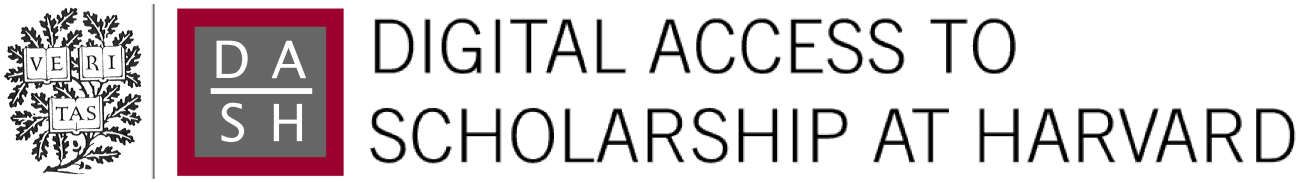

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Reduced Specificity of Hippocampal and Posterior Ventrolateral Prefrontal Activity during Relational Retrieval in Normal Aging

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ABSTRACT

Neuroimaging studies of episodic memory in young adults demonstrate greater functional neural activity in ventrolateral prefrontal cortex and hippocampus during retrieval of relational, as compared to item, information. We tested the hypothesis that healthy older adults – individuals who exhibit behavioral declines in relational memory – would show reduced specificity of ventrolateral prefrontal and hippocampal regions during relational retrieval. At study, participants viewed two nouns and were instructed to covertly generate a sentence that related the words. At retrieval, functional magnetic resonance images were acquired during item and relational memory tasks. In the relational task, participants indicated whether the two words were previously seen together. In the item task, participants indicated whether both items of a pair were previously seen. In young adults, left posterior ventrolateral PFC and bilateral hippocampal activity was modulated by the extent to which the retrieval task depended on relational processing. In older adults, activity in these regions was equivalent for item and relational memory conditions, suggesting a reduction in ventrolateral PFC and hippocampal specificity with normal aging.

Key Words: aging, relational memory, functional MRI, prefrontal cortex, medial temporal lobe

INTRODUCTION

Decades of cognitive aging research have shown that older adults do not perform as well as young adults on tests of episodic memory (for a review, see Hoyer and Verhaeghen, 2006). Episodic memory refers to the encoding and conscious retrieval of contextually-specific information, such as an event that occurred at a particular place and time (Tulving, 1983). Age differences have been found in memory for several types of contextual attributes, including perceptual features (Kausler and Puckett, 1981; McIntyre and Craik, 1987; Naveh-Benjamin, 2000; Pilotti, et al., 2003); spatial attributes (Denney et al., 1992; Park, et al., 1982, 1983); temporal order (Kausler and Puckett, 1981); and the source of information (Johnson, et al., 1993; Schacter, et al., 1991; Simons, et al., 2004). A review by Spencer and Raz's (1995), and another more recently by Old and Naveh-Benjamin (2008), indicate that age differences in memory for contextual details are twice as large as age differences in memory for content items.

Encoding and retrieval of contextual attributes is thought to rely on relational memory processing, which occurs when two previously unrelated items are linked together (e.g., Eichenbaum and Cohen, 2001). Two prominent theoretical views have been proposed to account for age-related deficits in contextual or relational memory. Whereas the *binding deficit* view suggests that older adults have a fundamental deficit in linking or integrating, the separate elements of a to-be-remembered episode (Bayen, et al., 2000; Burke and Light, 1981; Chalfonte and Johnson, 1996; Lyle, et al., 2006; Mitchell, et al., 2000; Naveh-Benjamin, 2000; Ryan, et al., 2007), the *control deficit* view asserts that older adults experience more generalized age-related declines in the processes under cognitive

control (Anderson and Craik, 2000; Craik, 1986; Craik and Byrd, 1982; Jennings and Jacoby, 1993; Light, et al., 2000; Moscovitch and Winocur, 1995; Smith et al.. 1998), such as the strategic manipulation, organization, or evaluation of features or contextual attributes, and the conscious, intentional retrieval of relational information (Dew and Giovanello, in press).

