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Research report

Overlapping effects of age on associative memory and the anterior hippocampus from middle to older age

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HIGHLIGHTS

- We assessed age-effects in associative memory and the hippocampus.
- Compared middle-aged and older adults and assessed sex-differences.
- Older adults had worse memory and less hippocampal volume and activation.
- Age-differences in memory were mirrored specifically in the anterior hippocampus.
- Age-effects in all modalities were more pronounced in men as compared to women.

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ABSTRACT

The anterior hippocampus has been implicated in associative memory, and along with hippocampal volume, this type of memory declines with age. However, few cross-sectional studies include middle-aged samples, making it unclear at what point these age-related changes occur. In addition, although men and women have been shown to differ in associative memory and rates of age-related hippocampal atrophy, sex-differences in aging are rarely studied. To address these issues, we assessed memory for word-pairs, hippocampal volume and activation during encoding and retrieval, across middle-aged (n = 39) and older (n = 44) participants, specifically in relation to sex. Older adults showed significantly poorer associative memory compared to middle-aged adults, paralleled by smaller anterior hippocampi and less activation during successful retrieval. The age-by-sex interaction observed in memory performance was also mirrored in the volume and activation of the hippocampus, indicating more pronounced age-effects in men as compared to women. These results indicate a specific role of the anterior hippocampus in verbal associative memory and suggest they both decline between middle-age and older age.

1. Introduction

Decline in both associative memory and the structural and functional integrity of the hippocampus is common in healthy aging [1–4]. There are however limitations to our knowledge about the effects of aging on the hippocampus and associative memory; such as older groups primarily being compared to young groups and rarely middle-aged, as well as age-related effects being assessed independently of sex, implying the assumption that age affects the hippocampus and associative memory equally in men and women – two groups that separately have been reported to differ in both associative memory performance and rates of age-related hippocampal atrophy [5,6]. Here, we assess the effects of age on associative memory performance and the volume and function of the hippocampus in middle-aged and older adults, specifically taking sex into account.

The hippocampus is thought to primarily contribute to memory processes requiring the formation and retrieval of associations between items [7–9], as reported in both patient studies [10–13] and neuroimaging studies on healthy young adults [14–17]. Hippocampal involvement is often evident in successful encoding and retrieval, as studied with event-related paradigms [18,19], and in general, associative memory commonly involves the anterior part of the hippocampus, with activation lateralized to the left when

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the material tested is verbal and otherwise most often to the right [19,20]. The volume of the anterior hippocampus is also predictive of associative memory performance in young adults [21].

As the hippocampus, and primarily its anterior regions, has been shown to be especially sensitive to age-related atrophy [2,3,22–26]; but see Ref. [27], it is plausible that associative memory is particularly susceptible to the effects of aging. This has in fact been reported by several studies [28,29]; see Ref. [30] for a meta-analysis], and termed the Associative Deficit Hypothesis (ADH). It predicts larger age-related deficits in associative memory as compared to single-item memory [1], and although it is most often compared between younger and older groups, it has also been demonstrated across a life-span sample including middle-aged participants [6].

The ADH has to some extent also been observed in hippocampal activation, with older groups, as compared to young, showing reduced activation during specifically associative encoding [31,32]. Performance differences between these age-groups have also been linked to reduced hippocampal activation during associative encoding in general [33], while comparable performance levels, on the other hand, have shown preserved activation during both encoding and retrieval [34]. Age-related differences in activation during associative memory tasks have by several studies been attributed to the anterior hippocampus [35–38], and additionally, reductions in anterior hippocampal volume have been linked to both changes in task-related activation and impaired associative memory performance in older individuals [4,21,25,36].

Although informative of the differences between young and older age, most of these studies do not include middle-aged samples, making our knowledge limited to two extreme time points, without insight as to when these differences occur. While linear decline in associative memory performance across participants in life-span samples has been reported [6,36,39], cross-sectional studies comparing young, middle-aged and older groups report less consistent results; some find significant memory impairments across all three age groups [40,41], while equal performance in middle-aged and older adults has been reported in both associative and non-associative memory [42,43]. These observations have, however, been differentially linked to hippocampal activation; with impaired performance paralleled by equal levels of activation during successful encoding [41], and comparable performance-levels linked to reduced activation during successful retrieval [43].

Altogether, there is converging evidence indicating a role of the anterior hippocampus in associative memory processes, in part validated by their parallel decline with age. However, there is some suggestion that men and women differ in rates of age-related brain atrophy, especially in the temporal lobes and the hippocampus. Although results are inconsistent and some find no differences between groups [2,22,44], because multiple studies do report sex-differences (greater atrophy in men: [5,26,45,46], greater atrophy in women: [47]; region-specific sex-differences: [48]), it is plausible that factors related to sex to some extent affect hippocampal aging. One such factor could be that women often outperform men in associative memory tasks [6,49,50], a group-difference that appears to be stable throughout adulthood as well as in more advanced old age [51,52].

In light of the reviewed findings, our aim was to assess associative memory and the hippocampus in older adults as compared to middle-aged, while providing a collective account of memory, hippocampal structure and function, and their inter-relatedness. Additionally, we considered potential age-differences specifically in relation to sex. For this purpose, we assessed block- and event-related functional MRI (fMRI) activation during the encoding and retrieval of word-pairs as well as hippocampal volume in middle-aged and older men and women. Although research comparing middle-aged and older groups is sparse, we expected potential age-effects to be primarily located in the anterior hippocampus, paralleled by age-related differences in associative memory. Given earlier reports of sex-differences, we expected age-effects on associative memory and the hippocampus to potentially differ between men and women.

The prefrontal cortex is also linked to associative memory in aging, [37,53–55], but as the main focus of this study was the hippocampus, results of whole-brain analyses are presented as Supplementary material.

