Research Report

Age-related changes in the three-way correlation between anterior hippocampus volume, whole-brain patterns of encoding activity and subsequent context retrieval

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ABSTRACT

Age-related declines in memory for context have been linked to volume loss in the hippocampal head (HH) with age. However, it remains unclear how this volumetric decline correlates with age-related changes in whole-brain activity during context encoding, and subsequent context retrieval. In the current study we examine this. We collected functional magnetic resonance imaging data in young and older adults during the encoding of item, spatial context and temporal context. HH volume and subsequent retrieval performance was measured in all participants. In young adults only there was a positive three-way correlation between larger HH volumes, better memory retrieval, and increased activity in right hippocampus, right ventrolateral prefrontal cortex (VLPFC) and midline brain regions during episodic encoding. In contrast, older adults exhibited a positive three-way association between HH volume, generalized activity in bilateral hippocampus and dorsolateral PFC across all encoding tasks, and subsequent spatial context retrieval. Young adults also engaged this network, but only during the most difficult temporal context encoding task and activity in this network correlated with subsequent temporal context retrieval. We conclude that age-related volumetric reductions in HH disrupted the structure–function association between the hippocampus and activity in the first general encoding network recruited by young adults. Instead, older adults recruited those brain regions young adults only engaged for the most difficult temporal task, at lower difficulty levels. This altered pattern of association correlated with spatial context retrieval in older adults, but was not sufficient to maintain context memory abilities overall.

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1. Introduction

Compared with young adults, older adults exhibit a disproportionate behavioral deficit in associative memory tasks, such as spatial and temporal context memory tasks (Naveh-Benjamin, 2000; Rajah et al., 2010b; Spencer and Raz, 1995). In young adults, there is substantial neuroimaging evidence implicating the hippocampus (Diana et al., 2007; Eichenbaum et al., 2007),

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particularly its anterior portion, in associative encoding (Jackson and Schacter, 2004; Prince et al., 2005; Sperling et al., 2003). Healthy older adults exhibit volumetric reductions in anterior hippocampus (hippocampus head; HH), which has been related to poorer retrieval of spatial and temporal context information with age (Rajah et al., 2010a). In addition, under-recruitment of the hippocampus during associative encoding in older adults predicts poorer subsequent memory for associations (Dennis et al., 2008). These findings indicate that region-specific changes in the structure and function of the hippocampus with age may contribute to associative memory deficits in healthy older versus younger adults.

It is generally accepted that the hippocampus contributes to encoding through interactions with neocortex (Eichenbaum, 2000; Moscovitch, 1992; Paller, 2002; Rugg et al., 2008). Supporting this view, neuroimaging studies in young adults have revealed that the hippocampus is functionally coupled with sensory areas, the prefrontal cortex (PFC), and parietal cortex at encoding (McCormick et al., 2010; Rajah et al., 1999; Ranganath et al., 2005). Recent studies have reported age-related changes in the whole-brain networks coupled with hippocampus during associative encoding (Dennis et al., 2008; Leshikar et al., 2010). For example, during a source encoding task, one study reported that older adults exhibited less connectivity between hippocampus and posterior regions, such as posterior cingulate and parietal lobe, but increased connectivity of hippocampus with PFC (Dennis et al., 2008).

Thus, independent studies have established that volumetric reductions in anterior hippocampus and age-related changes in hippocampal connectivity at encoding are associated with poorer associative memory in healthy older adults (Dennis et al., 2008; Rajah et al., 2010a). However, it remains unknown how individual differences in anterior hippocampal volumes directly influence encoding-related activity in this region and other brain regions implicated in context encoding, and how this affects subsequent context retrieval accuracy in young adults. Furthermore the impact of healthy aging on this three-way pattern of associations has not been directly tested. The current study was designed to address these issues. Young and older adults underwent functional magnetic resonance imaging during item, spatial context and temporal context encoding using face stimuli. In all tasks, the orienting task was a subjective pleasant/neutral judgment to each face. In addition, we used multivariate partial least squares (PLS; McIntosh et al., 2004) in the current study to examine the three-way association between HH volumes (which were determined in a previous study (Rajah

et al., 2010a)), encoding-related fMRI activation, and retrieval accuracy for item recognition, spatial context and temporal context tasks. In young adults, we hypothesized that larger HH volume would be related to increased activation in whole-brain encoding networks and to subsequent retrieval accuracy. We also hypothesized that age-related volumetric reductions in HH would alter the three-way association between HH volume, encoding activity, and subsequent retrieval, which may contribute to the episodic memory deficits observed in healthy older adults (Glisky and Kong, 2008; Naveh-Benjamin, 2000).

2. Results

The neuropsychological, behavioral and volumetric results have been reported elsewhere (Rajah et al., 2010a, 2010b). However, because we added 1 young subject for the current analysis, we present the updated results.

2.1. Neuropsychological results

Results are shown in Table 1. The independent samples T-test for CASE score was significant, t(33)=3.048, p=0.005. However, both group means were above the 94 score cut-off for individuals with 15+ years of education. The independent samples T-test for long form free recall CVLT was also significant, t(39)=3.217, p<0.005. This is consistent with studies indicating older adults have a deficit in free recall (Craik and Salthouse, 2000). There were no other significant differences between the groups on neuropsychological tests.

2.2. Behavioral results

Encoding RT and retrieval accuracy results are shown in Table 2. A group (2)×task (3) mixed ANOVA revealed a significant interaction F(2,82)=7.024, p<0.005 in encoding RT for the pleasantness judgment. Post-hoc T-tests revealed that young adults responded significantly faster than older adults in during item encoding, t(41)=−2.483, p<0.05 and spatial context encoding t(41)=−2.257, p<0.05, but not during temporal context encoding t(41)=−1.295, p>0.05. Post-hoc, within-group, one-way ANOVAs for task indicated that both young and older adults exhibited task differences in RT (young: F(2,42)=32.351, p<0.001, older adults: F(2,40)=12.831, p<0.001). Post-hoc T-tests on the within-group ANOVA in young revealed that they exhibited significantly faster RT during item encoding,

Table 1 – Group means for education and neuropsychological measures.									
Group		EDU	MMSE	BECK	GDS	CASE	LFCVLT	LCRCVLT	RGCVLT
Young adults	Mean	16.14	29.50	2.95	1.05	98.76*	13.90*	13.40	15.45
	S.E.	0.27	0.23	0.88	0.34	0.34	0.42	0.44	0.22
Older adults	Mean	15.29	29.38	4.19	0.90	97.28*	11.10*	12.00	15.10
	S.E.	0.56	0.19	0.78	0.21	0.35	0.75	0.73	0.32

Note: This table presents the group means and standard errors (S.E.) for education (EDU) in years, and other psychological measures taken. MMSE = mini-mental status examination; GDS = Geriatric Depression Scale; CASE = Cognitive Assessment Scale for the Older Adults, LFCVLT = CVLT, long-form free recall; LCRCVLT = CVLT, long-form category assisted recall; RGCVLT = CVLT, long-term recognition. Significant group differences (p<0.05) are highlighted with asterisks.

