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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.