2. Material and methods

2.1. Participants

Eighty-three participants in two age-groups (40–50 and 60–70 years old) were included from a larger sample of 122 healthy adults out of which only a subset was scanned with fMRI. After excluding behavioral outliers the final sample presented here consisted of 39 middle-aged (18 women/21 men, mean age 44.9 ± 3.3 years) and 44 older adults (19 women/25 men, mean age 65.0 ± 2.8 years) with comparable education length (see Table 1 for demographics). Participants were recruited from the city of Uppsala, Sweden, by newspaper ads and via mail to a sample from the population register. Inclusion criteria were right-handedness, no history of neurological disease or brain damage as well as no contraindications of undergoing magnetic resonance imaging (MRI; e.g. claustrophobia, metal implants). None of the women was receiving any hormone replacement therapy. All participants were native Swedish speakers and had normal or corrected-to-normal vision. Participants gave informed written consent and were compensated in the form of a gift voucher. The study was approved by the regional ethics review board in Uppsala.

2.2. Procedure

Testing took place on two occasions. At one occasion, a battery of cognitive tests was administered, the order counterbalanced across participants within sub-group (middle-aged men/women; older men/women). MRI scanning was performed on a separate occasion at the Uppsala University Hospital, during which participants completed encoding and retrieval phases of an episodic associative memory task in the scanner. All participants were at this time scanned both structurally and functionally.

2.3. Behavioral measures

2.3.1. Cognitive tests

Both age-groups were administered the Mini Mental State Examination (MMSE; [56]), and all participants scored above 24. They also completed a number of cognitive tests, including Trail Making Test parts A and B (TMT-A and TMT-B), measuring cognitive flexibility and visuomotor speed [57], Letter Digit Substitution Test (LDST) measuring cognitive processing speed [58], Synonyms from the Dureman-Sälde battery (SRB; [59]) measuring verbal function, Corsi Blocks assessing visuo-spatial working memory [60], Mental Rotation, and a verbal fluency task (FAS). A test assessing single-item memory for common Swedish nouns, consisting of 50 targets presented at encoding and again at recognition mixed with 25 distractors, was also included. In addition, participants completed the Montgomery-Åsberg Depression Rating Scale (MADR-S; [61]). The cognitive performance of all groups is presented in Table 1. As part of a larger project, participants also filled out the NEO PI-R questionnaire [62] and an in-house questionnaire on lifestyle factors, gave a sample of saliva for gene-analysis and a blood sample for hormone-analysis.

Table 1
Demographics and performance in the associative memory task and cognitive tasks (standard deviations in parentheses).

	Middle-aged			Older		
	Men	**Women**	**All**	**Men**	**Women**	**All**
Age, years	44.3 (3.3)	45.6 (3.2)	44.9 (3.3)	65.0 (2.8)	65.0 (3.0)	65.0 (2.8)
Education, years	16.9 (4.7)	16.8 (3.5)	16.8 (4.1)	15.9 (4.8)	17.6 (3.9)	16.6 (4.5)
MMSE[1]	*29.8 (.91)**	*28.5 (1.8)**	29.2 (1.5)	29.3 (1.0)	29.2 (1.6)	29.3 (1.2)
Associative memory[a]	0.69 (0.14)	0.63 (0.14)	**0.66 (0.14)****	*0.36 (0.19)**	*0.50 (0.26)**	**0.53 (0.23)****
Imagery success	0.70 (0.21)	0.67 (0.24)	0.69 (0.23)	*0.57 (0.24)**	*0.70 (0.16)**	0.64 (0.22)
Word-list memory[a]	0.71 (0.12)	0.66 (0.12)	**0.67 (0.12)****	0.58 (0.16)	0.63 (0.12)	**0.60 (.15)****
Corsi Blocks Forwards	5.4 (1.0)	4.9 (.94)	**5.2 (1.0)****	4.2 (1.1)	4.3 (.82)	**4.3 (1.0)****
Corsi Blocks Backwards	5.1 (0.4)	4.9 (0.64)	**5.1 (0.51)****	4.3 (1.1)	4.1 (0.81)	**4.2 (0.96)****
Letter-Digit Substitution	38.0 (7.5)	38.9 (5.9)	**38.5 (6.7)****	31.0 (5.7)	32.6 (6.0)	**31.7 (5.8)****
Mental Rotation	*26.6 (6.9)***	*12.6 (7.2)***	**20.1 (9.9)****	10.0 (11.3)	7.2 (7.3)	**8.8 (9.8)****
MADR-S[2]	4.9 (7.6)	4.1 (3.6)	4.5 (5.9)	3.6 (3.5)	3.8 (3.8)	3.7 (3.6)
SRB (Synonyms)	24.9 (3.2)	25.6 (1.5)	25.2 (2.6)	25.1 (2.6)	25.3 (3.0)	25.2 (2.7)
Trail-Making Test A (s)	26.5 (10.0)	30.7 (12.5)	**28.5 (11.3)****	38.3 (24.3)	38.9 (10.0)	**38.5 (19.2)****
Trail-Making Test B (s)	54.6 (17.5)	56.2 (17.9)	**55.3 (17.4)****	81.0 (36.8)	78.7 (26.6)	**80.0 (32.5)****
Verbal Fluency	49.6 (16.4)	49.4 (14.5)	49.5 (15.4)	43.4 (11.2)	49.5 (15.6)	46.1 (13.5)

Bold: Significant difference between age-groups; *Italics:* Significant sex-difference within age-group.
Note: Age-differences within sex mirrored the overall differences between age-groups, except for Imagery success*, and Word-list memory** where age-differences were only significant in men.
[1] Mini Mental State Examination.
[2] Montgomery-Åsberg Depression Rating Scale.
[a] Memory performance presented as adjusted recognition (rate of hits-false alarms).
* $p < 0.05$.
** $p < 0.001$.