Table 2 – Mean encoding reaction time and retrieval accuracy data with standard error.		Recognition	Spatial context	Temporal context
Young adults	Encoding reaction time	1257.48 (56)	1354.83 (64)	1406 (64)
	Retrieval accuracy	0.94 (0.11)	0.89 (0.17)	0.82 (0.22)
Older adults	Encoding reaction time	1464.79 (62)	1563.14 (66)	1464.5 (67)
	Retrieval accuracy	0.93 (0.10)	0.80 (0.19)	0.68 (0.21)

Note: Accuracy values shown are the proportion correct per task type with SE. Reaction time values are shown in milliseconds per task type with SE.

compared to both spatial (t(21)=−5.568, p<0.001) and temporal (t(21)=−7.693, p<0.001) context encoding, and also exhibited faster RT during spatial versus temporal context encoding, t(21)=−2.634, p<0.05. On the other hand, while older also exhibited significantly faster RT during item encoding versus both spatial (t(20)=−4.388, p<0.001) and temporal (t(20)=4.324, p<0.001) context encoding, they did not exhibit a significant difference in RT between spatial and temporal context encoding, t(20)=1.758, p>0.05.

A group (2)×task (3) mixed ANOVA revealed a significant interaction F(2,82)=16,248 p<0.001, in retrieval accuracy scores. Post-hoc T-tests that revealed the interaction was due to there being no difference in recognition accuracy between the two groups, t(41)=0.327, p=0.745, but a significant difference in spatial accuracy, t(41)=3.677, p=0.001 and temporal accuracy, t(41)=4867, p<0.001. A post hoc linear trend analysis was run to determine if there was a linear decrease in accuracy across

recognition, spatial and temporal tasks. The analysis revealed that there was a linear trend×group interaction, F(1,41)=31.328, p<0.001. The interaction was due to their being a smaller, albeit still significant linear trend in young, F(1,21)=40.08, p<0.001 than in older adults, F(1,20)=221.432, p<0.001.

2.3. Volumetric results

The volumetric results for this sample have been previously published (Rajah et al., 2010a). From this study, the interrater measurements for average HH was 0.91 (Rajah et al., 2010a). The interrater measurement for raters 1 and 2 was of 0.98 and 0.84, respectively. These measurements were within publishable range.

The 2-way ANOVA revealed that young adults had significantly larger HH volumes compared to older adults, F(1,39)= 8.858, p<0.05. There was no significant sex main effect.
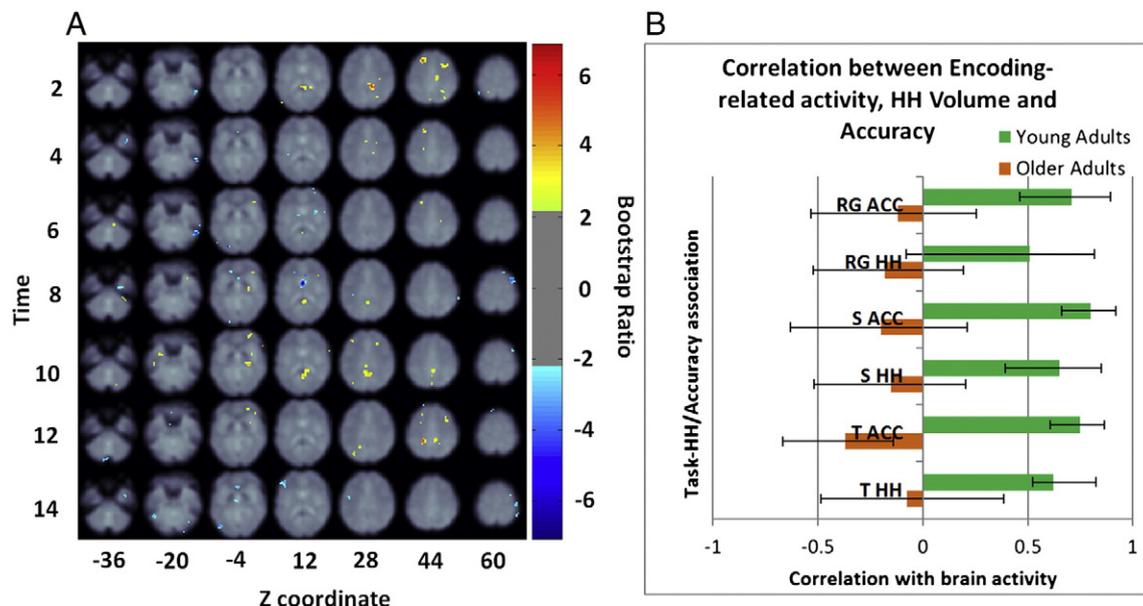

Fig. 1 – Singular image and the correlation profile for LV1 of the between-group PLS. A) The singular image for LV1 at a bootstrap of 3.5 (p<0.0005), which reflects stable and significant activations at 2 to 14 s after event onset. Z coordinates are reported in mm in MNI space. The color-bar represents the color code for the colorized activations on the singular image. Regions colored in red–orange–yellow are positively related with the experimental effect presented in (B). Regions colored in blue are negatively related with the experimental effect presented in (B). B) Correlation profile for LV1. The correlation profile shows how accuracy and HH volume correlate with the pattern of brain activity identified in the singular image in young and older adults. RG = Recognition, S = Spatial context, T = Temporal context, ACC = Accuracy, HH = Average hippocampus head volume.

