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# The importance of the ventromedial prefrontal cortex for associative memory in older adults: A latent structural equation analysis

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ABSTRACT

Older adults show relatively minor age-related decline in memory for single items, while their memory for associations is markedly reduced. Inter-individual differences in memory function in older adults are substantial but the neurobiological underpinnings of such differences are not well understood. In particular, the relative importance of inter-individual differences in the medio-temporal lobe (MTL) and the lateral prefrontal cortex (PFC) for associative and item recognition in older adults is still ambiguous. We therefore aimed to first establish the distinction between inter-individual differences in associative memory (recollection-based) performance and item memory (familiarity-based) performance in older adults and subsequently link these two constructs to differences in cortical thickness in the MTL and lateral PFC regions, in a latent structural equation modelling framework. To this end, a sample of 160 older adults (65–75 years old) performed three intentional item-associative memory tasks, of which a subsample (n = 72) additionally had cortical thickness measures in MTL and PFC regions of interest available. The results provided support for a distinction between familiarity-based item memory and recollection-based associative memory performance in older adults. Cortical thickness in the ventro-medial prefrontal cortex was positively correlated with associative recognition performance, above and beyond any relationship between item recognition performance and cortical thickness in the same region and between associative recognition performance and brain structure in the MTL (parahippocampus). The findings highlight the relative importance of the ventromedial prefrontal cortex in allowing for intentional recollection-based associative memory functioning in older adults.

Episodic memory, the ability to encode and retrieve memories for events with related contextual and/or temporal details (e.g., words, objects, faces, names, see review Tulving, 1972), is typically assessed experimentally in recognition paradigms, in which individuals are required to judge whether specific stimuli have been studied before (old) or not (new). Stimuli in this context can refer to single items (e.g., names, faces) or to associations between items (e.g., face-name). Dual-process theories state that recognition performance depends on the functionality of either one or two independent processes, namely familiarity or recollection (H. Eichenbaum, Yonelinas and Ranganath, 2007; Yonelinas, 1997, 2002). Whilst recollection involves retrieval of qualitative information (i.e., contextual, temporal or emotional; "remembering") linked to the previously studied stimulus, familiarity involves placing reliance on perceived memory strength (i.e., global and context-free; "knowing"; Mayes et al., 2010; Yonelinas et al., 2010). Different methods have been suggested to measure both processes as distinct as possible (e.g., Remember/Know paradigms, receiver operating characteristic (ROC), process dissociation, and lesion studies; Koen and Yonelinas, 2016; Yonelinas et al., 2002; Unsworth and Brewer, 2009; Yonelinas et al., 2007). Task-dissociation methods try to distinguish between the two different recognition processes using task conditions, which rely relatively more on one of the two processes. The involvement of the two processes seems to depend on whether single items or associations needs to be encoded and recognized (Davachi, 2006). For item recognition, the

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perceived memory strength exists only for the previously studied and not for the new stimuli, allowing for high recognition performance even if only familiarity-based processes are available. However, it is also possible to retrieve qualitative information about single items, or use the item as a cue for retrieving such information that may serve as information for the recognition decision, which means that recollection-based processes also may contribute to item recognition performance. In contrast, for associative recognition, all individual items have been studied before ("new" stimuli are seen items rearranged into novel pairs), which means that the perceived memory strength is equivalent for stimuli pairs that have been studied before relative to those that have not. Hence, associative recognition requires recall of detailed contextual information (e.g., co-occurrence of two stimuli), making recollection-based processes necessary for associative recognition performance.

Episodic memory functioning declines in older age, but not unitarily (Rönnlund et al., 2005). Older adults show no or only minor age-related reductions in memory for single items, while their memory for associations is markedly reduced in comparison to younger adults (Chalfonte and Johnson, 1996; Naveh-Benjamin, 2000). This associative deficit of older adults in comparison to younger adults has been found consistently with different materials (see special issues in Psychology & Aging edited by Naveh-Benjamin and Mayr, 2018; for words, objects, faces, names, see review Old and Naveh-Benjamin, 2008) and independent of task difficulty or reduced attentional resources (Kilb and Naveh-Benjamin, 2007; Naveh-Benjamin et al., 2004). In line with these findings, greater age-related loss has been reported for recollection-based than for familiarity-based recognition processes (Craik and McDowd, 1987; Danckert and Craik, 2013; Fandakova et al., 2015; Koen and Yonelinas, 2016; Lövdén et al., 2002; Old and Naveh-Benjamin, 2008; Spencer and Raz, 1995). Beyond the average pattern of age-related associative memory decline, individuals of the same age differ markedly in their memory performance.