2.3.2. Associative memory task

During scanning, participants performed a memory task requiring them to form and remember associations between words presented in pairs. The material had been piloted to allow for an optimal level of task difficulty and potential age-differences in performance. The task structure was a mixed design, adapted from that used by [34], allowing both block- and event-related analyses. The encoding phase of the task consisted of 64 pairs of unrelated words; common Swedish concrete nouns presented in white on a black background (e.g. DOCTOR-BEACH). There was no overlap in words between this task and the single-item word-list task administered during cognitive testing. Items were presented for 4 s in encoding blocks of four items; they were separated by a fixation cross located in the center of the screen (jittered between 1500 and 2500 ms). Participants were asked to create a mental image containing the two presented words, and for each pair indicate if they succeeded or not by pressing MRI-compatible response buttons (Tethyx Joystick, Current Designs Inc., Philadelphia, USA). In between the encoding blocks, participants completed a control task in which a fixation cross, after a duration of 1000–2500 ms, turned into a circle. The circle was presented for 500 ms before being replaced by a second fixation cross; lasting between 2000 and 3500 ms. Total duration of each cross-circle-cross trial was always 5s. Participants were instructed to press a button as soon as they saw the circle appearing. Like the encoding blocks, each control block included four trials. In total, the encoding phase consisted of 16 test blocks and 16 control blocks (lasting 24 s and 20s, respectively), with a total duration of 12 min.

The retrieval phase followed after an 11 min retention period during which the anatomical T1-weighted images were acquired. This phase followed the same structure as the encoding phase; 16 retrieval blocks consisting of 4 items each (separated by a jittered fixation cross; 1500–2500 ms), intermixed with 16 control blocks each containing 4 repetitions of the cross-circle-cross task. Word-pairs were now presented for 3s, making the entire session last 10.5 min. Here, all words were presented again but now with 32 of the original 64 word-pairs recombined to form new pairs, while 32 pairs appeared intact. Recombination meant leaving the left-hand word of a pair in its original position while rearranging right-hand words in order to create new combinations. As far as possible, recombination was made as to preserve the form of the original pair; a left-hand word was paired with a right-hand word with a similar number of syllables as the original one. Participants had to judge if the presented pair was intact or recombined and gave their answer by pressing the response buttons. For the analyses, answers were classified as hits, misses, false alarms and correct rejections and used to calculate the dependent measure of adjusted recognition (Hits-False Alarms) for each participant. Prior to scanning, participants received thorough instructions and completed a short practice version of the task. The experiment was constructed and run in E-Prime (Psychology Software Tools Inc., Pittsburgh, USA) and presented through goggles attached to the MRI head coil (Nordic Neuro Lab, Bergen, Norway).

2.4. MRI data acquisition

Scanning took place at Uppsala University hospital, on a Philips Achieva 3T scanner using an 8 channel head coil (Philips Medical Systems, Best, the Netherlands). Anatomical T1-weighted images were collected using a 3D magnetization prepared rapid gradient echo sequence (TR = 9 ms; echo time = 4 ms; flip angle = 9°; field of view = 240 × 240 mm^2; voxel size = 1 mm^3 isotropic voxels; 170 slices). Functional T2*-weighted images were collected with an echo planar imaging sequence (TR = 3000 ms; echo time = 35 ms; flip angle = 90°; field of view = 230 × 230 mm^2; voxel size = 3 × 3 × 5 mm; 34 coronal slices perpendicular to the longitudinal axis of the hippocampus).

2.5. MRI data preprocessing and analysis

All MRI data were preprocessed and analyzed in SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL, London, UK), through Matlab R2012b (Mathworks Inc., MA).

2.5.1. Voxel-based morphometry

Anatomical T1-weighted images were preprocessed for voxel based morphometry (VBM) analyses; segmented, normalized to MNI-space and smoothed with a Gaussian kernel of 8 mm full-width at half-maximum (FWHM). Total intracranial volume (TIV)

was controlled for by summing and entering grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) values as a covariate in all analyses using the ANCOVA option for global normalization. An explicit grey matter mask was used in all analyses; created from the segmented and normalized T1 images of all participants, to ensure only grey matter voxels were included in the analyses. Two types of volumetric analyses were then performed: a) independent-samples *t*-tests to compare groups (age-groups and men and women within and between age-groups) and b) regression analyses assessing potential associations between hippocampal volume, age and memory performance.

2.5.2. fMRI data

Functional images were spatially realigned to correct for head-movements during scanning (realignment parameters were later included as covariates in single-subject general linear model analyses), slice time corrected for acquisition order, normalized to MNI-space and smoothed with a Gaussian filter kernel of 6 mm FWHM. At single-subject level, a 128s high-pass filter was applied to the time-series in order to minimize low frequency noise, and the experimental conditions and events were modeled with a canonical hemodynamic response function. Statistical contrasts at single-subject level were created using the general linear model in two different ways; a) a block-design approach where blocks of encoding and retrieval were contrasted against blocks of the control task and b) an event-related design approach where activation for remembered items (hits) was contrasted with the activation for forgotten items (misses) during both encoding and retrieval, to identify activation related to successful encoding and retrieval specifically. At group level, contrasts were created using a random effects model; one-sample *t*-tests were used to assess over all activation within-group, and independent-samples *t*-tests were used to compare groups; age-groups and men and women within and between age-groups. Additionally, in the block-design approach, regression analyses assessed potential associations between hippocampal activation, age and memory performance. All contrasts, both in volumetric and activation analyses, were thresholded at a significance level of $p < 0.05$, corrected for multiple comparisons (FWE).