Research in neuropsychology and cognitive neuroscience suggests that such binding and control processes depend primarily upon the medial temporal lobe (MTL) and the prefrontal cortex (PFC), respectively. Whereas the MTL, particularly the hippocampus, serves to bind elements together into a learning event (e.g., Eichenbaum, et al., 2007; Moscovitch, 1992), PFC regions mediate consciously-controlled bias mechanisms that operate under effortful, intentional conditions (Buckner, 2003). For example, functional neuroimaging studies in young adults have shown greater hippocampal activity during the encoding (Chua et al., 2007; Henke et al., 1999; Jackson and Schacter, 2004; Davachi and Wagner, 2002) and retrieval (Giovanello et al., 2004, Yonelinas et al., 2001) of relational, relative to item, information. Additionally, fMRI studies in young adults have reported activity in left PFC during controlled encoding (Mottaghy et al., 1999; Fletcher et al., 2000; Lepage et al., 2000; Henson et al., 2002) and intentional retrieval (Badgaiyan et al., 2002, Bunge et al., 2004, Dobbins, et al., 2002; Rugg, et al., 1999; Velanova et al., 2003) of relational information.

The notion that age-related declines in relational memory may be linked to dysfunction in prefrontal cortex (PFC) and medial temporal lobe (MTL) regions fits well with structural, volumetric magnetic resonance imaging studies of older adults demonstrating that age-related atrophy differs across brain regions. For example, the

frontal lobes show the steepest rate of age-related atrophy (Pfefferbaum, et al., 1998; Raz et al., 2005; Resnick, et al., 2003), particularly inferior frontal subregions (Resnick, et al., 2003), and this atrophy corresponds to cognitive deficits (e.g., Gunning-Dixon and Raz, 2003). Additionally, memory structures within the MTL (e.g., entorhinal cortex, hippocampus, and parahippocampal gryus), exhibit differential rates of decline, with the hippocampus showing substantial atrophy and the entorhinal cortex demonstrating minimal changes (Raz et al., 2005). Consistent with this finding, Persson and colleagues (2006) reported reduced hippocampal volume in a group of older adults whose episodic memory performance declined over time compared to that of a group whose memory performance remained stable. More recently, Yonelinas and colleagues (2007) demonstrated that reductions in hippocampal volume resulted in decreased recollection of episodic memories. Finally, Chen and colleagues (2010) found hippocampal region-specific contributions to memory performance, reporting greater age-related reductions in the volume of anterior hippocampus relative to posterior hippocampus. Taken together, these findings suggest that age-related declines in PFC and the hippocampus may underlie the relational memory impairment observed in healthy older adults.

Prior functional neuroimaging studies of relational memory in healthy older adults have demonstrated age-related alterations in neural activity (Cabeza, 2006). Such alterations have taken the form of "under-recruitment" (i.e., failures to recruit specific brain regions to the same extent as young adults) or "non-selective recruitment" (i.e., recruitment of brain regions engaged beyond those of young adults), particularly when tasks place strong demands on relational processing. With regard to relational encoding, age-related under-recruitment has been observed during intentional learning of word pairs

(Cabeza et al., 1997). Compared to young adults, older adults show weaker activity in left ventrolateral PFC, a region that has been associated with semantic processing and verbal encoding (for reviews see Cabeza and Nyberg, 2000; Gabrieli et al., 1998).

