	2022 (650)	2158 (542)
IC	2065 (771)	2294 (746)
IL	2066 (694)	2301 (666)
ICL	2034 (739)	2267 (728)

Notes: All data are means and standard deviations (in parentheses). MMSE = Mini-mental Status Exam. Shipley = Shipley Vocabulary Test. Digit Span = Digit Span subtest from the Wechsler Adult Intelligence Scale–Revised. LM Immediate = Logical Memory Immediate Recall subtest from the Wechsler Memory Scale–Revised. LM Delay = Logical Memory Delayed Recall from the Wechsler Memory Scale–Revised. IO = Item Only. IC = Item and Color. IL = Item and Location. ICL = Item, Color, and Location.

Table 2

Clusters significantly correlated with the hippocampus during task, both common to and differentially effected by age

Contrast (Cluster size)	Peak Voxel (X, Y, Z)	Peak T	Regions in cluster	Brodmann area
Conjunction of OA and YA				
(13285)	−28, −12, −18	21.93	L Hippocampus	
	26, −20, −16	14.43	R Parahippocampal gyrus	27
	26, −8, −18	11.32	R Amygdala	
1095	−52, −46, 10	5.81	L Middle temporal gyrus	21
	−44, −74, 22	5.43	L Middle temporal gyrus	39
	−56, −42, 2	4.92	L Middle temporal gyrus	22
(112)	52, −38, 4	3.87	R Superior temporal gyrus	22
	50, −30, 0	3.43	R Superior temporal gyrus	41
	50, −30, 12	3.32	R Superior temporal gyrus	41
OA > YA				
(917)	30, −62, 10	4.56	R Posterior cingulate	30
	26, −52, 16	4.54	R Posterior cingulate	30
	34, −50, 8	4.39	R Parahippocampal gyrus	30
1054	−32, −42, 6	4.31	L Hippocampus	
	−26, −44, 22	4.28	L Caudate tail	
YA > OA				
(318)	−22, 16, 2	4.25	L Putamen	
	−10, 8, 8	3.52	L Caudate body	
	−12, 22, 14	3.31	L Caudate body	
(391)	40, 0, 58	4.09	R Precentral Gyrus	6
	46, −8, 60	3.83	R Precentral Gyrus	4
	30, −2, 58	3.54	R Middle Frontal Gyrus	6
OA > YA masked with DMN				
(14)	26, −60, 12	3.93	R Precuneus	31
(31)	−22, −64, 12	3.38	L Cuneus	17
	−22, −74, 12	3.17	L Cuneus	17
(15)	−62, −56, 12	3.38	L Middle temporal gyrus	21
(10)	66, −36, 8	3.02	R Superior temporal gyrus	22
YA > OA masked with DMN	(none)			

Notes. Coordinates in Montreal Neurological Institute standard space. Regions and Brodmann areas (approximate) obtained using Tailarach atlas.