2.5.3. Hippocampus ROI-analyses

Both structural and functional region of interest (ROI) analyses were performed using a sample-specific hippocampus mask created from the output images from Freesurfer's automated subcortical segmentation process [63,64]. Right and left hippocampal masks were then further divided into anterior (aHC) and posterior (pHC) sub-segments for analyses assessing possible region-specific effects of age and sex within the hippocampus. The anterior-posterior distinction was made just posterior to the uncal apex [65] and a gap of 4 mm separated the two ROI's. In MNI coordinates; the anterior mask extended from *y*: −2 to *y*: −18 and the posterior mask from *y*: −24 to *y*: −42.

3. Results

3.1. Behavioral measures

3.1.1. Cognitive tests

The middle-aged group outperformed the older group on nearly every cognitive test, as well as the single-item word-list task – however, there were no significant differences between groups in the SRB synonyms test or in verbal fluency (see Table 1). While middle-aged men outperformed middle-aged women on the Mental Rotation task, no such difference between men and women was present in the older group. The age-groups were comparable on both MMSE and MADR-S scores, although the middle-aged women scored significantly lower than the middle-aged men on MMSE. One middle-aged man had a MADR-S score corresponding to mild depression, but as his cognitive performance was normal, he was kept for the analyses. Assessing age-effects within sex, the pattern was the same for both men and women, and mirrored the general results between age-groups. However, there was a sex-specific age-difference in performance on the single-item word-list task where older men performed significantly worse compared to the middle-aged men, while there was no difference between age-groups within women.

3.1.2. Associative memory

Adjusted recognition scores (hits-false alarms) were entered into an ANOVA with age-group and sex as independent variables. A main effect of age-group was observed ($F = 29.40$, $p < 0.001$), with the older group performing significantly worse compared to the middle-aged group (see Table 1). There was also an interaction between age-group and sex ($F = 6.01$, $p = 0.02$), with a greater effect of age within men compared to women (Fig. 1A). In line with this, memory performance was negatively correlated with age in both men ($r = -0.79$, $p < 0.001$) and women ($r = -0.32$, $p = 0.06$), but significantly greater in men ($Z = 3.22$, $p < 0.001$). An effect of sex was only evident in the older group where women outperformed men ($t = -2.10$, $p = 0.02$).

Due to the middle-aged women scoring low on MMSE, an ANCOVA was run with MMSE scores as the covariate, again analyzing adjusted recognition in relation to sex and age-group. The results were in general the same, although the interaction effect now just fell short of significance ($F = 3.31$, $p = 0.07$). However, the negative correlation between memory and age remained significantly greater in men ($Z = 2.48$, $p = 0.007$).

Participants' responses during encoding, indicating whether or not they successfully could create a mental image containing both words of a pair (imagery success, presented in Table 1) were analyzed, showing that rates of reported imagery success were significantly correlated with recognition performance across all participants; $r = 0.35$, $p < 0.001$ (with coefficients ranging from $r = 0.26$ to 0.46 across subgroups). The interaction between age-group and sex was not significant ($F = 2.32$, $p = 0.13$), although *t*-tests showed that older men reported less imagery success than both middle-aged men ($t = -1.73$, $p = 0.05$) and older women ($t = -1.8$, $p = 0.04$), as well as there being no difference between middle-aged and older women ($t = -0.46$, $p = 0.33$), or between middle-aged men and women ($t = 0.46$, $p = 0.33$).

3.2. Hippocampal volume

Volume in the bilateral anterior, but not posterior, hippocampus was negatively associated with age across the whole group of participants; in the left hippocampus (LHC) a cluster of 24 voxels (peak voxel at MNI coordinate (xyz) −15, −7, −20; $t = 3.65$, $p = 0.006$) and in the right hippocampus (RHC) a smaller cluster of 6 voxels (16, −7, −20; $t = 3.39$, $p = 0.01$), see Fig. 2A,B. Volume values for each participant were extracted from these age-affected areas and entered into an ANOVA of sex and age-group to investigate the potential role of sex in the negative effect of age on aHC volume (results are presented in Fig. 1B). Although there was no significant interaction effect between sex and age-group ($F = 1.50$, $p = 0.22$), only men showed a difference between age-groups in these specific areas ($t = 3.04$, $p = 0.002$), whereas women did not ($t = 1.23$, $p = 0.12$). VBM analysis showed that older men displayed smaller volumes than middle-aged men in both LHC: 24 voxels ($t = 3.34$, $p = 0.004$); and RHC: 6 voxels ($t = 3.59$, $p = 0.001$), illustrated in Fig. 4A.