The link between age-related relational memory deficits and medial temporal lobe decline is supported by age-related decreases in medial temporal lobe activity during encoding (for example, Mitchell et al., 2000; Daselaar et al., 2003). More recently, Dennis et al. (2008) examined the effects of aging on the neural correlates of successful item and source memory encoding and showed age-related reductions in both hippocampal and prefrontal regions that were more pronounced for source memory than for item memory. During relational retrieval, age-related changes in PFC activity have been observed (for example, Cabeza et al., 1997; Cabeza et al., 2002). In one study, Cabeza and colleagues (1997) scanned participants while recalling word pairs and found age-related decreases in right PFC activity. Additionally, older adults showed activation in left ventrolateral PFC that was not displayed by young adults. As a result, prefrontal activity during relational memory retrieval was unilateral for young adults and bilateral for older adults – the neural pattern termed "non-selective" neural activity. Regarding medial temporal lobe activity, event-related fMRI studies have documented age-related changes in medial temporal lobe activity linked to relational memory performance (for example, Cabeza et al., 2004; Mitchell et al., 2000). In one study (Mitchell et al., 2000), older adults showed weaker MTL activity when binding objects to their locations). In another study (Cabeza et al., 2004), older adults showed weaker activity in the hippocampus but stronger activity in the parahippocampal gyrus during a recognition task with remember/know responses.

Although prior functional neuroimaging studies of relational memory have demonstrated age-related neural alterations in the form of "under-recruitment" or "non-selective-recruitment" in medial temporal lobe and prefrontal cortex regions, no studies have examined the specificity of activity in neural regions engaged by both young and older adult groups. That is, under conditions in which both young and older adults recruit the same neural regions (e.g., prefrontal cortex and medial temporal regions) during successful relational memory performance, it is unclear whether these regions mediate the same type of mnemonic information. The current study addressed this issue by examining the contribution of prefrontal cortex and hippocampus during recognition of item and relational information in young and older adults. Critically, we compared retrieval of item information and relational information, holding constant the stimuli and the encoding task for the two retrieval conditions (item and relational). In addition, we equated the level of recognition accuracy across young and older adult groups to assess whether age-related neural changes in prefrontal cortex and hippocampus would occur under conditions of age-equivalent relational memory performance, and if not, whether hippocampal and prefrontal activity in older adults exhibited the same specificity for relational information as activity associated with these regions in young adults. We hypothesized that young and older adults would recruit the prefrontal cortex and hippocampus during accurate retrieval, albeit for different memory conditions: we expected young adults were to recruit prefrontal cortex and the hippocampus during relational memory retrieval, whereas we expected older adults to recruit these regions for both item and relational memory conditions, thereby showing a reduction in processing specificity.

METHODS

Participants

Sixteen young adults between the ages of 20 and 29 years (M =22.8, SD=3.0) and sixteen older adults between the ages of 66 and 73 years (M = 69.6, SD = 2.3) were paid for their participation. Young adults had a mean education of 15.8 years (SD=.04) and older adults had a mean education of 15.9 years (SD=2.2). Young adults were recruited from flyers posted on the Harvard University campus and older adults were recruited from Cambridge, Massachusetts and the surrounding communities. Participants were right-handed, fluent English speakers with normal or corrected-to-normal vision. All participants were screened to ensure that they were healthy, reported no history of psychiatric (including depression and epilepsy) or neurological disorder (including diabetes), had no contra-indications for functional magnetic resonance imaging (fMRI), and were not taking psychotropic medication. Informed consent was obtained from all participants according to the institutional review board at Massachusetts General Hospital.

Neuropsychological Assessment

In addition, older adult participants were given a battery of neuropsychological tests to assess their mental functioning. The neuropsychological battery consisted of the Mini-Mental State Exam, subtests from the Wechsler Adult Intelligence Scale (WAIS)-Revised (Mental Arithmetic and Mental Control) and WAIS-III (Digit Span Backward), subtests from the Wechsler Memory Scale – Revised (Logical Memory I and Verbal Paired

Associates), the California Verbal Learning Test, the Wisconsin Card Sorting Test, and the Controlled Oral Word Association Test. The neuropsychological data, collected within six months of this study, are presented in Table 1. Participants whose performance was greater than one standard deviation below the mean on any test were excluded from the study.