2.4. PLS results

The between-group PLS identified two significant (p<0.05) LVs. The singular image, representing voxels with stable and significant activation, and the correlation profile for the first LV (LV1; p<0.05; percent cross-block covariance accounted for=16.76%), representing brain–accuracy and brain–HH volume correlations by task are shown in Fig. 1. Local maxima for this LV are presented in Table 3.

LV1 identified a pattern of encoding-related activity in young adults that was significantly correlated with both HH volume and subsequent memory accuracy for all task types (right side of Fig. 1B), although the confidence interval representing the correlation between HH volume and activity during item encoding suggests this association was not significant. In young adults increased activity in positive salience brain regions and

decreased activity in negative salience brain regions was significantly correlated with larger HH volumes and higher retrieval accuracy. In older adults, this effect was inverted and was not significant as indicated by the wide error bars crossing the zero-correlation mark. Regions of positive brain salience in LV1 included right hippocampus, right VLPFC, putamen and a number of regions thought to be part of the default-mode network (Buckner et al., 2008; Greicius et al., 2003), including precuneus, posterior cingulate, medial PFC and retrosplenial cortices. Negative brain salience regions included, bilateral occipital cortex, fusiform gyrus, and bilateral premotor cortex.

The second LV (LV2; p<0.001; percent cross-block covariance accounted for=23.50%) identified a three-way interaction effect that reflected group differences in encoding activity which in turn were also differentially correlated with HH volume and subsequent memory effects in young versus

Lag	BSR	Cluster size	X	Y	Z	Hem	Gyral location	Brodmann area
Table 3 – Local maxima for LV1 of the ST-bPLS analysis.								
Lag	BSR	Cluster size	X	Y	Z	Hem	Gyral location	Brodmann area
Positive saliences: in young, regions in which activity positively correlates with retrieval accuracy in all tasks and HH volume in the spatial and temporal tasks.								
1	6.87	66	−20	29	32	Left	Medial prefrontal	BA 9
1	6.52	97	0	−38	17	Medial	Retrosplenial cortex	BA 29/30
1	5.71	22	8	−21	38	Right	Cingulate gyrus	BA 24
1	4.62	15	44	−33	35	Right	Inferior parietal lobe	BA 40
1	4.59	24	36	18	43	Right	Middle frontal gyrus	BA 8
1	4.34	21	12	−65	25	Right	Precuneus	
2	5.91	16	−20	33	35	Left	Medial frontal cortex	BA 8/9
3	4.85	15	44	35	−8	Right	Inferior frontal gyrus	BA 47
3	4.36	15	20	−33	−32	Right	Cerebellum	
4	4.41	44	0	−49	21	Medial	Retrosplenial cortex	BA 29/30
4	4.13	16	24	7	−10	Right	Putamen	
5	4.94	186	4	−50	10	Right	Retrosplenial cortex	BA 29/30
5	4.79	15	12	−21	38	Right	Posterior cingulate	BA 31
5	3.40	9	24	−35	−8	Right	Hippocampus	
6	5.69	15	−20	−37	42	Left	Posterior cingulate	BA 31
6	4.59	31	0	−40	46	Medial	Precuneus	BA 7
Negative saliences: in young, regions in which activity negatively correlates with retrieval accuracy in all tasks and with HH volume in the spatial and temporal tasks.								
3	−6.52	16	−48	−81	4	Left	Occipital gyrus	BA 19
3	−5.25	15	59	−51	−14	Right	Fusiform gyrus	BA 37
3	−3.88	15	−20	−11	19	Left	Thalamus	
4	−7.06	111	0	4	11	Medial	Caudate nucleus	
4	−6.58	33	40	15	58	Right	Premotor cortex	BA 6
4	−5.50	52	32	−10	−37	Right	Inferior temporal gyrus	BA 20
4	−4.71	19	−16	3	70	Left	Premotor cortex	BA 6
6	−6.99	28	−8	−91	−32	Left	Cerebellum	
7	−6.82	57	16	11	69	Right	Premotor cortex	BA 6
7	−6.65	43	−48	−78	−3	Left	Occipital gyrus	BA 19
7	−5.36	15	0	27	−8	Medial	Anterior cingulate	BA 32
7	−4.85	35	−44	36	13	Left	Inferior frontal gyrus	BA 45/46
7	−4.44	7	28	−25	−26	Right	Parahippocampal gyrus	BA 36
7	−4.38	20	−63	−51	−11	Left	Fusiform gyrus	BA 37
7	−4.35	26	44	−66	−7	Right	Occipital gyrus	BA 19
7	−4.22	18	36	7	59	Right	Premotor cortex	BA 6

Note: Temporal lag represents the time interval (2 s each) after event-onset, when a cluster of voxels exhibited a peak bootstrap ratio reflecting the identified effect. The bootstrap ratio threshold (BSR) was set to +/− 3 for the hippocampus (HC), and +/− 3.5 for all other areas. The spatial extent refers to the total number of voxels included in the voxel cluster (threshold =/>5 for HC and =/>15 for all other areas). The stereotaxic coordinates are reported in Talairach coordinates, in mm, and the Brodmann Areas (BA) were determined by reference to Talairach and Tournoux (1988). Hem = Hemisphere.

older adults (for a list of local maxima, see Table 4, for singular image and correlation profile, see Fig. 2). No positive saliences were identified for this LV at the threshold specified. Thus we focus only on the pattern associated with negative saliences in the two age groups. In older adults, LV 2 identified a pattern of whole brain activity that was related to HH volume in all tasks, but to retrieval accuracy only in the spatial context memory task. In young adults, this same pattern of whole brain activity was identified during temporal context encoding and increased activity in these regions was significantly correlated with increased temporal retrieval accuracy and to larger HH volumes. These negative salience regions included bilateral hippocampus, left parahippocampal gyrus, bilateral premotor cortex, right VLPFC, bilateral dorsolateral PFC (DLPFC), bilateral anterior PFC, left fusiform gyrus and bilateral middle temporal gyrus (BA21).

3.　Discussion

The first goal of this study was to examine the three-way association between individual differences in HH volume, activity in whole-brain encoding networks and retrieval accuracy in young adults. We predicted that HH volume would be related to performance-related networks in the two context tasks, due to the associative nature of these encoding tasks. In addition we were interested in determining if age-related context memory deficits are related to alterations in this three-way association with age; as a result of age-related gray matter volume loss in the HH. Volumetric results confirmed that older adults exhibited a significant decrease in HH volume.