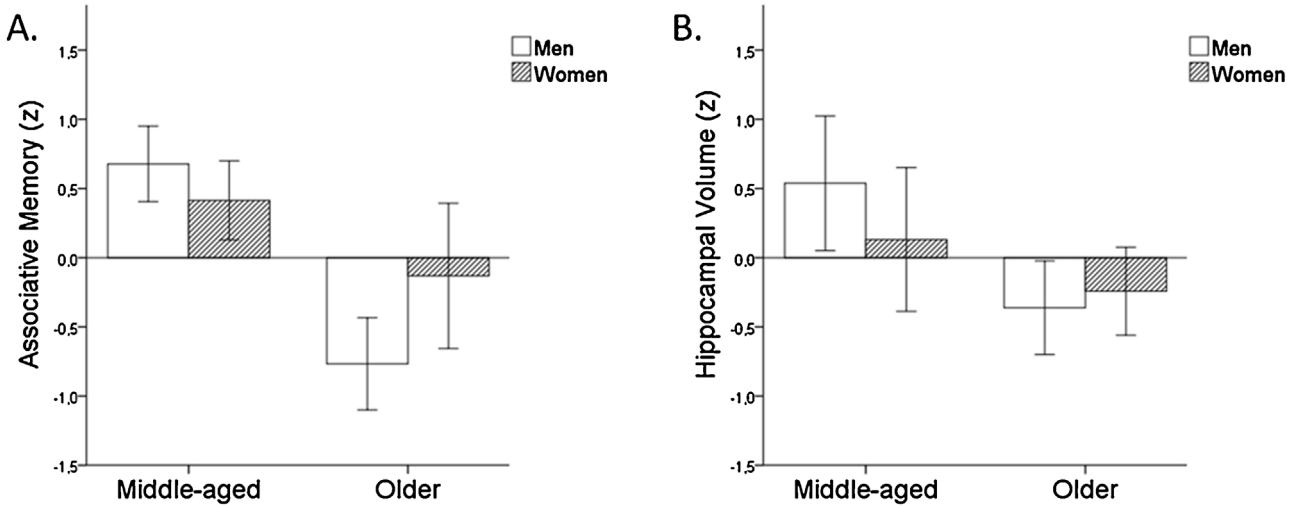

Fig. 1. Standardized values (Z) of (A) associative memory performance and (B) volume in the age-affected regions of the bilateral anterior hippocampus. (A) Memory performance showed a significant main effect of age ($p < 0.001$), as well as an age-by-sex interaction ($p = 0.02$). The difference between age-groups was greater in men ($p < 0.001$) as compared to women ($p = 0.04$). A sex-difference was only present in the older group ($p = 0.02$). (B) There was a main effect of age on hippocampal volume ($p = 0.004$). There was only a significant difference in volume between age-groups in men ($p = 0.002$).

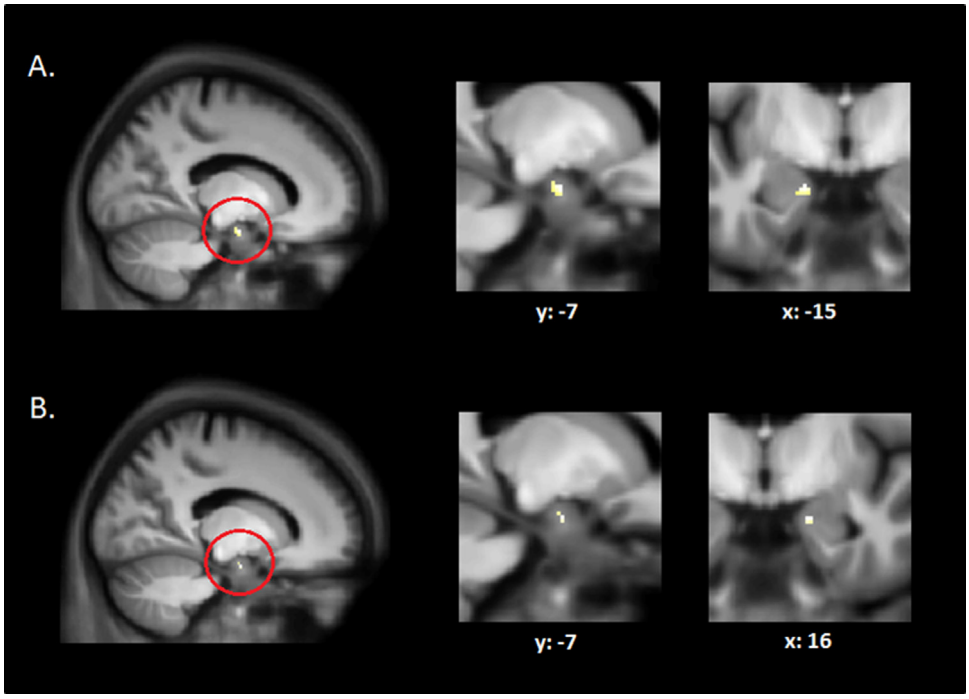

Fig. 2. Areas in the (A) left and (B) right anterior hippocampus showing a significant negative association with age across all participants (LHC: −15, −7, −20; $p = 0.006$; RHC: 16, −7, −20; $p = 0.01$).

3.2.1. Associations with memory performance

Volume values extracted from the bilateral anterior regions, where the negative effect of age was found, were analyzed to assess potential correlations with memory performance (results are presented in Table 2). There were positive correlations present across the entire group of participants (Table 2; column furthest to the right), controlled for age, indicating bigger anterior hippocampi being linked to better associative memory. However, after Bonferroni adjustment, these correlations were no longer significant. Considering the sub-groups separately, middle-aged women and older men showed the strongest associations between hippocampal volume and memory (Table 2; Fig. 3). The middle-aged women's correlation between right aHC volume and performance ($r = 0.51$) was significantly larger than that of the middle-aged men ($r = -0.04$; $Z = 1.72$, $p = 0.04$), but the older men's correlation ($r = 0.34$) was not significantly larger than the older women's ($r = -0.003$; $Z = 1.09$, $p = 0.14$).

3.3. Task-related hippocampal activation

3.3.1. Block-related activation

Both age-groups activated the aHC bilaterally (mainly to the left), and the left pHC during encoding. Group comparisons showed that there was no difference between middle-aged and older participants (see Table 3 for hippocampal activation results). In line with this, there was no association between hippocampal activa-

Table 2
Correlations (Pearson's r), between associative memory performance and (a) hippocampal volume in age-affected anterior regions, and (b) block-related activation during encoding.