Insert Table 1 Here

Stimuli and Cognitive Task

Stimuli were 288 one- to three-syllable unrelated nouns (M Freq= 56.3; SD=63.5). Following extensive practice outside the scanner, participants received two study/retrieval runs. During study, young participants simultaneously viewed two nouns (42 unrelated word pairs/run; total stimuli: 84), and were instructed to covertly create a sentence that incorporated the two words. For older participants, each study run consisted of the 42 unrelated word pair trials, with each trial randomly repeated 3 times throughout the course of the run (in an attempt to produce equivalent levels of recognition performance)[1]. As with young adults, older adults were instructed to covertly create a sentence that incorporated the two words. All participants indicated via button press that they had successfully created an encoding sentence for each trial. During retrieval, which started immediately following the study phase, functional MR images were acquired for a total of 192 trials while participants performed one of two recognition tasks (Associative and Item). In the Associative task, participants saw pairs of words previously seen

[1] Although not explicitly instructed to do so, all older adult participants reported that they generated the same encoding sentence for all repetitions of a word pair.

together (Intact Pair - IP), pairs of words previously seen, but not together (Rearranged Pair - RP), and pairs of novel words (New Pair - NP). Test stimuli appeared for 6 seconds each, during which participants indicated whether the two words were previously seen together. In the Item task, participants saw pairs of words previously seen, but not together (Rearranged Items - RI), pairs consisting of one old word and one new word, (Old/New Items - ONI), and pairs consisting of two new words (New Items - NI). They were asked to indicate whether both words of a pair were previously seen. Four task blocks alternated between self-paced associative recognition and item recognition (Figure 1). Each block consisted of 18 trials drawn from each of the task-appropriate experimental conditions types (Associative Block: 6 IP, 6 RP, 6 NP; Item block: 6 RI, 6 ONI, 6 NI), as well as 6 control trials during which participants viewed ampersands and number signs, and were instructed to indicate on which side of the screen the ampersands had appeared. Control trials were also used to introduce jitter during each scanner run. Trials were randomized within each task block. Starting task and stimulus conditions were counterbalanced across participants.

Insert Figure 1 Here

fMRI Data Acquisition and Analysis

Whole-brain gradient-echo, echo-planar images were collected during the test phase (3-mm slices, TR=2, TE=23) only using a Siemens 3T MR scanner. Slices were oriented along the long axis of the hippocampus with a resolution of 3.125mm x 3.125mm x 3mm. High resolution T1-weighted (MP-RAGE) structural images were collected for anatomic visualization. Stimuli were back-projected onto a screen and viewed in a mirror mounted

above the participant's head. For those participants requiring vision correction, subjects were given MRI compatible glasses with prescriptions matching their own. The task was presented using MacStim software (CogState Ltd, Melbourne, Australia). Responses were recorded using an MR-compatible response box. Head motion was restricted using a pillow and foam inserts.

All preprocessing and data analysis were conducted using SPM2 (Statistical Parametric Mapping; Wellcome Department of Neurology, UK). Slice acquisition timing was corrected by resampling all slices in time relative to the first slice, followed by rigid body motion correction. The functional data were then normalized spatially to the standard T1 Montreal Neurological Institute template. Images were re-sampled into 3-mm cubic voxels and smoothed spatially with a 5-mm full-width half-maximum isotropic Gaussian kernel.

For each participant, on a voxel-by-voxel basis, an event-related analysis was first conducted in which all instances of a particular event type were modeled through the convolution with a canonical hemodynamic response function. Each retrieval trial (6 seconds in duration) was modeled as three 2-second TRs. Because our interest centered on neural recruitment during successful retrieval, as well as the fact that we designed the paradigm to elicit high levels of accuracy from each age group, all memory conditions were modeled for correct decisions only. Effects for each event type were estimated using a subject-specific, fixed effects model. These data were then entered into a second order, random-effects analysis. Analyses contrasted activation as a function of recognition type (associative versus item) using the appropriate trial types (IP, RP, NP, RI, ONI, NI).

Regions consisting of at least five contiguous voxels that exceeded the threshold of p< 0.001 were considered reliable.