In regards to the neural underpinnings of episodic memory, structural and functional brain imaging confirm the involvement of a large-scale network including both the medio-temporal lobes (MTL) and the lateral prefrontal cortex (PFC; Buckner et al., 1999; Simons and Spiers, 2003; Squire, 2004). At a general level, the MTL is thought to be critical for relational binding processes (item-item, item-context) in long-term memory whilst the lateral PFC is thought to be more important for strategic control functions that support the creation, maintenance, and selection of durable memory representations through organization and elaboration of relevant stimuli (e.g., Badre and Wagner, 2007; Cabeza and Nyberg, 2000; Kirchhoff and Buckner, 2006; Kirchhoff et al., 2014; M. N. Rajah & D'Esposito, 2005).

Functional imaging studies in younger adults have found evidence for a functional differentiation within the MTL, with the hippocampus being especially involved in recollection-based processes and the memory of associations and the parahippocampal region being more involved in familiarity-based processes and the memory of single items (Davachi, 2006; Davachi and Wagner, 2002; Giovanello et al., 2004; Jackson and Schacter, 2004; Mayes et al., 2007; Qin et al., 2009; Sperling et al., 2003; Westerberg et al., 2012; for reviews see H. Eichenbaum et al., 2007; Skinner and Fernandes, 2007). In contrast, evidence for such a functional differentiation within the lateral PFC has not been as convincing. In younger adults, the dorsolateral and the ventrolateral PFC has been found to be relevant for recollection- as well as familiarity-based processes (Achim and Lepage, 2005; Daselaar et al., 2006; Frithsen and Miller, 2014; Johnson et al., 2013; Kafkas and Montaldi, 2012; see Scalici et al., 2017 for review) and the inferior lateral PFC has been linked specifically to associative memory performance (Achim and Lepage, 2005; Addis et al., 2014; Blumenfeld and Ranganath, 2007; Murray and Ranganath, 2007; Wong et al., 2013).

The MTL and PFC both demonstrate substantial age-related shrinkage as well as large inter-individual differences in function and structure (Lindenberger, 2014; Raz et al., 2005), which may account for the large inter-individual differences in episodic memory in older adults. The strongest negative association between age and regional volume has been observed in the prefrontal cortex with temporal and parietal regions trailing behind, and occipital areas showing the weakest effect of age (Raz et al., 2003). Functionally, age-related impairments in the hippocampus has been linked to older adults' difficulties in forming new item-item associations (Daselaar et al., 2003; Grady et al., 2003) and in separating new associations from existing memory traces stored in long-term memory (e.g., Daselaar et al., 2006; Wilson et al., 2006). Lateral PFC activity has been positively linked to associative memory functioning in older adults (Duarte et al., 2010; Fandakova et al., 2015; Sperling et al., 2003).

Structural brain imaging studies are less common and most often focusing exclusively on the link between hippocampus volume and associative memory functioning. In younger adults, results have ranged from showing zero or even a negative link (DeMaster et al., 2014; Schlichting et al., 2017; Van Peten, 2004) to a positive link (Poppenk and Moscovitch, 2011; M.N. Rajah, Kromas, Han and Pruessner, 2010) between hippocampal volume and associative memory performance. Similarly, structural results have varied in older adults, from no links (Becker et al., 2015; Rajah et al., 2010) to positive links between hippocampal volume and associative memory functioning (Carr et al., 2017; Nordin et al., 2017; Rodrigue and Raz, 2004; Shing et al., 2011). At the same time, familiarity and recollection were relatively more correlated with brain volume in entorhinal cortex and hippocampus, respectively (Yonelinas et al., 2007; Wolk et al., 2011). In general, the anatomical mappings of item memory and associative memory and the underlying processes of familiarity and recollection to brain structure in the MTL and the lateral PFC in older adults remains poorly understood.

Studies investigating structural brain correlates of both item and associative memory in both MTL and PFC regions in the same model are surprisingly rare. To our knowledge, only one study investigated the specific contribution of regional gray-matter volume in lateral PFC and MTL to associative memory and item memory in the same study. In this study, 54 60-year old adults intentionally learned face-scene pairs before performing separate recognition tasks for items and associations, respectively. Using voxel-based morphometry region-of-interest (ROI) analyses, older adults with better associative memory showed larger gray-matter volumes primarily in regions of the left and right lateral PFC, with no associations with hippocampal volume. These results suggest that the lateral PFC may more important than the MTL in accounting for interindividual difference in intentional learning of associations in older adults (Becker et al., 2015). This could be due to the greater age-related effects on the lateral PFC relative to the MTL, which may make brain structure in the lateral PFC and its organizational and strategic processes more important than the MTL and its relational binding processes for determining the level of associative memory ability in older adults.