	Middle-aged			Older			All Participants[a]
	Men	Women	All	Men	Women	All	
Volume							
Anterior, L	0.07	0.42*	0.26^	0.20	0.17	0.20	0.18*
Anterior, R	−0.04	0.51*	0.25^	0.34*	−0.003	0.20	0.19*
Encoding activation							
Anterior, L	0.21	0.38^	0.35*	0.22	0.26	0.23^	0.23*
Anterior, R	0.30	0.66**	0.49***	0.22	0.43*	0.33*	0.37***
Posterior, L	0.03	0.18	0.16	0.37*	0.27	0.32*	0.28**

Bonferroni adjusted sig. level across all participants = $p < 0.01$; within sub-groups = $p < 0.05$.
L = left; R = right.
^ $p < 0.07$.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[a] Correlation analyses including all participants are controlled for age.

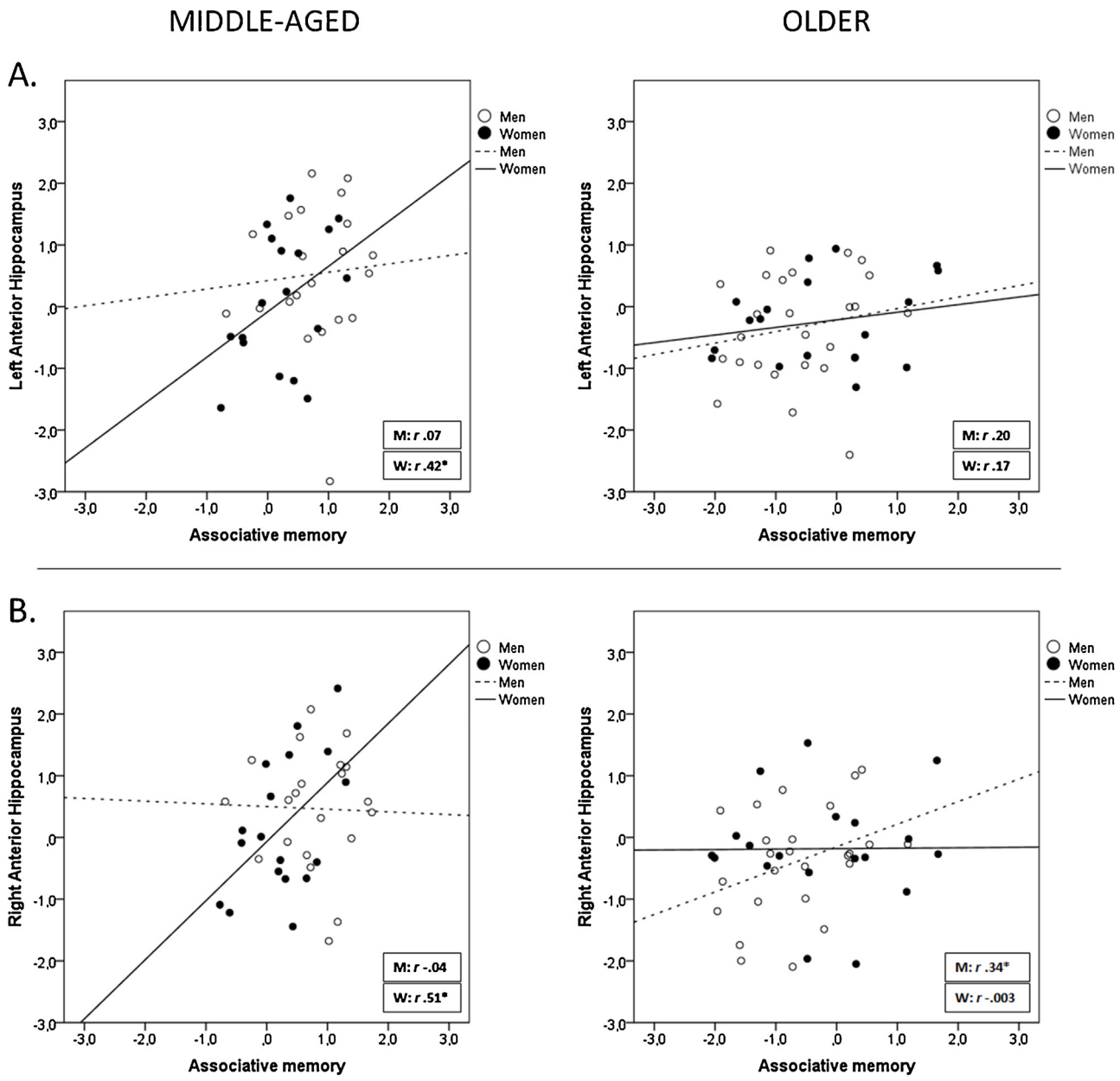

Fig. 3. Scatterplots illustrating correlations between standardized (Z) associative memory performance and volume in (A) the left anterior hippocampus and (B) the right anterior hippocampus, displayed for men (M) and women (W) within the middle-aged (left) and older (right) groups. * $p < 0.05$.

