Hippocampal subfield volumes contribute to working memory interference control in aging: Evidence from longitudinal associations over 5 years

P. Andersson [a,*], G. Samrani [b,c,d], M. Andersson [c,d], J. Persson [a,b]

[a] Center for Life-span Developmental Research (LEADER), School of Behavioral, Social and Legal Sciences, Örebro University, Sweden
[b] Aging Research Center (ARC), Karolinska Institute and Stockholm University, Sweden
[c] Department of Radiation Sciences, Umeå University, Sweden
[d] Department of Integrative Medical Biology, Umeå University, Umeå, Sweden

ABSTRACT

In memory, familiar but no longer relevant information may disrupt encoding and retrieval of to-be-learned information. While it has been demonstrated that the ability to resolve proactive interference (PI) in working memory (WM) is reduced in aging, the neuroanatomical components of this decline have yet to be determined. Hippocampal (HC) involvement in age-related decline in control of PI is currently not known. In particular, the association between HC subfield volumes and control of PI in WM has not been examined previously. Here we investigate the associations between mean level and 5-year trajectories of gray matter subfield volumes and PI in WM across the adult life span (N = 157). Longitudinal analyses over 5-years across all participants revealed that reduced volume in the subiculum was related to impaired control of PI. Age-stratified analyses showed that this association was most pronounced in older adults. Furthermore, we found that in older adults the effect of age on PI was mediated by GM volume in the HC. The current results show that HC volume is associated with the ability to control PI in WM, and that these associations are modulated by age.

1. Introduction

The constant accumulation of memory representations places high demands on a cognitive system that is efficient in controlling the content of memory in order to prevent interference from goal-irrelevant information. Proactive interference (PI) arises from existing memory representations conflicting with new target information. While PI has most commonly been investigated within the domain of episodic memory (Keppel, 1968; Roediger and McDermott, 1995), there is now much evidence that PI plays a critical role also in working memory (WM; Bunting, 2006; Emery et al., 2008). PI is also closely linked with performance levels on WM span tests (Kane and Engle, 2000; Lilienthal, 2017; Lustig et al., 2001; May et al., 1999).

While there is much evidence that WM declines with increasing age, evidence for age-related impairments in inhibition and interference control has been less consistent (Rey-Mermet and Gade, 2017; Verhaeghen, 2011). In general, it seems that in tasks in which conflicting information can be handled within the focus of attention show less of a decline compared to tasks in which the conflict arises from familiar, but no longer relevant information outside the focus of attention (Lustig and Jantz, 2014). One possibility is that age-related cognitive decline is mediated by deficits in interference control or other executive functions, with corresponding consequences on other aspects of cognition (Hasher and Zacks, 1988; McGabe et al., 2010). Indeed, an age-related decline in PI was recently demonstrated using a population-based life-span sample of adults (Samrani and Persson, 2021), and in this particular study PI was also found to predict mean level performance in other cognitive abilities.

Age-related impairments in interference control are most likely related to less efficient brain function, and changes in brain morphology and neuromodulation that occur with increasing age. Much of the work on the neural bases of interference control in WM has focused on the prefrontal cortex. There is a general consensus that the left inferior frontal gyrus, together with the anterior cingulate cortex, and the insula are key regions involved in successful resolution of PI in WM (Badre and Wagner, 2005; Burgess and Braver, 2010; Henson et al., 2002; Jonides and Nee, 2006; Marklund and Persson, 2012; Nelson et al., 2009; Persson et al., 2013; Samrani et al., 2019). Recent evidence suggests that the hippocampus (HC) is critical for interference control (Öztekin et al., 2008). However, little is known about how these regions contribute to resolving PI in WM and in particular what role the HC plays. This is particularly important in studies on aging given the well documented effects of aging on HC gray matter volume (Gorbach et al., 2017; Persson et al., 2012; Raz et al., 2004; Raz et al., 2003).

* Corresponding author. Center for Life-span Developmental Research (LEADER), School of Behavioral, Social and Legal sciences, Örebro University, Fakultetsgatan 1, 702 81, Örebro, Sweden.
E-mail address: pernilla.andersson@oru.se (P. Andersson).

While the HC has been the focus of research of long-term memory functions for decades, its role in WM is less understood. There are indications that the HC may contribute to WM processes; activation in the HC has been demonstrated during fMRI WM tasks (Axmacher et al., 2008; D E Nee et al., 2007), and patients with HC lesions are impaired in WM tasks (Cashdollar et al., 2009; Hannula et al., 2006; Nichols et al., 2006). There is also some recent functional imaging evidence showing that the HC is involved in successful resolution of PI (Öztekin et al., 2008). In particular, the HC may play a key role in distinguishing older from newer information in long term memory (Barredo et al., 2015; Caplan et al., 2007; Yassa and Stark, 2011), and WM (Leszczynski, 2011; Nauer et al., 2015; Ranganath & D'Esposito, 2001; Öztekin et al., 2010) thereby reducing PI. The HC could also contribute to resolving PI by providing contextual information (Beukers et al., 2021). Specifically, contextual information about the temporal position of items could help facilitate the distinction between familiar but no longer goal-relevant items (presented in the incorrect temporal position) from goal-relevant target items (presented in the correct temporal position). Such item-context associations have been found to be important for controlling interference in working memory (Samrani et al., 2017; Szmalec et al., 2011). This key function may be critical for both long-term memory and WM.

In contrast to episodic memory, the neuroanatomical underpinnings of interference control have received much less attention despite its likely role in age-related cognitive impairments. To the best of our knowledge, only one study to date has examined the cerebral morphological properties underlying interference control across the adult life span using both cross-sectional and longitudinal data (Samrani et al., 2019), and this particular study focused on frontal regions only. We focus here on the HC because of their known role in memory functions. In the current study, we use data from a population-based cohort study (N = 151) to examine cross-sectional and longitudinal associations between HC subfield gray matter, and PI in WM across the adult life span. We hypothesize that larger gray matter volume in the HC should be related to better interference control (i.e., less PI). Since it has been demonstrated that brain function and volume might be differentially linked to cognition in younger and older adults (Koen and Rugg, 2019; Park et al., 2004; Rieckmann et al., 2018; Van Petten, 2004), and that brain volume – cognition interactions may be stronger in older adults (Burzynska et al., 2012) we performed age-stratified analyses within groups on younger/middle-aged and older adults, as well as across the whole sample. We also obtained HC subfield volumes to investigate potential differential involvement of different sub-fields. Given the differential involvement of HC subfields in pattern separation and completion and recent evidence that such processes may be active also in working memory (Newmark et al., 2013), we wanted to explore if PI was related to these processes. While the n-back task used in the present study was not designed to measure pattern separation, the overlapping context across stimuli may require the engagement of such, or similar, processes in order to overcome PI during presentation of lure trials. Furthermore, evidence suggest that resolving PI arising from familiarity requires recollection of temporal information (Jonides and Nee, 2006; Oberauer, 2005; Szmalec et al., 2011), which may rely differentially on the subiculum (e.g., Chi et al., 2022; Hartopp et al., 2019) and the CA1 (e.g., Wang and Diana, 2016) subfield. We believe that this study takes critical steps to advance our understanding of hippocampal contributions to interference control across the adult life span.