Conjunction analyses (using the masking function in SPM2) then examined what neural regions were: (1) commonly activated by young and older participants during relational retrieval and (2) differential activated by young or older participants during relational retrieval. For conjunction analyses examining commonalities between groups, the threshold for each contrast entered in to a conjunction analysis was set at $p < .01$ (such that the conjoint probability of the conjunction analysis, using Fisher's estimate (Fisher, 1950; Lazar et al., 2002) was $p < .001$). For analyses examining differences between groups, the threshold for the first contrast entered in the analysis was set at $p < .01$, while the threshold for the second contrast entered into the analysis was set at $p<.001$ (such that the conjoint probability of the conjunction analysis, using Fisher's estimate was $p<.0001$). Voxel coordinates are reported in Montreal Neurological Institute (MNI) coordinates and reflect the most significant voxel within the cluster.

RESULTS

Behavioral Data

The proportion of studied and unstudied stimuli endorsed as "old" are shown in Table 2. Behaviorally, associative recognition accuracy was calculated as the difference between "old" judgments to intact stimulus pairs (hits) and "old" judgments to recombined stimulus pairs (false alarms), while item recognition was calculated as the difference in "old" judgments to recombined items (hits) and "old" judgments to new items (false alarms). An analysis of variance (ANOVA) with memory type (item, relational) and response type (IP hits, NP false alarms, RI hits, NI false alarms) as within-subjects

factors, and group (young old) as a between-subjects factor revealed a main effect of memory type ($F(1, 30) = 42.69$, $p<.0001$), indicating that greater accuracy in the relational task than the item task, as well as a main effect of response type ($F(1,30) = 865.26$, $p<.0001$, indicating that studied stimuli were correctly endorsed "old" at a higher rate than non-studied relations or items. There was no main effect of group $F < 1$, nor a group x memory type x condition interaction, indicating that both groups performed equivalently well on the item and relational memory tasks.

Insert Table 2 Here

Functional Neuroimaging Data

Neural regions commonly associated with young and older adults during accurate relational memory retrieval

We hypothesized that young and older adults would recruit the prefrontal cortex and the medial temporal lobe (i.e., hippocampus) during accurate retrieval, albeit for different memory conditions. As such, we contrasted all memory conditions greater than the control condition (IP+RP+RI+ONI+NI > control)[2] for both groups to assess common regions generally contributing to accurate memory performance. This analysis revealed activity in several neural regions, including left ventrolateral and dorsolateral prefrontal cortex, left superior parietal cortex, left inferior frontal gyrus, and right hippocampus for both groups (see Table 3). To examine which conditions elicited retrieval-related activity

[2] Of note, direct comparisons between memory types (i.e., associative and item) yielded the same pattern of results as those reported. We chose to report the comparison of all memory conditions greater than the control condition because this contrast allowed us to extract the percent signal change in the same regions for all memory conditions (IP+RP+RI+ONI+NI) in both age groups.

in the PFC and hippocampus, we extracted the signal change in these regions (left ventrolateral PFC, left dorsolateral PFC and hippocampus) for each group. Based on the t-test, there were two significant clusters within the left ventrolateral PFC (one anterior region located in BA 47 and one posterior region located in BA 44), one cluster within dorsolateral PFC (BA 46) and one cluster within the right hippocampus. The data, shown in Figure 2, illustrate that young adults recruited right hippocampus and left posterior ventrolateral PFC during retrieval of relational information, whereas older adults recruited these regions during retrieval of item and relational information. More specifically, young adults showed greater hippocampal activity to intact pairs than to any other memory condition, while older adults recruited right hippocampus for several mnemonic conditions, both relational and item. Similarly, young adults activated left posterior ventrolateral PFC during retrieval of intact and recombined pairs, while older adults activated this region during both relational and item memory. Such findings point to age-related reductions in processing specificity for hippocampal and left posterior ventrolateral PFC regions. A different pattern emerged, however, in left anterior ventrolateral PFC and left dorsolateral PFC (see Figure 2). Here, both groups recruited these regions during retrieval of item and relational information, indicating no loss of processing specificity with age.

Insert Figure 2 Here

Regions showing a stronger correspondence to accurate memory in young adults than in older adults.