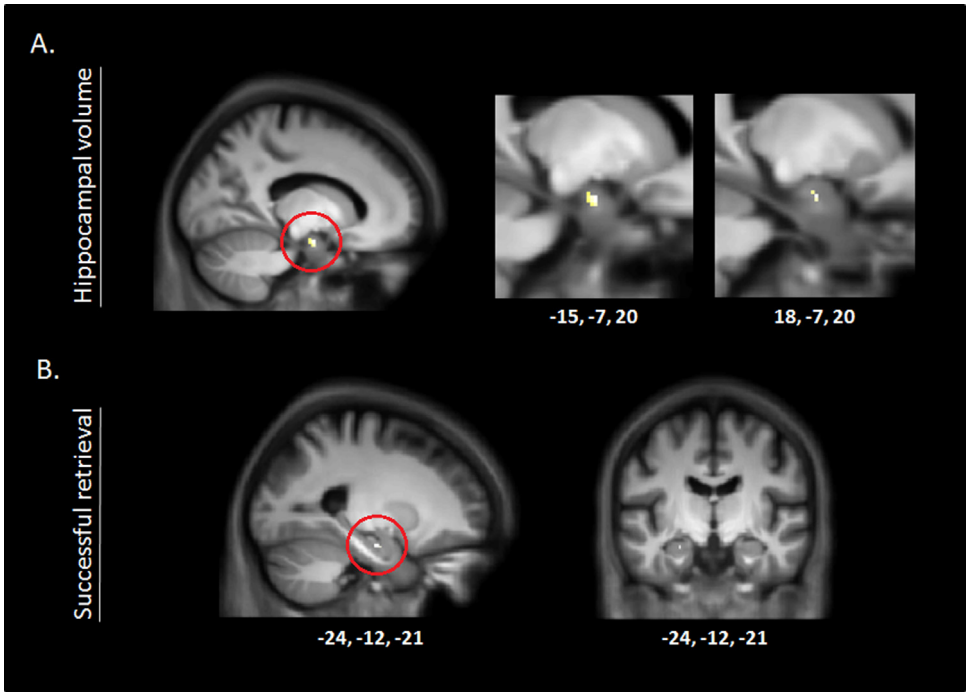

Fig. 4. Areas in the anterior hippocampus where middle-aged men showed (A) greater hippocampal volume and (B) greater activation during successful retrieval, as compared to older men.

Table 3
Block-related and event-related activation in the hippocampus during associative encoding and retrieval.

	x	y	z	voxels	*t*-value
Encoding					
Middle-aged					
Anterior, L	−21	−18	−15	194	7.93
Anterior, R	21	−13	−20	14	4.16
Posterior, L	−26	25	−12	125	9.57
Older					
Anterior, L	−22	−16	−17	149	7.80
Anterior, R	18	−12	−18	31	4.86
Posterior, L	−26	−25	−12	108	7.23
Retrieval					
Middle-aged					
Posterior, L	−15	−37	0	2	3.80
Older					
Posterior, L	−16	−39	0	5	4.75
Middle-aged < Older					
Posterior, L	−27	−24	−15	10	3.38
Successful retrieval					
Middle-aged					
Anterior, R	24	−15	−23	31	4.68
Posterior, L	−26	−33	−8	25	4.69
Older					
Posterior, L	−33	−25	−14	6	3.77
Middle-aged > Older					
Anterior, R	22	−16	23	12	4.21
Successful retrieval within men					
Middle-aged > Older					
Anterior, L	−24	−12	−21	5	3.61

L = left; R = right.

tion and age. During retrieval, both age-groups activated only the left pHC, and activation in a small area in the left pHC was positively associated with age (10 voxels, −27, −24, −15; t = 3.38, $p = 0.02$). There were no age-group differences within either men or women specifically, and no sex-difference within either age-group.

3.3.2. Event-related activation

There was no additional encoding activation for subsequently remembered word-pairs compared to subsequently forgotten word-pairs either within the whole hippocampus or within the anterior/posterior hippocampal sub-regions, across all participants

or within age-groups or sub-groups. However, both middle-aged and older adults showed greater hippocampal activation during hits as compared to misses during retrieval, thus displaying hippocampal involvement in successful retrieval (Table 3). The middle-aged group activated the right aHC and the left pHC, while the older group only significantly activated an area in the left pHC. In line with this, the older group activated an area in the right aHC significantly less compared to the middle-aged group (12 voxels, 22, −16, 23; t = 4.21, $p = 0.007$). Older men showed less activation in the left aHC compared to middle-aged men (5 voxels, −24, −12, −21; t = 3.61, $p = 0.03$, presented in Fig. 4B), but there was no such age-difference within women. There were no sex-related differences within either age-group.

3.3.3. Associations with memory performance

Values corresponding to signal-change during encoding and retrieval were analyzed to assess possible correlations with memory performance (results are presented in Table 2). Activation in the anterior hippocampus, primarily to the right, was overall positively related to memory performance across all participants and within each subgroup. The difference in correlations between middle-aged men ($r = 0.30$) and women ($r = 0.66$) for right aHC activation just fell short of significance (Z = 1.38, $p = 0.08$), while there was no significant difference between older men ($r = 0.22$) and women ($r = 0.43$; Z = 0.72, $p = 0.24$). Activation in the left pHC was predominantly correlated with memory in the older group, and showed no significant difference in strength between men and women within age-groups. There were no significant correlations between hippocampal activation during retrieval and memory performance.

3.3.4. Associations with hippocampal volume

In order to test the possibility that the observed age-differences in task-related activation were a result of the differences in hippocampal volume between age-groups, we re-ran the three SPM contrasts producing age-differences, this time entering the individual volume values from the areas in the anterior hippocampus negatively associated with age as a covariate. Results showed that no voxels now exceeded the FWE corrected $p < 0.05$ level. When assessed at a FWE uncorrected level of $p < 0.001$, age-differences however remained relatively unchanged.

4. Discussion

The aim of the present study was to assess associative memory and hippocampal integrity in older as compared to middle-aged adults, providing information on age-related impairments not available in previous research due to the dominating focus on comparisons between young and older groups. In addition, we specifically assessed if age-effects in associative memory and hippocampal volume and function are equal in men and women, or if sex acts as a modifying variable.

Overall, our results demonstrate a link between associative memory and the anterior hippocampus, with age-related memory differences mirrored by smaller anterior hippocampal volumes and less task-related activation. As such, the hippocampus reflected the age-by-sex interaction observed in memory performance, indicating greater age-related effects in men as compared to women. However, it is necessary to further evaluate this interaction, taking specific aspects of the behavioral results into consideration.