2. Material and Methods

2.1. Participants

Participants were recruited from *The Betula prospective cohort study: Memory, health, and aging* (Nilsson et al., 1997), a deeply phenotyped longitudinal cohort. Participants were included from samples for which MRI measures were collected in 2008-2010 and 2013-2014. The age of

the participants at baseline ranged from 25 to 90 years (mean = 56.9, standard deviation [SD] = 12.1; 49% female), and mean education level was 13 years (SD = 4.0 years). Individuals with clinical dementia and other neurological disorders at baseline were excluded as were participants with missing longitudinal data. Participants were screened with the Mini-Mental State Examination (MMSE; Folstein et al., 1975), and those scoring 25 and above at both baseline and follow-up were included. Participants with extremely low performance on the n-back task (proportion hits minus proportion false alarms < .1), indicating a very low adherence to task instructions, were not included. Thus, the total sample consisted of 157 participants. For a drop-out analysis, see Nyberg et al. (2019). To retain the diversity of the sample, exclusions were not made for: diabetes, hypertension, mild depressive symptoms, and other moderately severe medical conditions, which are common among the elderly. The Betula study was approved by the Regional Ethical Review Board in Umeå, and written consent was obtained from every participant. We investigated whether age modulated the relationship between brain volume and PI by dividing participants into two groups: one consisting of younger and middle-aged adults (25–65 years at baseline), and one consisting of older adults (70–90 years at baseline). A complementary analysis was also performed by dividing participants into three groups: one consisting of younger adults (25–45 years), one consisting of middle-aged adults (50–60 years) and one consisting of older adults (65–85). The number of participants within different age groups can be found in Fig. 1. Demographic information and cognitive performance can be found in Table 1.

2.2. Attrition analysis

Those who dropped out of the study between baseline and follow-up were older (t(279) = 2.89, P = .004), were less educated (t(279) = 2.66, P = .026), scored lower on the MMSE (t(279) = 2.59, P = .01), had smaller hippocampal volume (whole HC: (t(279) = 3.63, P < .001; Subiculum: t(279) = 2.39, P = .026; CA1: t(279) = 3.08, P = .002; DG: t (279) = 5.25, P < .001; CA3: t(279) = 3.81, P < .01), and had higher systolic blood pressure (t(279) = 4.69, P < .001) at baseline compared to those that remained in the study. There were no differences between drop-outs and returnees in proactive interference (t(279) = 0.62, P = .53), sex distribution (t(279) = 0.029, P = .97), diastolic blood pressure (t (279) = 1.36, P = .18) or total intracranial volume (t(279) = 0.067, P = .94).

2.3. Cognitive measures

PI was measured using a verbal 2-back WM task which included familiar lure items (Fig. 2, Gray et al., 2003; Marklund and Persson, 2012; D E Nee et al., 2007) occurring either 1 or 2 trial(s) after the target position. The task included 40 trials; 21 non-familiar trials, 9 target trials, 8 3-back lures, and 2 4-back lures. *Target trials* matched the same stimuli as presented two trials earlier and required a 'Yes' response. *Lure*
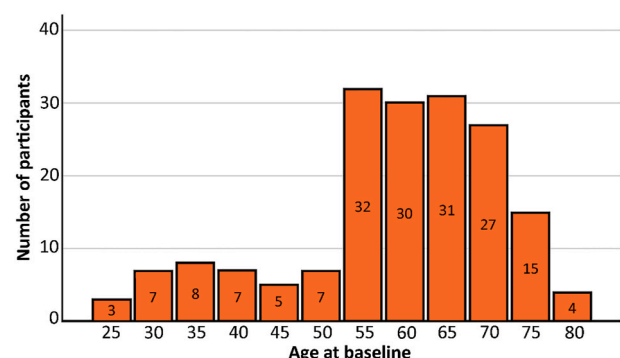
Fig. 1. Age distribution of the included sample.

Table 1
Demographic and cognitive measurements.

	Younger and middle-aged adults	Older adults	
Demographics			P-value
Number of participants	87	64	
Sex (females/males)	39/48	30/34	.76
Education (SD)	14.4 (3.2)	12.7 (4.8)	.009
Cognitive and health data			
Baseline			
Age (range)	50.9 (25–60)	69.0 (65–80)	<.001
Vocabulary (SD)	24.3 (3.4)	23.8 (4)	.46
MMSE (SD)	28.6 (1.3)	28.3 (1.4)	.17
2-back target accuracy (SD)	80.6 (16)	75.7 (15)	.07
Blood pressure (systolic) (SD)	128.7 (15.8)	138.2 (14.9)	<.001
Blood pressure (diastolic) (SD)	79.6 (9.3)	80.7 (8.9)	.48
Follow-up			
Age (range)	55.6 (30–65)	74.0 (70–85)	<.001
Vocabulary (SD)	26.8 (7.8)	23.3 (7.6)	.007
MMSE (SD)	28.4 (1.2)	28.2 (1.4)	.31
2-back target accuracy (SD)	85.2 (16.1)	71.2 (17.8)	<.001
Blood pressure (systolic) (SD)	133.7 (14.4)	143.5 (18.6)	<.001
Blood pressure (diastolic) (SD)	80.6 (7.9)	81 (8.9)	.75

MMSE = Mini-mental state examination; SD = Standard deviation.

trials consisted of stimuli already presented 3- or 4 trials earlier and required a 'No' response. *New trials* were non-familiar trials that had never been presented and required a 'No' response. Stimuli and trial conditions were presented in the same fixed order for all participants. Stimuli consisted of Swedish nouns and were presented one at a time for 2.5 s, with an inter trial interval of 2 s. For each presented word, participants were instructed to press the "m" key on a standard Swedish keyboard, which corresponds to 'Yes' ("Yes, the word I now see has been shown two words ago") and the "x" key for 'No' ("No, the word I now see has not been shown two words ago"). Participants were instructed to answer as quickly and accurately as possible.

PI scores were calculated by combining the relative proportional difference in RT and accuracy between non-familiar trials (new trials) and 3- and 4-back familiar trials (lure trials). The PI scores based on accuracy and RTs were positively correlated, both at baseline (r = 0.295, P < .0005) and follow-up (r = 0.372. P < .0005), indicating shared variance between the two measures of PI. Median RTs were used to reduce the influence of extreme values. Accuracy data for working memory performance in the n-back task is also reported under section 3.1.

2.4. MRI data acquisition and analyses

The MRI data was collected using a 3T GE scanner, equipped with a 32-channel head coil. The same scanner was used for baseline and follow-up data collection. T1-weighted images were acquired with a 3D fast spoiled gradient echo sequence (180 slices with a 1 mm thickness; TR: 8.2 ms, TE: 3.2 ms, flip angle: 12°, field of view: 25 × 25 cm).