The aim of this study was to investigate the relative contribution of inter-individual differences in the structure of the MTL and the lateral PFC in accounting for inter-individual differences in associative and item memory in older adults. To this end, we first evaluated the empirical support for a distinction between associative memory (recollection-based processes) and item memory (familiarity-based processes) at a behavioural level and subsequently linked inter-individual differences in associative and item memory ability to inter-individual differences in brain structure in MTL and lateral PFC regions of interest, in a latent structural equation modelling framework. In line with Becker et al. (2015), we hypothesized the lateral PFC to be mostly involved in the recognition of associations, due to the strategic recollection-based processes involved, while item memory can more strongly rely on familiarity-based processes, which require less lateral PFC but can be solved through MTL (i.e., perirhinal and parahippocampal) involvement.

## 1. Methods

### 1.1. Participants

The recruitment procedure and study sample has been described in detail previously (Berggren et al., 2019; Nilsson et al., 2018). In brief, 169 healthy older adults aged between 65 and 75 years fulfilled study criteria and were recruited, of which 160 participants subsequently completed the study. Participants who expressed an interest, were right-handed and did not have any MR contraindications were invited to undergo the MR assessments. A total of 82 participants were assigned MR, of which 72 completed the assessments with good gray matter segmentation quality. The MR subsample (n = 72) was highly representative of the total study sample (N = 160) in regards to age ($M_{total}$ = 69.35, $SD_{total}$ = 2.76; $M_{MR}$ = 69.53, $SD_{MR}$ = 2.83), percent females ($\%_{total}$ = 62.5, $\%_{MR}$ = 62.5) and performance on a word-word associative recognition test ($H\text{-}FA_{total}$ = 0.54, $SD_{total}$ = 0.26; $H\text{-}FA_{MR}$ = 0.53, $SD_{MR}$ = 0.26). The study was approved by the ethical review board in Stockholm (case number 2015/2284-31/2) and conducted in accordance with the Declaration of Helsinki.

### 1.2. Study design and procedure

The study was designed to investigate the effects of foreign language learning on cognition and brain in older adults. To this end, the study included three phases: pre intervention, intervention, and post intervention. For the intervention phase, participants were randomly allocated to attend an entry level Italian language course (experimental condition) or a relaxation course (control condition), both lasting for 11 weeks. In the *pre- and post-intervention phases*, all participants completed an extensive cognitive test battery and the MR subsample underwent brain imaging. We have previously reported that the Italian language course did not result in any statistically significant and differential performance change relative to the relaxation course in any of the latent cognitive abilities: associative memory, item memory, working memory, spatial intelligence and verbal intelligence (Berggren et al., 2019). We have also demonstrated that neither the experimental nor the control condition resulted in any detectable change in hippocampal volume or in cortical thickness in any of the language-relevant regions of interest: pars triangularus, pars opercularis, and the superior temporal gyrus (Nilsson et al., 2018). Consequently, for the purposes of the present study, we considered the pre- and post-intervention assessments to be repeated measures of assumed unchanged constructs, which justified merging the data of the two intervention groups over time.

*Item-associative memory tests (IAMTs)*. All participants performed three IAMTs (see Naveh-Benjamin, 2000) at pre- and post-intervention assessments, which entailed all the same structure but varied in regards to the stimuli material used: word-word pairs, face-name pairs or picture-picture pairs. Each IAMT consisted of three phases: encoding, item recognition, and associative recognition. During *encoding*, participants were instructed to memorize 40 stimuli pairs, presented one pair at a time for 6000 ms. Afterwards, two self-paced recognition tests were administered. During *item recognition*, participants were presented with one stimulus at a time (i.e., randomized order compared to encoding but fixed across subjects) and were asked to indicate whether they had seen that stimulus during encoding or not. In total, 40 items were presented, of which 20 had been seen during the encoding phase (targets) and 20 had never been seen before (foils). During *associative recognition*, participants were presented with stimulus pairs and asked to indicate whether they had seen that particular pair during encoding. Again, the presentation order of stimuli was randomized compared to study, but fixed across individuals. In total, 40 pairs were presented, 20 of which had been paired together during encoding (target pairs) and 20 re-arranged pairs, means all stimuli had been presented during encoding but not paired together (foil pairs). Performance in the item and associative memory tasks were defined as the proportion of hits minus the proportion of false alarms (H-FA).