In line with our predictions, and earlier research reporting the anterior hippocampus as especially vulnerable to age-related atrophy [3,22,23], there was a negative main effect of age on hippocampal volume in bilateral anterior regions specifically. This age-effect in volume mirrored the significant difference between age-groups in memory performance; with the inferior associative memory of the older group paralleled by significantly smaller anterior hippocampi as compared to the middle-aged group. This observation in part accounted for the finding that older adults showed less anterior activation related to successful retrieval and over-recruitment of a posterior area during retrieval in general, as differences were reduced when controlling for volume; indicating quantitative differences and possible compensatory efforts due to volume reductions in the anterior hippocampus.

The two age-groups nonetheless displayed comparable levels of hippocampal activation during encoding, and no activation specific to successful encoding (i.e. activation for subsequently remembered word-pairs contrasted with activation for subsequently forgotten word-pairs). Possibly, this indicates that encoding was less affected than retrieval by the volumetric differences between age-groups, and that the hippocampus' functional contribution to the differences in memory performance observed here was greater during retrieval than encoding. In line with this, encoding-related activation was positively correlated with memory performance in similar ways in both age-groups. While these results do not replicate findings from comparisons of older and younger adults, where older groups show reduced activation during both associative encoding in general [33] and successful encoding in specific [31], they are in line with the only previous neuroimaging study observing differences in associative memory between middle-aged and older adults; also reporting encoding-activation and its relation to memory performance as unaffected by age [41].

The age-related effects in hippocampal volume and activation were greater in men as compared to women, mirroring the age-by-sex interaction found in memory performance. Importantly, only men displayed significant age-differences across all measures; associative memory, hippocampal volume and task-related activation, while women showed weaker effects of age in all modalities. This is in line with the middle-aged women performing unexpectedly poor in the associative memory task, and in contrast to earlier findings of marked sex-differences in associative and episodic memory [6,49–52]. Taken together with their overall low MMSE-score, we may hypothesize that the lack of age-differences within women was due to the middle-aged group simply being a low-performing and unrepresentative sample. Since associative memory performance in general was reflected in the hippocampus it is likely that age-related differences, similar to those found in men, would be evident in women as well, if comparing the older women to a group of more typically performing middle-aged women.

Another aspect of the behavioral data contributing to the interaction effect is participants' reported rates of imagery success during encoding. Based on the observation that single-item memory is less affected by age than associative memory [1], unitizing separate features into integrated items during encoding has been proven a successful strategy benefitting associative memory performance and decreasing age-related memory impairments [29,66]. Here, participants' reported rates of imagery success during encoding were in fact positively correlated with later recognition performance in all groups. The fact that older men reported the lowest rates of imagery success, indicating poor unitization, likely magnified the performance-difference between age-groups in men, while also contributing to the sex-difference specific to the older group.

The significant difference in memory performance between older men and women was not reflected in volumetric or functional differences in the hippocampus. A question arising from this is to what extent sex-differences in memory performance are qualitative in nature and, as such, to what extent they should be expected to be paralleled by differences in the hippocampus. In contrast to differences between age-groups in memory performance, that are both greater in magnitude and related to change in individuals over time, sex-differences may not necessarily be paralleled

by differences in the structure and function of the hippocampus. Since earlier research suggests sex-differences in age-related hippocampal atrophy [5,45,46], it is nonetheless important to continue accounting for potential sex-related differences in the effects of aging on memory and the hippocampus, even if differences in memory between men and women in themselves may not be qualitatively mirrored in the hippocampus.

While encoding-related activation in general was positively correlated with memory, most consistently in the right anterior hippocampus, hippocampal volume showed more inconsistent correlations with performance across sub-groups. We expected positive correlations between memory and anterior hippocampal volume, based on their common decline with age. However, it has been suggested that significant positive structure-function correlations mainly arise as an effect of pathology where performance is impaired, such as in Alzheimer's disease or Mild Cognitive Impairment, with normal levels of hippocampal volume and memory performance being less associated – even in healthy aging, where correlations show an increase in variability rather than in positive strength [67]. Interestingly, although correlations between memory performance and volume in general did not significantly differ between sub-groups, it was the middle-aged women and the older men, the two groups displaying deficiencies, who showed the largest correlation coefficients.

There are some limitations to this study, the first related to the cross-sectional design, which do not allow for the assessment of age-related changes in memory and the hippocampus, only the evaluation of differences between age-groups. Further, our results should be considered preliminary, as the large number of measures presented here is obtained from a relatively small sample divided into smaller sub-groups. In the assessment of age-effects on the structural and functional hippocampal correlates of memory, future studies should use larger samples and adopt longitudinal designs where possible. Another limitation of this study, potentially affecting the power of the event-related analyses, is the fairly small number of word-pairs included in the associative memory task. Increasing the number of events would perhaps increase the chances of observing hippocampal activation specific to successful encoding, something we did not observe here but that has been reported earlier [18,31,68–70]. On the other hand, analyses of successful retrieval in fact yielded significant activation within both age-groups, indicating that the lack of effects observed for encoding should not be due solely to the number of hits and misses analyzed. The cost of increasing word-pairs would have been a decrease in memory performance, already quite low since all words presented at retrieval had previously been seen during encoding. This in turn is a strength of the current design, reducing the impact of novelty introduced by new items as distractors during retrieval.

Here, we report age-differences in associative memory mirrored in both hippocampal volume and activation between middle-aged and older adults. In line with earlier findings in young adults [19,71,72], we demonstrate a link between associative memory and the anterior hippocampus. As previous research assessing memory and the hippocampus in older age most often use young control groups and limits assessments to either the structural or functional integrity of the hippocampus, our study contributes by conjunctively providing behavioral, structural and functional results in the comparison of older adults to middle-aged.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2016.10.002.

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