To extract HC volumes, T1-weighted images were processed using the Freesurfer image analysis suite. Hippocampal subfield segmentation was performed using the longitudinal stream (Reuter et al., 2012) of the Hippocampal Subfield module of FreeSurfer v.6.0 (https://surfer.nmr. mgh.harvard.edu/fswiki/HippocampalSubfields). The technical details of these procedures are described in prior publications (Dale et al., 1999; Fischl et al., 2002, 2004; Jovicich et al., 2006). Automated cortical and subcortical parcellation tools in the FreeSurfer software were used for

volumetric segmentation, cortical surface reconstruction, and parcellation to quantify the brain volumes of interest. Cortical reconstructions and volumetric segmentations were performed on all images by executing a semi-automatic processing step (recon-all) within this software (Dale et al., 1999; Fischl et al., 2002). Identification of hippocampal subfields using FreeSurfer 6.0 should be considered probabilistic, since it uses prior knowledge from ex vivo brains scanned at 7 T MRI combined with the available contrast information from MR images (Iglesias et al., 2016).

All T1-weighted (T1w) images were visually inspected for artefacts and poor quality that could influence Freesurfer segmentation and estimation of GM volumes. In addition to excluding participants with deviant brain morphology, participants with poor quality T1w images were also excluded from analyses of GM volume (n = 13).

2.5. Scanner stability

From baseline to follow-up data collection, changes were implemented to the scanner software, and it is critical to check that these did not affect image quality. A quality assurance program based on Friedman and Glover (2006) was therefore run on a weekly basis on the scanner. For the structural data, the same T1-weighted fast spoiled gradient echo protocol as in the study was used to obtain volume data for the GE phantom. A threshold well above the noise level and the selected voxels were used to calculate the volume of the phantom. The relative volume change between the beginning of the quality assurance measurements and the time for T6 data collection was 0.45%, which is small compared to the expected average volume change in cortical regions in healthy elders (Fjell et al., 2009). Furthermore, the positive change in the measured volume of the phantom suggests that any significant volumetric decline observed in the study might be slightly underestimated.

2.6. Definition of cognitive and volumetric change

Change in proactive interference was estimated by dividing the PI-score from follow-up by the baseline PI-score, with positive values indicating increase in PI and negative values indicating decrease in PI over time. Similarly, we measured change in brain volumes by dividing the values from the second time point by the values from the first time point. The relative change from time points 1 to 2 takes into account the brain size for each individual, thus controlling for brain size without including TIV as a covariate in the analysis. Significant negative correlations between baseline level and rate of change in proactive interference were observed in both age cohorts (Pearson's *r* were −0.574 for younger/middle-aged adults and −0.704 for older adults). Individuals with low initial performance tended to improve or decline less rapidly and individuals starting with high levels of performance seemed to display more decline.

2.7. Selection of regions of interest

In order to reduce the number of comparisons, and because we did not have any specific hypotheses regarding laterality, we averaged volumes of the left and right hemisphere. For HC subfield analyses, we included the combined left and right CA1, dentate gyrus (DG), CA3, and subiculum subfields. We also performed analyses using total HC volume.

2.8. Statistical analyses

In the current study, relationships between cross-sectional estimates of brain volume and PI, as well as brain markers of change and change in PI were assessed using ordinary correlation coefficients. Separate models were employed to examine pair-wise correlations between PI and HC subfield volumes. All analyses were performed on the standardized residuals controlling for age and education (for proactive

interference) and age, education and TIV (total intracranial volume; for HC volumes). Cross-sectional analyses were performed on the average PI and HC volume of baseline and follow-up. Longitudinal analyses were additionally controlled for baseline level of PI. Partial eta squared (η_p^2) was used to measure effect size. Statistical analyses were performed using SPSS software ver. 26.0 (IBM, Armonk, NY, USA). Analyses were first performed across the whole age span, but since the relationship between local brain volume and cognition might change with increasing age (Burzynska et al., 2012; Razlighi et al., 2017), we also tested for associations within each of the two age groups. Multivariate outliers were identified using Mahalanobis distance at a P < .001. The inter-quartile range (IQR; quartile 3 – quartile 1) rule of IQR × 3 was used for detecting the presence of outliers in memory performance. No outliers were detected at neither baseline nor follow-up.

In addition to analyses across the whole sample, we also tested whether there are age differences in the GM volume – PI associations. To do this, and similar to other studies (e.g. Andersson et al., 2022; Razlighi et al., 2017), we stratified participants into one group of younger and middle-aged (age at baseline: 25–65), and one group of older (age at baseline: 70–85) adults. However, we also performed age-stratified analyses using one group of younger adults (age at baseline: 25–45), one group of middle-aged adults (age at baseline: 50–60), and one group of older adults (age at baseline: 65–85).

Moderation and mediation analyses were performed using the PROCESS macro (Hayes, 2013) implemented in SPSS. Using moderation analyses, we examined whether age was a significant moderator of the relationship between HC volume and PI. Moderation analyses were carried out in both cross-sectional and longitudinal data to investigate age x HC volume interaction effects. Mediation analyses were carried out to test whether the relation between the predictor (age) and the outcome (PI) was mediated – in total or in part – by a mediator variable (HC volume at baseline). For both moderation and mediation analyses, a bootstrapping resampling strategy was implemented using 5000 boot-strap samples. For the mediation analysis, path *a* describes the direct effect of age on HC volume, path *b* represents the direct effect of HC volume on PI, and path *c* represents the direct effect between age and PI. Finally, path *c′* indicates the total effect of age on PI when HC volume is included in the model (Fig. 4). Bias-corrected 95% confidence interval (CI) was computed to evaluate the contribution of the mediator (indirect effect, path a × b). CI reached significance when the interval range did not include zero. In order to examine the hypothesis that mediation would only be present in older adults, separate mediation analyses were carried out in younger/middle-aged and older adults, as well as in the whole sample. Standardized coefficients are reported for all mediation analyses.

3. Results

3.1. Older age was associated with higher levels of proactive interference

Accuracy for non-familiar lures (98%) was significantly higher than for both familiar lures (63%; F(175) = 110, p < .001, η_p^2 = 0.381) and targets (78%; F(175) = 264, p < .001; η_p^2 = 0.597) and is on par with other studies using the modified version of the n-back task to induce familiarity based PI (Loosli et al., 2014; Samrani et al., 2017; Samrani and Persson, 2021) in older adults. Similarly, RT for non-familiar lures (1011 ms) was faster than for both familiar lures (1424ms; F(175) = 311, p < .001, η_p^2 = 0.639) and targets (1101 ms; F(175) = 19.4, p < .001, η_p^2 = 0.098).

Moreover, older individuals had a lower ability to control interference as indicated by the positive correlation between age and PI (r = 0.365, P < .0001). The relationship between change in PI over 5 years and age was, however, not significant (P > .1).