Retrieval accuracy results revealed that compared to young adults, older adults performed equivalently on item recognition,

Table 4 – Local maxima for LV2 of the ST-bPLS analysis.

Lag	BSR	Cluster size	X	Y	Z	Hem	Gyral location	Brodmann area (BA)
Negative saliences: regions in which activity in the temporal task positively correlates with retrieval accuracy and HH volume in young, and in which activity during the spatial task correlates with accuracy and HH volume in older adults.
1	−5.46	21	−59	1	22	Left	Premotor cortex	BA 6
1	−4.77	22	12	−15	4	Right	Thalamus	
1	−4.34	39	48	−16	−3	Right	Superior temporal gyrus	BA 22
2	−4.45	18	−4	15	69	Left	Premotor cortex	BA 6
2	−4.41	29	−8	−46	6	Left	Retrosplenial cortex	BA 29
3	−4.50	15	48	6	33	Right	Inferior frontal gyrus	BA 44
3	−4.26	19	12	−76	33	Right	Occipital gyrus	BA 19
3	−3.11	13	−32	−16	−9	Left	Hippocampus	
4	−7.91	1384	−44	−31	2	Left	Middle temporal gyrus	BA 21
4	−6.32	526	4	−44	43	Right	Precuneus	
4	−6.18	26	−24	3	−20	Left	Parahippocampal gyrus	BA 28
4	−5.22	31	32	66	8	Right	Anterior frontal	BA 10
4	−5.15	42	−28	62	1	Left	Anterior frontal	BA 10
4	−4.20	25	−59	−62	7	Left	Fusiform gyrus	BA 37
5	−6.98	81	−44	−20	−9	Left	Middle temporal gyrus	BA 21
5	−6.26	439	−36	−56	−34	Left	Cerebellum	
5	−5.63	40	−55	−7	11	Left	Precentral gyrus	BA 42/6
5	−5.29	565	8	−80	33	Right	Occipital gyrus	BA 19
5	−5.20	112	51	43	15	Right	Anterior dorsolateral	BA 46/10
5	−4.99	48	−40	52	23	Left	Anterior dorsolateral	BA 9/10
5	−4.93	15	51	−68	−30	Right	Cerebellum	
5	−4.63	27	−32	58	−3	Left	Anterior frontal	BA 10
5	−4.63	129	51	−15	4	Right	Superior temporal gyrus	BA 22
5	−4.43	124	63	−39	−11	Right	Middle temporal gyrus	BA 21
5	−4.04	34	24	−20	60	Right	Precentral gyrus	BA 4
6	−6.72	321	44	−32	−9	Right	Hippocampus	
6	−5.49	196	32	−87	−23	Right	Cerebellum	
6	−5.38	62	−32	−28	−25	Left	Cerebellum	
6	−4.67	29	−12	2	33	Left	Anterior cingulate	BA 24
6	−4.66	60	−59	−27	9	Left	Superior temporal gyrus	BA 42
6	−4.23	25	−28	−87	−26	Left	Cerebellum	
6	−4.20	21	−51	−59	−7	Left	Fusiform gyrus	BA 37
7	−5.64	46	−59	−51	−1	Left	Middle temporal gyrus	BA 21
7	−4.82	22	24	−1	63	Right	Premotor cortex	BA 6

Note: Temporal lag represents the time interval (2 s each) after event-onset, when a cluster of voxels exhibited a peak bootstrap ratio reflecting the identified effect. The bootstrap ratio threshold (BSR) was set to +/− 3 for the hippocampus (HC), and +/− 3.5 for all other areas. The spatial extent refers to the total number of voxels included in the voxel cluster (threshold =/>5 for HC and =/>15 for all other areas). The stereotaxic coordinates are reported in Talairach coordinates, in mm, and the Brodmann Areas (BA) of the peak coordinate were determined by reference to Talairach and Tournoux (1988). Hem = Hemisphere.
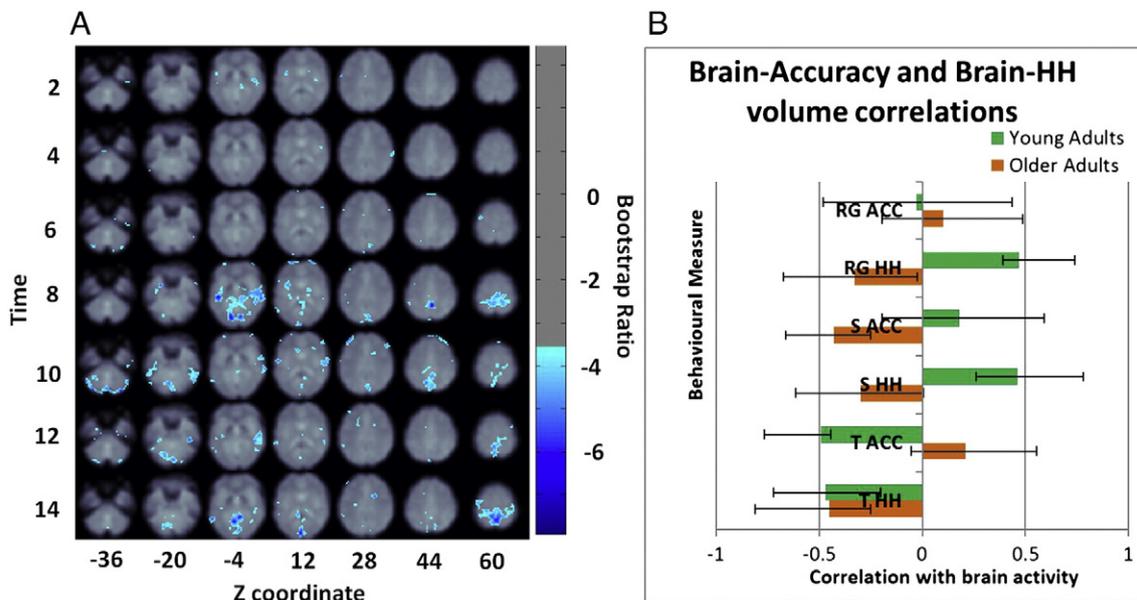
Fig. 2 – Singular image and correlation profile for LV2 of the between-group PLS. A) The singular image for LV2 at a bootstrap of 3.5 (p < 0.0005), which reflects stable and significant activations at 2 to 14 s after event onset. Z coordinates are reported in mm in MNI space. The color-bar represents the color code for the colorized activations on the singular image. Regions colored in red–orange–yellow are positively related with the experimental effect presented in (B). Regions colored in blue are negatively related with the experimental effect presented in (B). B) Correlation profile for LV2. The correlation profile shows how accuracy and HH volume correlate with the pattern of brain activity identified in the singular image in young and older adults. RG = Recognition, S = Spatial context, T = Temporal context, ACC = Accuracy, HH = Average hippocampus head volume.