We examined neural regions uniquely activated by young (i.e., young>old) adults during accurate memory retrieval. This contrast showed greater activity in bilateral inferior frontal gyrus, left middle frontal gyrus, left hippocampus, and bilateral occipital cortex for young adults relative to older adults (see Table 3).

Regions showing a stronger correspondence to accurate memory in older adults than in younger adults.

Finally, we examined neural regions uniquely activated by older (i.e., old>young) adults during accurate memory retrieval. This contrast showed greater activity in bilateral superior and middle frontal gyri, as well as left middle temporal gyrus for older adults relative to young adults (See Table 3).

Insert Table 3 Here

DISCUSION

Under conditions in which stimuli and encoding tasks were held constant and behavioral performance was equivalent between young and older adults, both groups showed neural activity in left ventrolateral PFC, left dorsolateral PFC, and right hippocampus during accurate retrieval. Whereas young adults' neural activity in left posterior ventrolateral PFC and right hippocampus was modulated by the extent to which the retrieval task depended on relational processing, older adults activated these regions during the retrieval of relational, as well as item, information, suggesting an age-related reduction in processing specificity in these regions. No age-related differences in processing

specificity, however, were observed in anterior ventrolateral PFC or dorsolateral PFC: activity in these regions was observed during retrieval of item and relational information for both groups, demonstrating that not all regions showed age-related reductions in specificity for our task.

Behaviorally, increased repetition of relational information at encoding for older adults equated young and older adults' relational memory performance. Such findings demonstrate that with encoding support (i.e., multiple repetitions at study) older adults can overcome their relational memory deficit. This finding is consistent with prior behavioral reports demonstrating the benefit of encoding support to older adults' source memory performance. For example, Glisky and her colleagues (2001) found that only a subset of their older adult participants showed deficits in source memory, namely those with below average frontal function, and these deficits could be eliminated by requiring participants at study to consider the relation between an item and its context. The current behavioral findings demonstrate that memory for other types of contexts (i.e., the inter-item associations formed between two words) can be equated between young and older adults with encoding support.

At the neural level, hippocampal activity in young adults was modulated by the extent to which the retrieval task depended upon relational processing. This finding is consistent with several findings indicating a critical role for the hippocampus during the encoding (Chua et al., 2007; Davachi and Wagner, 2002; Henke et al., 1999; Jackson and Schacter, 2004; Prince et al., 2005; Sperling et al., 2001; Sperling et al., 2003) and retrieval of relational information (Giovanello et al., 2004, 2009; Yonelinas et al., 2001). Similarly, activity in left posterior ventrolateral PFC observed in the current study is

consistent with prior reports that this region is involved in the retrieval of temporal order, spatial location, and presentation modality (Cabeza et al., 2003; Hayes et al., 2004; Henson, et al., 1999; Nolde et al., 1998; Ranganath, et al., 2000), and may reflect the processing of relevant features (e.g., semantic, phonological, or orthographic) of stimuli (i.e., intra-item associations) or the degree of controlled selection that is engaged (see Blumenfeld and Ranganath, 2007).

In contrast, older adults showed significant neural activity in right hippocampus and posterior ventrolateral PFC, but activity in these regions was observed for both item and relational memory conditions, suggesting dedifferentiation or loss of regional specialization. Such age-related dedifferentiation is consistent with a prior report that documented declining ventral visual cortex specificity in older adults for whom face regions were also more responsive to places than in young adults where regions responded discriminately to one category (Park et al., 2004). Moreover, Payer and colleagues (2006) observed ventral visual dedifferentiation in older adults during working memory encoding, together with prefrontal overactivation, raising the possibility that frontal regions may compensate for lost perceptual specificity. In the current study, neural activity in bilateral middle and superior frontal regions was greater for older adults than for younger adults, again potentially suggesting the frontal regions may compensate for reduced hippocampal specificity, particularly under conditions in which no age-related behavioral differences are observed.