3.2. Cross-sectional and longitudinal effects of age on hippocampal brain volume

Linear regression analyses showed that higher age was a significant predictor of lower total HC volume (r^2 = 0.323, β = −0.437, P < .0001). Similarly, analyses of HC sub-field volumes showed that age was a significant predictor of CA1 volume (r^2 = 0.253, β = −0.255, P < .001) CA3 volume (r^2 = 0.331, β = −0.189, P = .007), DG volume (r^2 = 0.34, β = −0.303, P < .001) and subiculum volume (r^2 = 0.262, β = −0.377, P < .001).

3.3. Cross-sectional associations between hippocampus volume and proactive interference in working memory

For the analyses across the whole sample, the relationship between mean level PI and total HC volume was not significant (r = .038, p = .62). Moreover, none of the associations with HC subfield volume were significant (all Ps > .1).

When analyses were performed for each age group separately, we found that in both younger and middle-aged adults and older adults, the associations between PI and HC volume were not significant (all Ps > .1). None of the associations between HC subfields and PI were significant (all Ps > .1).

3.4. Longitudinal associations between hippocampus volume and proactive interference in working memory

The correlation between 5-year change in HC volume and PI across the whole sample was not significant (r = −0.097, P = .232). However, analyses on sub-field volume showed a significant, negative, correlation between change in subiculum volume and change in PI (r = −0.186, $p\text{uncorrected}$ = .022, $p\text{FDR}$ =) with decreased subiculum volume correlating with increased PI. All other correlations were non-significant (P > .1).

Age-stratified analyses for the total HC volume revealed a significant, negative correlation (r = −0.269, $p^{\text{uncorrected}}$ = .039, p^{FDR} = .05) in older adults. Analyses on sub-field volumes showed that in older adults, change in HC sub-field volume was negatively associated with change in PI (Fig. 3; CA1: r = −0.275, $p^{\text{uncorrected}}$ = .029, p^{FDR} = .05; Subiculum: r = −0.269, $p^{\text{uncorrected}}$ = .033, p^{FDR} = .05; DG: 0.264, $p^{\text{uncorrected}}$ = .037, p^{FDR} = .05) with decreased sub-field volume correlating with increased PI. Moderation analyses showed that age was not a significant moderator for the relationship between change in HC sub-field volume and change in PI. However, for the subiculum, results from the Johnson-Neyman procedure showed that this relationship was significant in participants above 58 years of age. All correlations were non-significant in the group of younger/middle aged adults.

3.5. Complementary analysis with three age groups

Because of the large age range in the younger/middle-aged age group, we also performed analyses in which we divided the sample into three age groups (see Methods). Note that the older age group was similarly defined as in the two-groups analyses. We did not observe any significant differences in HC volume – PI associations between the younger and middle-aged age groups, neither in the cross-sectional nor the longitudinal analyses. This further indicates that the observed associations between 5-year change in HC volume and PI in working memory were restricted to the group of older adults.

3.6. Mediation analyses

Single mediation analysis across all participants showed that HC volume was not a significant mediator of the effect of age on PI (Fig. 4) (estimated effect: .027; lower level (LL) CI: 0.108, higher level (HL) CI: 0.047). Direct effects between age and HC volume (b = −0.424, LLCI:

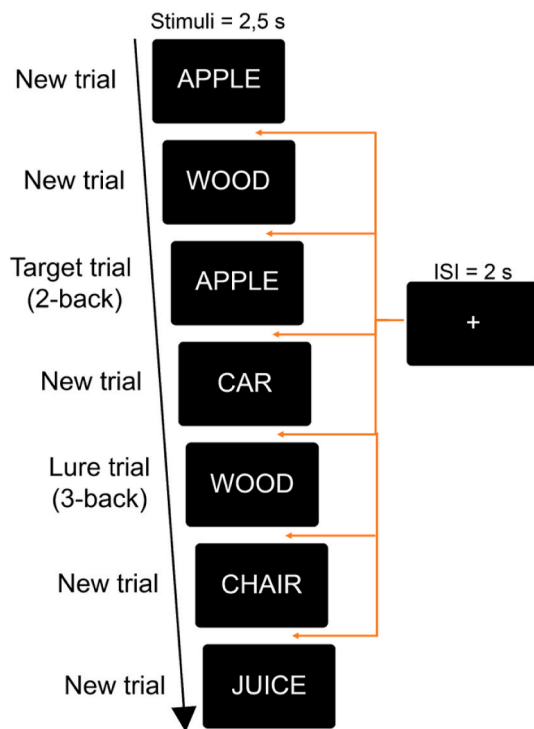**Fig. 2. N-back task.** Experimental design and trial organization.

Fig. 3. Correlations between relative interference score and GM volume. (Top) Correlations between relative interference score and HC volume at baseline for young/middle-aged and older adults. Standardized residuals are corrected for age, education, and TIV. (Bottom) Correlations between relative interference score and HC sub-field volumes (CA1 and CA3/DG) at baseline for young/middle-aged and older adults. Standardized residuals are corrected for age, education, and TIV.

0.043, HLCI: 0.021, P < .001) and age and PI ($b = 0.43$, LLCI 0.014, HLCI: 0.032, P < .001) were significant, but the effect between HC volume and PI was not significant ($b = 0.064$, LLCI: 0.068, HLCI: 0.157, P = .434). Age-stratified mediation analysis showed that for younger/middle-aged adults HC volume was not a significant mediator of the effect of age on PI (estimated effect: 0.008; LLCI: 0.052, HLCI: 0.053). The direct effect between age and PI was significant ($b = 0.375$, LLCI: 0.011, HLCI: 0.036, P < .001), but the direct effects between and age and HC volume ($b = -0.109$, LLCI -0.024 HLCI: 0.008, P = .296) and HC volume and PI ($b = -0.074$, LLCI: 0.218, HLCI: 0.098, P = .451) were non-significant. For older adults, however, HC volume was a significant mediator of the effect of age on PI (estimated effect: 0.136; LLCI: 0.317, HLCI: 0.001). The direct effect between age and HC volume was significant ($b = -0.495$, LLCI: 0.157, HLCI: 0.056, P < .001), but the direct effect between age and PI ($b = 0.245$, LLCI: 0.006, HLCI: 0.075, P = .092) and HC volume and PI ($b = 0.274$, LLCI: 0.008, HLCI: 0.363, P = .061) were not significant. Thus, significant mediation in older adults were based on the difference in (non-significant) effect sizes (i.e., both the direct effect and the total effect were non-significant).