but performed worse on both spatial and temporal context tasks, consistent with prior reports of an age-related deficit in context memory (Spencer and Raz, 1995). Furthermore, in both groups, accuracy across the item recognition, spatial context and temporal context tasks followed a decreasing linear trend. In young adults, RT for the pleasantness judgment at encoding followed the opposite trend, being fastest during item encoding and slowest during temporal context encoding. In older adults, RT was significantly faster in the item recognition task compared to both context tasks, but was not significantly different between the spatial and temporal context tasks.

The between-group PLS analysis identified two significant LVs, both of which reflected group differences in brain activity–accuracy and brain activity–HH volume correlations. In the following sections we first present a detailed interpretation of the results obtained from young adults. We then discuss how healthy aging impacts HH volume and alters the pattern of association between HH volume, encoding activity and subsequent memory retrieval.

3.1. Young adults: three-way association between HH volume, encoding activity and retrieval accuracy

The first LV from the PLS analysis identified a pattern of structure–function–behavior associations that was unique to young adults. Specifically, this LV identified a network of brain regions which exhibited greater activity during all encoding tasks, as a function of larger HH volume. Furthermore, increased activity in this context encoding network correlated with subsequent retrieval accuracy. Therefore, in young adults LV1 identified a

general episodic encoding network that was positively correlated with HH volume, and was associated with subsequent retrieval.

The brain regions identified in LV 1 included right hippocampus and right VLPFC (BA 47). Activity in hippocampus and VLPFC has been routinely reported in studies of subsequent memory (Kim, 2011) and the interaction between these two regions is thought to be important to successful encoding (Simons and Spiers, 2003). Therefore, young adults with larger HH volumes activated these two nodes of a traditional face encoding network (Rajah et al., 1999) to a greater degree, and increased activity in this network correlated with increased subsequent retrieval.

Of additional interest is that many of the brain regions identified in LV 1 were located along the midline: medial PFC, posterior cingulate, precuneus and retrosplenial cortices. These brain regions have been characterized as being part of the default mode network (DMN), which has been defined as a set of functionally connected brain regions that exhibit task-induced deactivation and increase activation at rest (Buckner et al., 2008; Deco et al., 2011; Raichle and Snyder, 2007). Although the role of the DMN in cognition remains unclear, there is some evidence that this network engaged during mind-wandering and self-referential processing (Addis et al., 2009; Buckner et al., 2008; Christoff et al., 2009). Interestingly, a recent meta-analysis of encoding activity found that all regions of the DMN are associated with subsequent forgetting (Kim, 2011). It was suggested that activation of these regions at encoding may reflect mind-wandering, or lapses in attention, thus leading to poorer subsequent memory (Kim, 2011). However, this association does not extend to all

encoding tasks, as increased activation in midline DMN regions has also been reported to predict subsequent memory when a subjective, social or self-referential orientation task is employed at encoding (Harvey et al., 2007; Macrae et al., 2004; Mitchell et al., 2004). In the current study subjects made a subjective pleasantness judgment during encoding. Therefore, it is possible that the observed positive correlation between larger HH volume and increased activity in hippocampus, VLPFC and midline brain regions during all encoding tasks, reflected the ability of young adults with larger HH volumes to more effectively encode face stimuli using the self-referential subjective pleasantness judgment associated with these stimuli; which in turn benefitted these subjects' subsequent retrieval.

Young adults also activated a second network of brain regions, but only during temporal context encoding (LV 2 from the PLS analysis). Activity in this network was positively correlated with having large HH volume and with better subsequent temporal context retrieval. Brain regions exhibiting this pattern of association in young adults included bilateral hippocampus and bilateral DLPFC. In the current study, young adults exhibited significantly longer RT during temporal context encoding than during the encoding of item and spatial context, likely reflecting additional processing/effort during this task. Moreover, young adults performed the worst on the subsequent temporal context retrieval task, compared to spatial context retrieval and item recognition. Therefore, the temporal context task was the most difficult task at encoding and retrieval in young adults. Increased DLPFC activity has been associated with increases in task effort and concomitant demands on strategic processing (Rajah et al., 2008), and increased hippocampal activity has been associated with increases in the number of associations formed at encoding (Staresina and Davachi, 2008). Moreover, in a recent study, Blumenfield et al. observed greater DLPFC activity during the encoding of inter-item relations versus the encoding of item-specific details/associations (Blumenfeld et al., 2011). However, it is unclear if in that study subjects found the encoding or retrieval of inter-item relations more difficult than item-specific context encoding and retrieval. Taken together these findings suggest that in the current study temporal context encoding required the additional recruitment of brain regions related to implementing a strategy for forming inter-item relations, which is necessary for encoding the relative recency of items (increased DLPFC activity) and for the actual formation of these additional relational associations (increased hippocampal activity). The PLS results also indicate that young adults with larger HH volumes were better able to recruit this second network during temporal context encoding and this benefitted their subsequent temporal context retrieval. Furthermore, our behavioral data suggest that encoding and retrieving inter-item relations (i.e. in the temporal context task) was more difficult than encoding and retrieving item-specific associations (i.e. in the spatial context task) in young adults.