However, a different pattern emerged in the anterior ventrolateral PFC and dorsolateral PFC. In these regions, neural activity was similar between young and older adult groups, with activity present for both item and relational memory conditions. Prior

studies in young adults suggest that activation of anterior ventrolateral PFC is enhanced during the general selection of semantic information, while dorsolateral PFC is involved in the organization or comparison of relationships among items that are active in memory (see Paller and Wagner, 2002; Ranganath, 2010). For instance, Murray and Ranganath (2007) reported that anterior ventrolateral prefrontal (BA 45/47) activity at encoding predicted successfully memory for both items and relations, while dorsolateral prefrontal (BA 46) activity predicted successful memory for relational information only. The current findings in anterior ventrolateral PFC dovetail nicely with those of Murray and Ranganath (2007), extending their observation at encoding to activity at retrieval and documenting similar patterns of activity in this region in young and older adults. The current findings in dorsolateral PFC, however, appear inconsistent those reported by Murray and Ranganath (2007), as we observed retrieval-related activity in this region for both item and relational information. Future studies will need to address whether this apparent inconsistency is due to the stage of memory examined (encoding versus retrieval) or some other factor.

Finally, we also examined neural regions showing a stronger correspondence to accurate memory in young adults than in older adults (young>old), as well as regions showing the opposite effect (old > young). For neural regions uniquely activated by young adults (i.e., young>old) during accurate memory retrieval, we observed activity in bilateral inferior and middle PFC, bilateral occipital cortex, and left hippocampus. These findings are consistent with several studies documenting retrieval-related activity in these regions in young adults (e.g., Badgaiyan et al., 2002; Bunge et al. 2004; Dobbins, et al., 2002; Giovanello, Schnyer, and Verfaellie, 2004, 2009; Rugg,, Fletcher et al., 1999;

Velanova et al., 2003). For neural regions uniquely activated by older adults (i.e., old > young) during accurate memory retrieval, we observed bilateral superior and middle frontal gyri, as well as left middle temporal gyrus. As noted above, such age-related over-recruitment, particularly in PFC, has been reported previously and may reflect frontal compensation, as it has been associated with underactivation in medial temporal and ventral visual cortex, as well as improved performance (e.g., Davis et al., 2007; Gutchess et al., 2005). These findings, known as the posterior-to-anterior shift in aging (*PASA*, Davis et al., 2007) have been observed previously under conditions of age-related under recruitment in posterior regions (i.e., MTL and ventral visual cortex). The current findings document the presence of the PASA pattern under conditions of age-related reductions in processing specificity.

In summary, our data showed that left posterior ventrolateral PFC and bilateral hippocampal activity was modulated by the extent to which a retrieval task depended on relational processing in younger, but not older, adults. These findings suggest a reduction in ventrolateral PFC and hippocampal specificity with normal aging, and might help to understand such phenomena of normal aging as increased susceptibility to memory distortion. A number of studies have shown that older adults are sometimes more prone to making memory errors that reflect generic or nonspecific memory for previously studied information (e.g., Dodson and Schacter, 2002; Jacoby and Rhodes, 2006; Koutstaal and Schacter, 1997). It will be interesting to examine whether susceptibility to such memory errors is related to the kind of reduced specificity of PFC and hippocampal processing documented here. Elsewhere we have provide evidence that hippocampal dysfunction may be implicated in some memory errors committed by older adults

(Giovanello, et al., 2010), but further research is need to examine whether reduced specificity of hippocampal or PFC processing also contributes to mistakes that older adults make when attempting to remember past events.

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Table 1. Group Characteristics

Measure	Young (*n* = 16)	Old (*n* = 16)
Age	22.8 (3.0)	69.6 (2.3)
Gender	8/16 female	11/16 female
Education	15.8 (0.04)	15.9 (2.2)
MMSE	-	29.7/30 (0.06)
California Verbal Learning Test	-	13/16 (2.5)
Controlled Oral Word Association Test	-	44.9 (14.6)
WAIS-R Mental Arithmetic	-	14.1/19 (2.0)
WAIS-R Mental Control	-	6/6 (0.8)
WAIS-III Backward Digit Span	-	8.1/14 (2.3)
WMS-R Logical Memory I	-	39.9/50 (9.0)
WMS-R Verbal Paired Associates I	-	19.2/24 (4.3)
Wisconsin Card Sorting Task (categories)		

Note: Standard deviations are in parentheses. For the California Verbal Learning Test, the measure reported is the number of items retrieved on the long delay cued recall test.