4. Discussion

There is much evidence from patient and functional neuroimaging studies implicating HC as critical for efficient resolution of PI in WM. The current findings confirm the importance of the HC in interference control and suggest that this region is differentially involved in PI resolution in younger and older adults. Cross-sectional analyses did not reveal any significant association between HC volume or sub-field volume in the whole sample or in age-stratified groups. Across all participants, HC volume was not significantly associated with PI. Longitudinal analyses showed that in older adults, 5-year decrease in total HC volume as well as in subiculum, CA1, and DG subfield volume was related to decreased control of PI over 5 years. Finally, age-stratified mediation analyses revealed that, in older adults, whole HC volume significantly mediated the age – PI relationship. These results provide important insights into the neural architecture underlying interference control in WM.
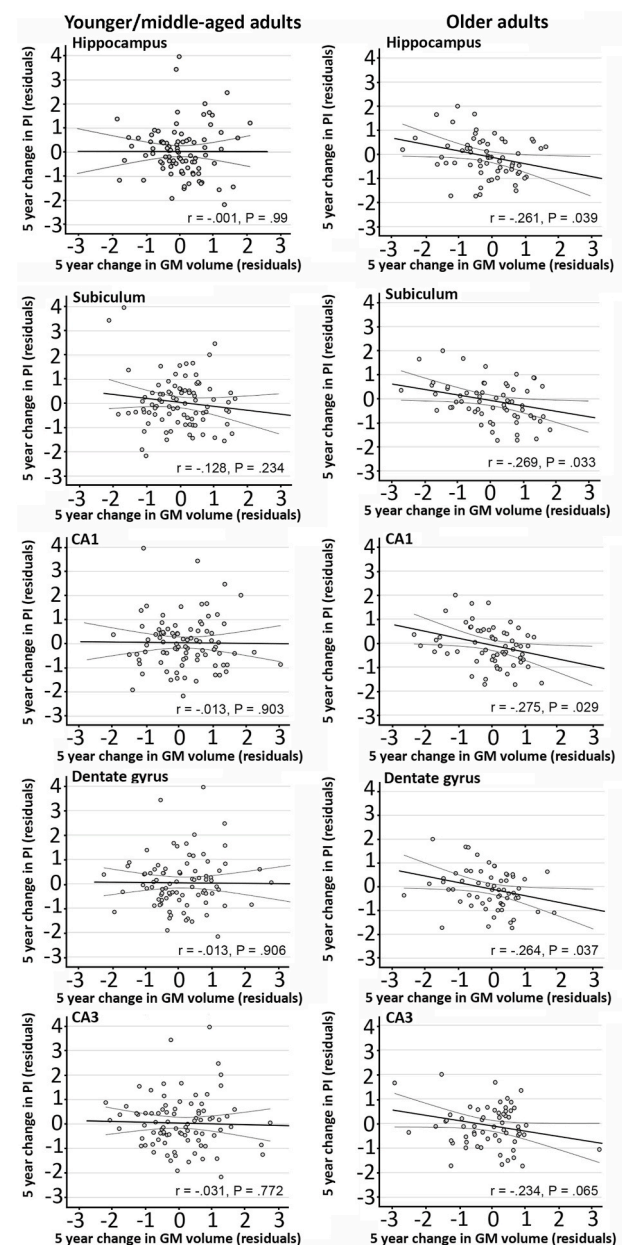
Based on previous findings of a negative association between frontal cortex volume and PI (Samrani et al., 2019), along with data from fMRI of a link between HC activation and PI (D E Nee et al., 2007; Samrani and Persson, 2022; Öztekin et al., 2008), we expected that larger HC volume would be linked to less PI. Cross-sectional analyses of the relationship between HC volume and PI did not reveal any significant associations for the whole sample or for the separate age-groups. Likewise, sub-field volume was not found to be significantly associated with PI.

Longitudinal analyses of change across 5 years demonstrated that decreased HC volume was associated with decreased control of PI across all participants, but only in the subiculum. Age-stratified analyses found that decreased volume in the HC and in the CA1, subiculum, and DG
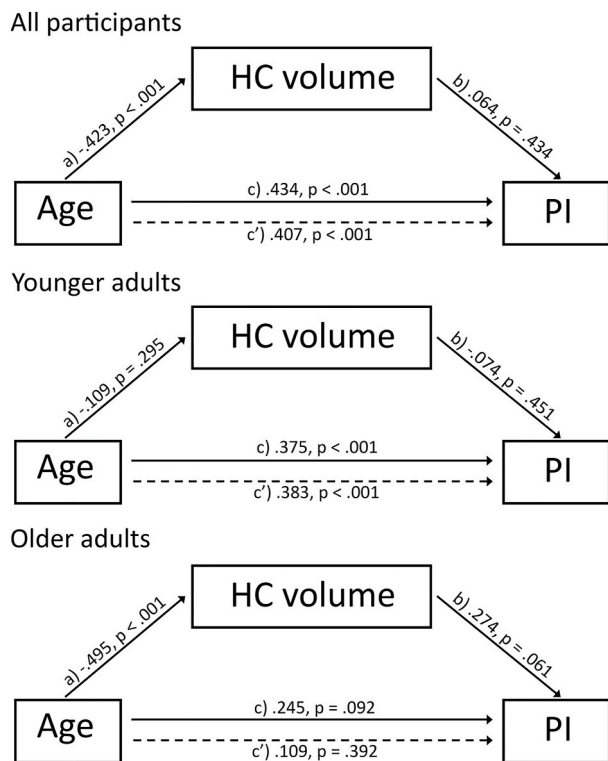
All participants

Younger adults

Older adults

Fig. 4. Mediation analysis. Mediation analysis investigating the three-way association between age, HC volume and PI. (A) Mediation analysis (model A) where "a" indicates the effect of age on HC volume, "b" indicates the effect HC volume on PI, "c" indicates the direct effect of age on PI, and "c'" indicates the total effect (direct and indirect) of age on PI.

subfields, respectively, was significantly correlated with concurrent increase in PI in the older group. These findings corroborate previous cross-sectional findings that demonstrate a relationship between hippocampal function and PI in long-term memory (Blumenfeld and Ranganath, 2007; Wanjia et al., 2021). Moreover, it was recently demonstrated that 4 weeks of mindfulness training both improved the ability to control interference in WM and also resulted in an increase in HC volume (Greenberg et al., 2018). Importantly, the authors also found that mindfulness-related increase in HC volume was related to reduced PI.

While pattern separation and completion processes were not explicitly addressed with the current task paradigm, the context similarity across stimuli may require engagement of such processes in order to overcome PI during presentation of lure trials. The differential involvement of HC sub-fields in pattern separation and completion processes have been primarily studied in the context of long-term memory. From such studies, there are major consensus that pattern separation differentially engages the DG and CA3 sub-fields (Azab et al., 2014; Berron et al., 2016; Stevenson et al., 2016; Yassa et al., 2011) while pattern completion processes rely more on the CA1 sub-field (Bakker et al., 2008). The involvement of the subiculum in these processes has not been discerned as a relationship has been observed for both pattern separation (Bouyeure et al., 2021; Potvin et al., 2009) and completion (Bakker et al., 2008).

However, studies investigating the presence of pattern separation/completion processes in working memory are scarce. To our knowledge, only one study has been conducted on pattern separation/completion and HC subfields in working memory (Newmark et al., 2013). This study found that pattern separation in working memory was related to increased activity in the CA3/DG, subiculum, and CA1 sub-fields and pattern completion was related to increased activity in the CA1, subiculum, and entorhinal cortex. While the results of this study are

consistent with our predictions of pattern separation contributing to resolving PI, much more research would be needed to make any inferences. Furthermore, additional studies investigating PI using paradigms specifically targeting pattern separation/completion processes are needed to draw conclusions about their potential involvement in this process.