In summary, the young adult results indicate that HH volume was associated with increased activity in two distinct encoding-related networks, identified in LV1 and LV2. The first network (LV1) included right hippocampus, right VLPFC and midline brain regions. Increased activity in this network was positively correlated with HH volume and retrieval accuracy, across all tasks. Thus, this LV identified a general encoding network which was engaged when subjects were required to encoded face stimuli using a subjective judgment of pleasantness decision. Individual differences in HH volume in young adults were also positively correlated with a second network of brain regions that exhibited greater activity only during temporal context encoding only (LV2). This network included bilateral hippocampus and DLPFC, regions thought to be important for forming inter-item associations during temporal context encoding. Interestingly, increased activity in this second relational encoding network was also positively correlated with better subsequent temporal context retrieval accuracy in young adults. Therefore in young adults, individual differences in HH volume were positively correlated with increased activity in both general encoding and relational encoding networks, and with subsequent episodic retrieval. These results are consistent with models that emphasize hippocampus–neocortical interactions as the key mediator of memory formation (Alvarez and Squire, 1994; Eichenbaum, 2000).

3.2.   Older adults: reduced HH volume, and altered HH volume–activity–accuracy association

We had previously reported the hippocampal volumetric results for HH, hippocampal body and hippocampal tail of this sample (Rajah et al., 2010a). In this previous study we noted that older adults exhibited significantly reduced HH volume compared to young adults. The current study indicates that there was also an age-related change in the association between HH volume, encoding-related activity and retrieval accuracy. Specifically, LV 1 from the PLS results shows that older adults did not exhibit a significant three-way association between HH volume, activity in the general encoding network engaged by young adults, which included VLPFC and DMN regions, and subsequent retrieval.

As noted above, activity in VLPFC is thought to be important for mediating successful face encoding. The young adult results (see above) indicate that having larger HH volumes was correlated with increased encoding activity in right VLPFC, which correlated with successful subsequent context retrieval. The right VLPFC has been postulated to play an important role in mediating episodic encoding (Machizawa et al., 2010), and prior studies have shown that age-related deficits in VLPFC activity during encoding are related to subsequent retrieval deficits (Dennis et al., 2008; Grady et al., 1995). Interestingly, Logan et al. have previously reported that under-recruitment of VLPFC during encoding in older compared to younger adults, can be ameliorated if a semantic encoding strategy is employed; but this amelioration of VLPFC activity did not remove the age-related deficit in subsequent retrieval (Logan et al., 2002). This raises the possibility that even when under-recruitment in VLPFC is corrected for in older adults, there remains an underlying deficit which prevents successful encoding. Our results suggest that this underlying deficit may be HH volume loss, which in turn disrupts the positive associations between the HH volume and activity in VLPFC and other brain regions (discussed below) that are important for successful memory encoding, particularly context encoding.

In addition to this age-related change in VLPFC activity during encoding, several studies have demonstrated age-related changes in DMN regions at encoding (de Chastelaine et al., 2011; Duverne et al., 2009; Gutchess et al., 2010; Miller et al., 2008). These studies have reported either attenuation of activation/deactivation in these regions, or a reversal of the relationship between activation and subsequent memory with age. For example, during an item encoding task for adjective stimuli encoded in reference to a friend, Gutchess et al. (2010) reported subsequent memory effects in medial PFC, anterior cingulate and posterior cingulate cortices in young, but subsequent forgetting effects in the same areas in older adults. Furthermore, this pattern of results was inverted when the adjectives were encoded in a self-referential manner. In the present study, we found that midline DMN regions did not contribute to subsequent memory in older adults, and further demonstrated that in contrast with young adults, activity in these regions in older adults was not related to HH volume. Taken together, our results indicate that there is a disruption of the three-way association between encoding activity in right VLPFC and DMN, HH volume and subsequent retrieval with age, which may be due to reduced volume in HH.

However, in the current study, we also observed preserved structure–function associations between HH volume and increased activity in brain regions identified in LV 2 from the PLS analysis, which included bilateral hippocampus and DLPFC. However, in older adults this pattern of association was observed *during all encoding tasks*; in young adults, this pattern of encoding activity was correlated with larger HH volume only during temporal context encoding. This suggests that there was a more generalized recruitment of this network in older adults, compared to young adults during memory encoding. Moreover, increased activity in this network was correlated with subsequent spatial context retrieval in older adults. In young adults, activity in this network was positively correlated with subsequent temporal context retrieval.

In young adults, increased encoding activity in bilateral hippocampus and DLPFC during temporal context encoding was interpreted as reflecting the engagement of an inter-item relational strategy and associative encoding processes during this most difficult, temporal context encoding task. If it is assumed that the functional processes mediated by distinct brain regions remain constant with increasing age (Rajah and D'Esposito, 2005), then our current results suggest that older adults with larger HH volumes engaged relational strategies and associative encoding processes during all encoding tasks, which may reflect attempted compensation for the aforementioned deficits in structure–function associations in a general context encoding network (see above). This altered pattern of recruitment was directly correlated with improved subsequent spatial context retrieval, albeit at a reduced level compared to young adults. Moreover, it is possible that this altered pattern of structure–function association supported the maintenance of item recognition at the levels equivalent to young adults, but due to behavioral ceiling effects the correlation with behavior was not observed in older adults.

Our older adult results are broadly consistent with the neural inefficiency hypothesis (Morcom et al., 2007), and compensation-related utilization of neural circuits hypothesis (CRUNCH) of aging (Reuter-Lorenz and Cappell, 2008), and suggest that due to processing inefficiencies, older adults recruit additional brain regions to perform easier tasks, such as the spatial context memory task, which young adults recruit to perform more difficult tasks, such as the temporal context memory task in the current study. As a result older adults have limited resources to perform these more difficult tasks, and thus exhibited the greatest deficit on temporal context memory tasks (Craik and Byrd, 1982).