Table 2. Proportion of studied and unstudied stimuli endorsed as "old" and corrected accuracy (hits – false alarms) as a function of age. Standard deviations are shown in parentheses.

	Young	Old
Item Memory		
Recombined Items (Hits)	.74 (.14)	.71 (.17)
Old Item/New Item (False alarm)	.26 (.15)	.17 (.11)
New Items (False Alarms)	.05 (.08)	.05 (.09)
Relational Memory		
Intact Pair (Hits)	.87 (.10)	.91 (.09)
Recombined Pair (False Alarms)	.08 (.10)	.12 (.12)
New Pair (False Alarms)	.02 (.03)	.02 (.05)
Item Accuracy	.69 (.15)	.66 (.18)
Relational Accuracy	.79 (.16)	.79 (.17)

Table 3. Regions of significant neural activity during accurate retrieval in young and older adults.

Location	Hemisphere	BA	MNI coordinates *x*	*y*	*z*	*t*-value
Common Neural Activity for Young and Older adults						
Inferior frontal gyrus	L	44	-42	6	33	7.09
	L	47	-39	33	0	6.70
Thalamus	L	n/a	-12	-18	9	5.76
Inferior frontal gyrus	L	45	-54	24	21	5.10
Middle frontal gyrus	R	10	39	57	0	4.91
Superior parietal	L	7	-30	-69	42	4.88
Lingual gyrus	R	19	24	-60	-3	4.86
Inferior temporal gyrus	L	20	-48	-45	-18	4.61
Middle frontal gyrus	L	46	-45	51	0	4.58
Inferior frontal gyrus	L	47	-45	36	-6	4.50
Hippocampus	R	n/a	24	-21	-9	4.46
Superior Occipital gyrus	L	19	-24	-78	24	4.43
Middle frontal gyrus	L	6	-42	9	54	4.39
Neural Activity greater for Younger than Older Adults						
Inferior frontal gyrus	R	47	39	27	−6	7.08
Occipital cortex	R	19	15	−78	15	7.04
Inferior frontal gyrus	R	47	33	33	0	5.53
Superior parietal	L	7	−30	−63	48	5.61
			−36	−57	48	5.52
Middle frontal gyrus	L	6	−45	0	54	5.44
			−39	6	51	5.43
			−30	−9	51	5.34
Occipital cortex	R	18	6	−78	18	5.26
Occipital cortex	L	19	−18	−78	15	5.21
Inferior frontal gyrus	L	47	−36	27	3	5.15
			−36	27	−9	5.11
Hippocampus	L	n/a	−24	−21	−9	4.63
Neural Activity greater for Older than Younger adults						
Middle temporal gyrus	L	21	-51	-42	-3	6.30
			-63	-39	-3	4.85
Middle frontal gyrus	R	10	42	60	-6	5.31
Middle frontal gyrus	L	9	-36	12	36	4.75
Superior frontal gyrus	R	6	39	-12	30	4.60
Superior frontal gyrus	L	10	-33	60	0	4.48

FIGURE CAPTIONS

Figure1. Event-related task design with alternating blocked task periods of relational memory ("together previously?") and item memory ("both old?"). Abbreviations: IP - Intact Pair, RP - Rearranged Pair, NP - New Pair, RI - Rearranged Items, OI - Old/New Items, and NI - New Items.

Figure2. Neural activity in right hippocampus, left ventrolateral prefrontal cortex, and left dorsolateral prefrontal cortex during accurate retrieval of item information and relational information in young and older adults. In each region, the mean percent signal change is graphed for each memory condition and standard errors are shown. Abbreviations: IP - Intact Pair, RP - Rearranged Pair, NP - New Pair, RI - Rearranged Items, OI - Old/New Items, and NI - New Items.