While the subiculum has received less attention than HC subfields commonly considered part of the HC proper, recent studies suggest that this region may play an important role in memory (Chi et al., 2022; Hartopp et al., 2019; Ku et al., 2017). For example, the region has been implicated in recognition memory and task memory load (Ku et al., 2017) and in memory recollection (Chi et al., 2022; Hartopp et al., 2019). Generally, PI is assumed to arise due to familiarity of a recently presented item conflicting with the contextual information for that item (contextual information about the item's temporal position). Thus, it has been proposed that familiarity-based PI can be resolved by the recollection of contextual information about temporal position (e.g., Jonides and Nee, 2006; Oberauer, 2005; Szmalec et al., 2011). Given evidence of a role for the subiculum in recollection-based recognition, the findings of reduced subiculum volume being associated with increased PI might reflect a reduced ability to recollect the contextual information required to resolve PI.

Interestingly, in a recent study, Hartopp et al. (2019) found that subiculum volume significantly correlated with fornix microstructure and that this association contribute to memory recollection in episodic memory. Similar observations have also been made in relation to the DG subfield (Hayek et al., 2020). Similar investigations of the relationship between changes in fornix microstructure and volumetric changes in HC sub-fields have, to our knowledge, not been conducted in working memory. However, a recent study investigating associations between white matter integrity and control of PI in working memory found that reduced fornix FA was associated with reduced ability to control PI across five years (Andersson et al., 2022). Follow-up analyses combining volumetric and microstructural measures could shed light on whether fornix – HC sub-field associations also contribute to the ability to control PI in working memory. Potentially, through a connection with increased memory recollection providing the contextual information needed to resolve PI.

It is important to emphasize that we do not imply that the HC is uniquely involved in interference control. Rather, we believe that this region belongs to a network of regions, including the inferior frontal gyrus, anterior cingulate cortex, and insula that are all involved in control of PI. For example, animal tract-tracing studies have demonstrated direct connection between the HC and prefrontal cortex (Pandya et al., 1981; Suzuki and Amaral, 1994) and anterior cingulate cortex (Morris, Pandya, & Petrides). Moreover, numerous human diffusion-tensor imaging (Draganski et al., 2008) and functional connectivity (D E Nee and Jonides, 2014) studies provide evidence for HC connectivity with the prefrontal cortex.

The current study has some notable limitations that need to be mentioned. First, our longitudinal analyses contained only data from two measurement points. Therefore, we were not able to examine long-term trajectories of change, and this design also did not permit independent estimations of retest effects, which are known to influence longitudinal data. Future studies that include three or more time points could provide data on long-term trajectories of change that we are unable to show in the current study design and may also provide more accurate estimation of retest effects. Second, the relatively low number of participants that remained for follow-up testing may have resulted in low statistical power in detecting longitudinal effects.

Taken together, our results support the idea that the hippocampus plays a noticeable role in controlling PI in WM. Additionally, we demonstrate that the HC is differentially involved in PI resolution in younger and older adults. We provide new evidence that reduced HC subfield volumes over 5-years was related to concurrent increase in PI in older adults. Furthermore, we demonstrate that HC volume significantly

mediates the relationship between age and PI in older, but not younger/middle aged adults. We believe that these results provide new and important insights into the neural architecture underlying interference control in WM.

Author contribution

P.A: Writing - Original Draft Preparation, Writing - Review & Editing.

G.S: Investigation, Writing - Original Draft Preparation.

M.A: Formal Analysis, Investigation,

J.P: Conceptualization, Formal Analysis, Writing - Original Draft Preparation, Writing - Review & Editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

Andersson, P., Li, X., Persson, J., 2022. The association between control of interference and white-matter integrity: a cross-sectional and longitudinal investigation. Neurobiol. Aging 114, 49–60.

Axmacher, N., Schmitz, D.P., Weinreic, I., Elger, C.E., Fell, J., 2008. Interaction of working memory and long-term memory in the medial temporal lobe. Cereb. Cortex 18, 2868–2878.

Azab, M., Stark, S.M., Stark, C.E.L., 2014. Contributions of human hippocampal subfields to spatial and temporal pattern separation. Hippocampus 24 (3), 293–302.

Badre, D., Wagner, A.D., 2005. Frontal lobe mechanisms that resolve proactive interference. Cereb. Cortex 15 (12), 2003–2012.

Bakker, A., Brock, C., Kirwan, B., Miller, M., Stark, C.E.L., 2008. Pattern separation in the human hippocampal CA3 and dentate gyrus. Science 319 (5870), 1640–1642.

Barredo, J., Öztekin, I., Badre, D., 2015. Ventral fronto-temporal pathway supporting cognitive control of episodic memory retrieval. Cereb. Cortex 25 (4), 1004–1019.

Berron, D., Schütze, H., Maass, A., Cardenas-Blanco, A., Kuijf, H., Kumaran, D., Düzel, E., 2016. Strong evidence for pattern separation in human dentate gyrus. J. Neurosci. 36, 7569–7579.

Beukers, A.O., Buschman, T.J., Cohen, J.D., Norman, K.A., 2021. Is activity silent working memory simply episodic memory? Trends Cognit. Sci. 25 (4), 284–293.

Blumenfeld, R.S., Ranganath, C., 2007, 3. Prefrontal Cortex and Long-Term Memory Encoding: an Integrative Review of Findings from Neuropsychology and Neuroimaging, vol. 13, pp. 280–291.

Bouyeure, A., Patil, S., Mauconduit, F., Poiret, C., Isai, D., Noulhiane, M., 2021, 11. Hippocampal Subfield Volumes and Memory Discrimination in the Developing Brain, vol. 31, pp. 1202–1214.

Bunting, M., 2006. Proactive interference and item similarily in working memory. J. Exp. Psychol. Learn. Mem. Cognit. 32 (2), 183–196.

Burgess, G.C., Braver, T.S., 2010. Neural mechanisms of interference control in working memory: effects of interference expectancy and fluid intelligence. PLoS One 5 (9).

Burzynska, A.Z., Nagel, I.E., Preuschhof, C., Gluth, S., Bäckman, L., Li, S.C., Heekeren, H. R., 2012. Cortical thickness is linked to executive functioning in adulthood and aging. Hum. Brain Mapp. 33, 1607–1620.

Caplan, J.B., McIntosh, A.R., De Rosa, E., 2007. Two distinct functional networks for successful resolution of proactive interference. Cerebr. Cortex 17 (7), 1650–1663.

Cashdollar, N., Malecki, U., Rugg-Gunn, F.J., Duncan, J.S., Lavie, N., Düzel, E., 2009. Hippocampus-dependent and -independent theta-networks of active maintenance. Proc. Natl. Acad. Sci. U. S. A. 106 (48), 20493–20498.