It is noteworthy that in the current study older adult performed worse than young adults on context retrieval. Therefore, it is questionable whether the same pattern of encoding activation results would be observed if context retrieval accuracy was matched between age groups. Keeping in mind that our current analyses included *both* behavior and HH volume as covariates of interest in the PLS analysis, it is possible that if older adults performed equivalently *and had preserved HH volumes*, then the patterns of activity observed would be indistinguishable from the young since there would be no group differences in either neural or behavioral measures. However, if young and older adults' context retrieval performance was matched, but age-related differences in HH volume were still present, it is unclear what outcome would have been observed since no study to date has examined fMRI activity during context *encoding*, when subsequent context retrieval was matched in young and older adults. One possibility, given our current interpretation that older adults did not show the three-way association identified in LV1 for young adults due to HH volume reduction with age, is that even if subsequent context retrieval was equated between age groups, older adults would not exhibit a significant three-way association between HH volume, retrieval accuracy and encoding activity in brain regions identified in LV1, since HH volume deficits would still be present. In contrast, given that we interpreted older adults' over-generalized recruitment of LV2 as reflecting functional compensation for the aforementioned disruption, it is possible that if there was age-equivalence in subsequent context retrieval, then older adults would continue to over-generalize and possibly over-recruit brain regions identified in LV2, particularly DLPFC, during all encoding tasks. This prediction is supported by previous studies that have examined encoding activity when performance on a subsequent item recognition task was matched and reported over-recruitment in DLPFC (Dennis et al., 2007; Gutchess et al., 2005; Morcom et al., 2003). For example, Dennis et al. (2007) reported greater event-related over-recruitment in left DLPFC in older versus younger adults during successful encoding, when subsequent retrieval performance was matched. Gutchess et al. (2005) reported over-recruitment of DLPFC, particularly left DLPFC, in older versus younger adults during the encoding of complex scenes when subsequent item recognition was matched.

However, Morcom et al. (2003) observed that over-recruitment of bilateral DLPFC in older, versus younger adults, during encoding, was independent of whether performance was matched between age groups. This suggests that over-recruitment of DLPFC may not be performance related in older adults. Furthermore, in the aforementioned encoding studies (Dennis et al., 2007; Gutchess et al., 2005; Morcom et al., 2003), over-recruitment of medial PFC and age-equivalent

recruitment of VLPFC (areas identified in LV1, see Table 3) were also reported. Therefore, it is also possible that under conditions in which subsequent context retrieval was equivalent between young and older adults, that older adults would over-recruit PFC regions from LV1 (the general encoding network in young adults), despite having HH volume reductions. To discriminate between these alternative possibilities a future study examining the association between HH volume, context encoding activity, and subsequent context retrieval in young and older adults needs to be conducted in which both age groups perform equivalently in context retrieval.

3.3.   Conclusions

This study demonstrated that there are group differences in the three-way association between larger HH volume, whole-brain encoding activity and subsequent retrieval accuracy in young and older adults. Young adults recruited a general encoding network that included right hippocampus, right VLPFC and midline brain regions which positively correlated with having a larger HH volume, and subsequent retrieval accuracy. Young adults also recruited a second network which included bilateral hippocampus and bilateral DLPFC specifically during the most demanding temporal encoding task, which may have reflected the use of additional relational encoding resources in this task. In contrast, older adults exhibited volumetric reductions in HH and altered associations between HH volume and encoding-related activity in VLPFC and midline brain regions, which may have contributed to diminished performance on both context memory tasks. However, we observed that older adults with larger HH volumes may have attempted to compensate for this deficit by recruiting the network that young adults reserved for the most difficult temporal context tasks, *during all encoding tasks* (Cabeza et al., 1997; Grady, 1996). This generalization of structure–function association between HH volume and bilateral hippocampal and DLPFC activity correlated with improved spatial context retrieval, but retrieval performance on this task and the temporal context tasks remained significantly lower in older versus younger adults; thus highlighting that there are limitations to compensation with age.

4.   Experimental procedure

4.1.   Subjects

22 young (age range, 19–34, mean = 23.5) and 21 older (age range, 60–80, mean = 67.48) subjects participated in the study. Volunteers were right-handed and fluent in English. They were administered a battery of neuropsychological tests which included the Language and Social Background Questionnaire (LSBQ; Bialystok et al., 2005, 2007), the Mini-Mental Status Exam (MMSE; Folstein et al., 1975), the Beck Depression Inventory (BDI; Beck, 1987; Beck et al., 1961), the Geriatric Depression Scale (GDS; Brink et al., 1982), the Cognitive Assessment Scale for the Older Adults (CASE; Geneau and Gjedde, 1996), the California Verbal Learning Task (CVLT) long-form free recall, CVLT long-form category assisted free recall and CVLT long-term recognition (Delis et al., 1987, 1988). Independent sample

T-tests were conducted to assess any age differences on these measures. Exclusion criteria for the elderly sample included family history of Alzheimer's disease, the diagnosis of diabetes, the presence of cataracts or glaucoma, high cholesterol levels left untreated in the past 2 years, and high or low blood pressure left untreated in the past 2 years. All participants signed a consent form, and the study was approved by the ethics boards of the Douglas Hospital, the Montreal Neurological Institute and McGill University.

4.2.   Behavioral procedure

Subjects were told that they would be participating in a memory study for non-famous, age-variant human faces. The experiment consisted of 24 encoding lists of 12 face stimuli, 8 per encoding task, each followed by a 1 minute break, and a retrieval task. This yielded a total of 96 encoding events, and 48 retrieval events for each task. During encoding, subjects were presented with twelve face stimuli, one at a time, for 2 s, either on the left or right of the computer screen. They were asked to rate each face as being pleasant (button 1) or neutral (button 2). They were also asked to intentionally encode the stimuli for an upcoming item recognition, spatial context or temporal context retrieval task. The encoding phase was identical across all tasks, but subjects were informed of which retrieval task would follow. Faces were presented in black and white, were cropped from the neck upward and were rated as pleasant or neutral by two independent raters. More details about stimulus construction are described by Rajah et al. (2008).

After each encoding list, a 1 minute distraction task followed, in which subjects were asked to alphabetize two simultaneously presented words. This was followed by an item recognition, spatial context or temporal context retrieval task. In all three tasks, two faces were simultaneously presented on the top and bottom of the computer screen. In the recognition task, one of these was "old" (had been previously seen by the subject) and the other was new. Depending on the retrieval cue, the subject was asked to respond to the old/new face. In the spatial context memory task, two "old" faces were presented, one of which had appeared on the left side of the screen at encoding and the other on the right. Subjects were asked to respond to the face that had been presented on the left/right, depending on the retrieval cue. In the temporal context memory task, subjects were presented with two "old" faces and, depending on the retrieval cue, asked to respond to the one that had been presented most/least recently. Hence, two alternative forced-choice decisions were made in all three retrieval tasks. Stimuli were presented in such a way that spatial information could not inform a temporal judgment and vice versa. They were also oriented vertically to avoid masking effects. Two group (2) × task (3) mixed ANOVAs were performed to assess main effects and group by task interactions in 1) encoding reaction time (RT) and 2) retrieval accuracy. Post-hoc tests were conducted to clarify the results.