Chi, C.H., Yang, F.C., Chang, Y.L., 2022. Age-related volumetric alterations in hippocampal subiculum region are associated with reduced retention of the "when" memory component. Brain Cognit. 160, 105877 https://doi.org/10.1016/j.bandc.2022.105877.

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9, 179–194.

Draganski, B., Kherif, F., Klöppel, S., Cook, P.A., Alexander, D.C., Parker, G.J., Frackowiak, R.S., 2008. Evidence for segregated and integrative connectivity patterns in the human Basal Ganglia. J. Neurosci. 28 (28), 7143–7152.

Emery, L., Hale, S., Myerson, J., 2008. Age differences in proactive interference, working memory, and abstract reasoning. Psychol. Aging 23 (3), 634–645.

Fischl, B., Salat, D.H., Busa, e., Albert, M., Dieterich, M., Haselgrove, C., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D., Dale, A. M., 2004. Automatically parcellating the human cerebral cortex. Cerebr. Cortex 14 (1), 11–22.

Fjell, A.M., Walhovd, K.B., Fennema-Notestine, C., McEvoy, L.K., Hagler, D.J., Holland, D., Dale, A.M., 2009. One-year brain atrophy evident in healthy aging. J. Neurosci. 29 (48), 15223–15231.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12 (3), 189–198.

Friedman, L., Glover, G.H., 2006. Report on a multicenter fMRI quality assurance protocol. J. Magn. Reson. Imag. 22 (6), 827–839.

Gorbach, T., Pudas, S., Lundquist, A., Orädd, G., Josefsson, M., Salami, A., Nyberg, L., 2017. Longitudinal association between hippocampus atrophy and episodic-memory decline. Neurobiol. Aging 51, 167–176.

Gray, J.R., Chabris, C.F., Braver, T.S., 2003. Neural mechanisms of general fluid intelligence. Nat. Neuosci. 6 (3), 316–322.

Greenberg, J., Romero, V.L., Elkin-Frankston, S., Bezdek, M.A., Schumacher, E.H., Lazar, S.W., 2018. Reduced interference in working memory following mindfulness training is associated with increases in hippocampal volume. Brain Imag. Behav. 13 (2), 366–376. https://doi.org/10.1007/s11682-018-9858-4.

Hannula, D.E., Tranel, D., Cohen, N.J., 2006. The long and the short of it: relational memory impairments in amnesia, even at short lags. J. Neurosci. 26 (32), 8352–8359.

Hartopp, N., Wright, P., Ray, N.J., Evans, T.E., Metzler-Baddeley, C., Aggleton, J.P., O'Sullivan, M.J., 2019. A key role for subiculum-fornix connectivity in recollection in older age. eCollection 2018 Front. Syst. Neurosci. 12 (70). https://doi.org/10.3389/fnsys.2018.00070.

Hasher, L., Zacks, R.T., 1988. Working memory, comprehension, and aging: a review and a new view. In: Bower, G.H. (Ed.), The Psychology of Learning and Motivation, vol. 22. Academic Press, New York, pp. 193–225.

Hayek, D., Thams, F., Flöel, A., Antonenko, D., 2020. Dentate gyrus volume mediates the effect of fornix microstructure on memory formation in older adults. Front. Aging Neurosci. 12, 79. https://doi.org/10.3389/fnagi.2020.00079.

Hayes, A.F., 2013. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression Based Approach. Guildford Press.

Henson, R.N.A., Shallice, T., Josephs, O., Dolan, N.J., 2002. Functional magnetic resonance imaging of proactive interference during spoken cued recall. Neuroimage 17, 543–558.

Iglesias, J.E., Van Leemput, K., Augustinack, J., Insausti, R., Fischl, B., Reuter, M., 2016. Bayesian longitudinal segmentation of hippocampal substructures in brain MRI using subject-specific atlases. Neuroimage 141, 542–555.

Jonides, J., Nee, D.E., 2006. Brain mechanisms of proactive interference in working memory. Neuroscience 139 (1), 181–193.

Jovicich, J., Czanner, S., Greve, D., Haley, E., van der Kouwe, A., Gollub, R., Dale, A.M., 2006. Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. Neuroimage 30, 436–443.

Kane, M.J., Engle, R.W., 2000. Working-memory capacity, proactive interference, and divided attention: limits on long-term memory retrieval. J. Exp. Psychol. Learn. Mem. Cognit. 26, 336–358.

Keppel, G., 1968. Retroactive and proactive inhibition. In: Dixon, T.R., Horton, D.L. (Eds.), Verbal Behavior and General Behavior Theory. Prentice Hall, Englewood Cliffs, NJ, pp. 172–213.

Koen, J.D., Rugg, M.D., 2019. Neural dedifferentiation in the aging brain. Trends Cognit. Sci. 23 (7), 547–559.

Ku, S.P., Nakamura, N.H., Maingret, N., Mahnke, L., Yoshida, M., Sauvage, M.M., 2017. Regional specific evidence for memory-load dependent activity in the dorsal subiculum and the lateral entorhinal cortex. Front. Syst. Neurosci. 11, 51. https://doi.org/10.3389/fnsys.2017.00051.

Leszczynski, M., 2011. How does hippocampus contribute to working memory processing? Front. Hum. Neurosci. 5 (1–2).

Lilienthal, L., 2017. Individual differences in proactive interference in verbal and visuospatial working memory. Memory 25 (8), 1110–1116.

Loosli, S.V., Rahm, B., Unterrainer, J.M., Weiller, C., Kaller, C.P., 2014. Developmental change in proactive interference across the life span: evidence from two working memory tasks. Dev. Psychol. 50 (4), 1060–1072.

Lustig, C., Jantz, T., 2014. Questions of age difference in interference control: when and how, not if? Brain Res. (in press).

Marklund, P., Persson, J., 2012. Context-dependent switching between proactive and reactive working memory control mechanisms in the right inferior frontal gyrus. Neuroimage 63 (3), 1552–1560.

May, C.P., Hasher, L., Kane, M.J., 1999. The role of interference in memory span. Mem. Cognit. 27 (5), 759–767.

McGabe, D.P., Roediger, H.L.I., McDaniel, M.A., Balota, D.A., Hambrick, D.Z., 2010. The relationship between working memory capacity and executive functioning: evidence for a common attention contruct. Neuropsychology 24 (2), 222–243.

Nauer, R.K., Whiteman, A.S., Dunne, M.F., Stern, C.E., Schon, K., 2015. Hippocampal subfield and medial temporal cortical persistent activity during working memory reflects ongoing encoding. Front. Syst. Neurosci. 9 (30).

Nee, D.E., Jonides, J., 2014. Frontal–Medial temporal interactions mediate transitions among representational states in short-term memory. J. Neurosci. 34 (23), 7964–7975.

Nee, D.E., Jonides, J., Berman, M.G., 2007. Neural mechanisms of proactive interference-resolution. Neuroimage 38 (4), 740–751.

Nelson, J.K., Reuter-Lorenz, P.A., Persson, J., Sylvester, C.Y., Jonides, J., 2009. Mapping interference resolution across task domains: a shared control process in left inferior frontal gyrus. Brain Res. 1256, 92–100.

Newmark, R.E., Schon, K., Ross, R.S., Stern, C.E., 2013. Contributions of the hippocampal subfields and entorhinal cortex to disambiguation during working memory. Hippocampus 23 (6), 467–475. https://doi.org/10.1002/hipo.22106.

Nichols, E.A., Kao, Y.C., Verfaellie, M., Gabrieli, J.D.E., 2006. Working memory and long-term memory for faces: evidence from fMRI and global amnesia for involvement of the medial temporal lobes. Hippocampus 16 (7), 604–616.

Nilsson, L.G., Bäckman, L., Erngrund, K., Nyberg, L., Adolfsson, R., Bucht, G., Winblad, G., 1997. The Betula prospective cohort study: memory, health and aging. Aging Neuropsychol. Cognit. 4 (1), 1–32.

Nyberg, L., Andersson, M., Lundquist, A., Salami, A., Wåhlin, A., 2019. Frontal contribution to hippocampal hyperactivity during memory encoding in aging. Front. Mol. Neurosci.

Oberauer, K., 2005. Binding and inhibition in working memory: individual and age differences in short-term recognition. J. Exp. Psychol. Gen. 134 (3), 368–387. https://doi.org/10.1037/0096-3445.134.3.368.

Öztekin, I., Curtis, C.E., McElree, B., 2008. The medial temporal lobe and inferior prefrontal cortex jointly support interference resolution in working memory. J. Cognit. Neurosci. 21 (10), 1967–1979.

Öztekin, I., Davachi, L., McElree, B., 2010. Are representations in working memory distinct from representations in long-term memory? Neural evidence in support of a single store. Psychol. Sci. 21 (8), 1123–1133.

Pandya, D.N., Van Hoesen, G.W., Mesulam, M.M., 1981. Efferent connections of the cingulate gyrus in the rhesus monkey. Exp. Brain Res. 42, 319–330.

Park, D.C., Polk, T.A., Park, R., Minear, M., Savage, A., Smith, M.R., 2004. Aging reduces neural specialization in ventral visual cortex. Proc. Natl. Acad. Sci. U. S. A. 101 (35), 13091–13095.

Persson, J., Pudas, S., Lind, J., Kauppi, K., Nilsson, L., Nyberg, L., 2012. Longitudinal structure-function correlates in elderly reveal MTL dysfunction with cognitive decline. Cerebr. Cortex 22 (10), 2297–2304.

Persson, J., Larsson, A., Reuter-Lorenz, P.A., 2013. Imaging fatigue of interference control reveals the neural basis of executive resource depletion. J. Cognit. Neurosci. 25 (3), 338–351.

Potvin, O., Doré, F.Y., Goulet, S., 2009. Lesions of the dorsal subiculum and the dorsal hippocampus impaired pattern separation in a task using distinct and overlapping visual stimuli. Neurobiol. Learn. Mem. 91 (3), 287–297.

Ranganath, C., D'Esposito, M., 2001. Medial temporal lobe activity associated with active maintenance of novel information. Neuron 31 (5), 865–873.

Raz, N., Rodrigue, K.M., Kennedy, K.M., Head, D., Gunning-Dixon, F., Acker, J.D., 2003. Differential aging of the human striatum: longitudinal evidence. Am. J. Neuroradiol. 24 (9), 1849–1856.

Raz, N., Rodrigue, K.M., Head, D., Kennedy, K.M., Acker, J.D., 2004. Differential aging of the medial temporal lobe: a study of a five-year change. Neurology 62, 433–438.

Razlighi, Q., Oh, H., Habeck, C., O'Shea, D., Gazes, E., Eich, T., Stern, Y., 2017. Dynamic patterns of brain structure–behavior correlation across the lifespan. Cerebr. Cortex 27 (7), 3586–3599.

Rey-Mermet, A., Gade, M., 2017. Inhibition in aging: what is preserved? What declines? A meta-analysis. Psychonomic Bull. Rev. https://doi.org/10.3758/s13423-017-1384-7.

Rieckmann, A., Johnson, K.A., Sperling, R.A., Buckner, R.L., Hedden, T., 2018. Dedifferentiation of caudate functional connectivity and striatal dopamine transporter density predict memory change in normal aging. Proc. Natl. Acad. Sci. U. S. A. 115 (40), 10160–10165.

Roediger, H.L., McDermott, K.B., 1995. Creating false memories: remembering words not presented in lists. J. Exp. Psychol. Learn. Mem. Cognit. 21, 803–814.

Samrani, G., Persson, J., 2021. Proactive interference in working memory is related to adult age and cognitive factors: cross-sectional and longitudinal evidence from the Betula study. Neuropsychology, Development and Cognition. Section B Aging, Neuropsychology and Cognition 28 (1), 108–127.

Samrani, G., Persson, J., 2022. Automatic and effortful control of interference in working memory can be distinguished by unique behavioral and functional brain representations. Neuroimage 253 (119098).

Samrani, G., Bäckman, L., Persson, J., 2017. Age-differences in the temporal properties of proactive interference in working memory. Psychol. Aging 32 (8), 722–731.

Samrani, G., Bäckman, L., Persson, J., 2019. Interference control in working memory is associated with ventrolateral prefrontal cortex volume. J. Cognit. Neurosci. 31 (10), 1491–1505.

Stevenson, B., Vieweg, P., Gao, F., Gilboa, A., Wolbers, T., Black, S.E., Rosenbaum, S., 2016. The human dentate gyrus plays a necessary role in discriminating new memories. Curr. Biol. 26 (19), 2629–2634.

Suzuki, W.A., Amaral, D.G., 1994. Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. J. Comp. Neurol. 350, 497–533.

Szmalec, A., Verbruggen, F., Vandierendonck, A., Kemps, E., 2011. Control of interference during working memory updating. J. Exp. Psychol. Hum. Percept. Perform. 37 (1), 137–151.

Van Petten, C., 2004. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia 42, 1394–1413.

Verhaeghen, P., 2011. Aging and executive control: reports of a demise greatly exaggerated. Curr. Dir. Psychol. Sci. 20 (3), 174–180.

Wang, F., Diana, R.A., 2016. Temporal context processing within hippocampal subfields. Neuroimage 134, 261–269. https://doi.org/10.1016/j.neuroimage.2016.03.048.

Wanjia, G., Favila, S.E., Kim, G., Molitor, R.J., Kuhl, B.A., 2021. Abrupt hippocampal remapping signals resolution of memory interference. Nat. Commun. 12 (4816).

Yassa, M.A., Stark, C.E.L., 2011. Pattern separation in the hippocampus. Trends Neurosci. 34 (10), 515–525.

Yassa, M.A., Mattfeld, A.T., Stark, S.M., Stark, C.E., 2011. Age-related memory deficits linked to circuit-specific disruptions in the hippocampus. Proc. Natl. Acad. Sci. U. S. A. 108 (21), 8873-8868.