4.3.   fMRI procedure

4.3.1.   Data acquisition
Structural and functional images were acquired using a 3T Siemens Trio scanner at the Montreal Neurological Institute.

T1-weighted image volumes were acquired at the start of the experiment using a 9.35 min gradient-echo (GRE) ADNI (Alzheimer's Disease Neuroimaging Initiative) sequence (TR 2300 ms, TE 2.94 ms, flip angle 30°, 160 1 mm sagittal slices, $1 \times 1 \times 1.2$ mm voxels, field of view — FOV = 256 mm^2). BOLD images were acquired using a fast echo-planar imaging (EPI) pulse sequence (TR = 2000 ms, TE = 30 ms, FOV = 256 mm^2, matrix size = 64 × 64, in-plane resolution = 4 × 4 mm, 340 whole brain acquisitions/11:20 min run) while subjects performed the aforementioned behavioral tasks.

4.3.2. Structural image processing and analysis

Images were converted to MNC format and subsequently processed in DISPLAY software (Collins et al., 1994; Pruessner et al., 2000). In order to make comparisons between subjects and groups, all structural scans underwent signal-intensity normalization, non-uniformity correction, and linear transformation into standard stereotaxic space using the MNI template prior to volume segmentation (Collins et al., 1994, 1998; Pruessner et al., 2000; Sled et al., 1998). Two independent raters segregated the hippocampus into tail, body and head (HH) portions using the protocol outlined by Pruessner et al. (2000, 2001). The volume of each sub-region was then averaged across the two hemispheres. Only average ((Left + Right)/2) HH volume is of interest in the current study. Intra-class correlation (3, 1, ICC; Shrout and Fleiss, 1979) was conducted to assess inter-rater and intrarater reliability of HH volume measures. Furthermore, a 2-way age-group × sex ANOVA was conducted to assess the effects of these factors on HH volume.

4.3.3. Functional image processing and analysis

Images were converted to ANALYZE format and subsequently pre-processed in SPM2 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). Functional images were spatially realigned to the first image, spatially normalized to the MNI EPI-template available in SPM2, and smoothed using 10 mm full-width half maximum (FWHM) isotropic Gaussian kernel. The smoothed images were used in the spatio-temporal partial least squares (PLS) analysis (McIntosh et al., 2004), performed using the PLSGUI software (http://www.rotman-baycrest.on.ca/index.php?section=84). For all our analyses, we included only encoding events that were successfully remembered during retrieval.

4.3.4. Spatio-temporal behavior PLS

The goal of the present study was to assess the relationship between HH volume, whole-brain encoding activation and retrieval accuracy. To investigate whole-brain performance-related networks related to HH volume, we used the "Behavior PLS" option in PLSGUI (ST-bPLS; McIntosh et al., 2004; Protzner and McIntosh, 2007). This procedure allows the investigation of the covariance between brain activation, task design and a set of exogenous variables. In this case, the two exogenous variables were HH volume, and accuracy in each of the three retrieval tasks. ST-bPLS identifies a set of mutually orthogonal LVs which maximally relates the activation data to these variables.

Each subject's fMRI data was entered into a matrix, referred to as data matrix, or "datamat". The rows of the datamat represent the mean data for one subject in one condition. In the present experiment, there were three conditions: item recognition, spatial and temporal context tasks. The columns of the datamat contain data for each voxel, at each of 7 time lags. Each time lag contains data for a 2 second period, with the first time lag coinciding with an event onset. Hence, we considered activation for 14 s after event onset, to encapsulate the entire breadth of the hemodynamic response function (HRF). The datamat's rows are organized such that conditions are nested within each subject, and the columns are organized such that time lags are nested within each voxel. All the subjects' data matrices were then stacked together into a single, between group datamat.

This datamat was then cross-correlated with a matrix containing the average HH volume, and accuracy scores for each task and each subject. Singular value decomposition (SVD) was then applied to this correlation matrix, to generate latent variables (LVs) which consist of a singular value, a singular image and a correlation profile for both HH volume and retrieval accuracy. The correlation profile shows how accuracy and HH volume correlate with the pattern of brain activity identified in the singular image in young and older adults. The singular image indicates which brain voxels exhibit the strongest correlation in activity with accuracy and HH volume in young and older adults at each time lag after event onset. A singular image consists of negative and positive brain saliences, which are numerical weights assigned to each voxel at each time lag, and represents a spatio-temporal pattern of whole-brain activity for the entire time series (seven 2 s TRs/time lags after event-onset). Brain regions with positive voxel saliences are positively related to the correlation profile for accuracy and HH volume depicted for young and older adults for a given LV, and those with negative voxel saliences are negatively related to the correlation profiles. Thus the relationship between the singular image and the correlation profile is symmetrical. The singular value indicates the strength of the correlation between encoding-related activity in all brain voxels and the two exogenous variables.

The statistical significance of each LV pair was determined by conducting 500 permutation tests, on the singular values, which represented the proportion of the covariance matrix accounted for by each LV pair (McIntosh and Lobaugh, 2004; McIntosh et al., 1998, 1999, 2004). Permutations were conducted with sampling without replacement so that the event-type order was rearranged for each subject. The probability that the permuted singular values exceed the observed singular values was calculated and only LVs for which this probability was p < 0.05 were deemed significant. To identify dominant and stable voxels within a dot product image, a bootstrap analysis of standard errors was conducted (Efron and Tibshirani, 1986). We conducted 100 bootstrap samples, which allowed us to identify voxels that reliably contributed to the experimental effect within each LV. We considered local maxima within the medial temporal lobes (MTL) to be reliable if they were above a 3 (p < 0.005) threshold (cluster size >5). For local maxima outside the MTL, we used a more restrictive threshold of 3.5 (p < 0.0005) with a spatial extent of 15 or more voxels. Peak coordinates were converted from MNI to Talairach space, and the Tailarach and Tournoux atlas (Talairach and Tournoux, 1988) was used to identify the Brodmann area (BA) localizations of significant activations.

Disclosure statement

Acknowledgments

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