### 1.3. Magnetic resonance imaging

Two MR assessments were conducted with 14 weeks apart, one week before and two weeks after the intervention period. Scanning was performed using an 8-channel coil on a GE Discovery MR-750 3.0-T scanner (General Electric, Milwaukee, WI, USA), located at the Karolinska University Hospital, in Solna, Sweden. Structural images were acquired with a standardized T1 spoiled gradient BRAVO sequence with 0.94 $mm^3$ isotropic voxels, a field of view of 240 mm (240 × 240 matrix), repetition time/echo time = 6.4/2.808 msec, and flip angle 12°. Cortical reconstruction and volumetric segmentation of the T1-weighted images were performed using the FreeSurfer imaging analysis suite (https://surfer.nmr.mgh.harvard.edu/; version 6.0). To extract reliable volume and thickness estimates, images where automatically processed with the longitudinal stream in FreeSurfer (Reuter et al., 2012). Motivated by previous literature (Achim and Lepage, 2005; Becker et al., 2015; Bunge et al., 2004; Kirchhoff and Buckner, 2006; Rodrigue and Raz, 2004), measures of cortical thickness and volume were extracted from the hypothesized gray matter regions in the lateral PFC and the MTL using the Desikan-Killiany cortical parcellation available in Freesurfer, for each individual participant, in the right and left hemisphere, at pre and post intervention (Desikan et al., 2006). Specifically, for the lateral PFC, cortical thickness measures were extracted from the pars triangularus, pars opercularis, pars orbitalis, caudal middle frontal gyrus, rostral middle frontal gyrus and the superior frontal gyrus, and for the MTL, from the entorhinal and parahippocampal cortex. For the MTL, hippocampal (HC) volumes at pre- and post- intervention assessments, in the left and right hemisphere, were additionally extracted from the subcortical FreeSurfer segmentation and adjusted for total intracranial volume (ICV) as follows:

$$adjusted\ HC\ volume = raw\ HC\ volume - b\ X\ (ICV - average\ ICV)$$

where b is the slope of regression of the raw HC volume on ICV. No such adjustment was performed for the cortical thickness measures, which, in contrast to raw regional volumes, do not tend to be reliably associated with total intracranial volume (see SI-1 for relevant correlations in the study dataset).

### 1.4. Statistical analysis

SEM was performed using the lavaan package (Rosseel, 2012) in the R programming environment (R Core Team, 2014), employing the SEM function ('sem') to fit the model estimate the parameters. All observed variables were standardized before being entered into the model. Model fit was evaluated using the Comparative Fit Index (CFI) and the Root Mean Square Error of Approximation (RMSEA) and full-information maximum likelihood estimation was used to deal with missing data (for effective sample sizes for all measures, see the supplementary information (SI-1). Full-information maximum likelihood requires that data is missing at random or completely at random (Schafer and Graham, 2002). Whilst it is impossible to empirically demonstrate that the assumption of missingness at random is fully met when participants can self-select into (parts of) a study, we found it reasonable to assume that the selection variables for the MR subsample, which included willingness to complete the assessment and absence of MR contraindications (e.g., metal implants), were unrelated to measures of cortical thickness and volume, after accounting for observed information included in the model (e.g., memory performance). All available data was used in all models, allowing the cognitive latent variables to be derived from the full study sample (n = 160) in all models whilst the brain latent variables were derived from the MR subsample (n = 72). This procedure ensures the maximum precision with which the parameters of the model are estimated, and maximum power with which statistical tests are conducted, is

attained. In all models, the variances of the latent factors were fixed to unity and all factor loadings were freely estimated, allowing covariances between latent factors to be interpreted as correlations. All model comparisons were performed using $\chi 2$ -difference tests and a significance threshold of $p = .05$.

As previously stated, recognition performance for associations requires recollection-based retrieval processes, while recognition of single items can be based on familiarity- and recollection-based retrieval processes. Associative memory (AM) was therefore modelled as the shared variance among the three associative recognition tests and the three item recognition tests, with the aim to capture the recollection-based retrieval processes that the tests have in common (cognitive model; Fig. 1A). Item memory was modelled as the shared variance among the three item recognition tests (ITEM) to separate the variance assumed to be specific to the item tests: familiarity-based retrieval processes. Importantly, individual performance in the three IAMTs were also represented by a latent factor, that is, as the shared variance of the respective tests collected at pre- and post-intervention assessments. Given that the recognition phase for item and associative memory was based on the same encoding phase and stimulus material, the residual terms for each test (picture-picture, word-word, face-name) were allowed to correlate. Statistical support for the cognitive model (Fig. 1A), which specifies an associative and an item memory factor (dual-process model), was evaluated by comparison to a model in which the specific ITEM memory factor was removed and thus only included a single memory factor (single-process model). The relationship between the latent associative

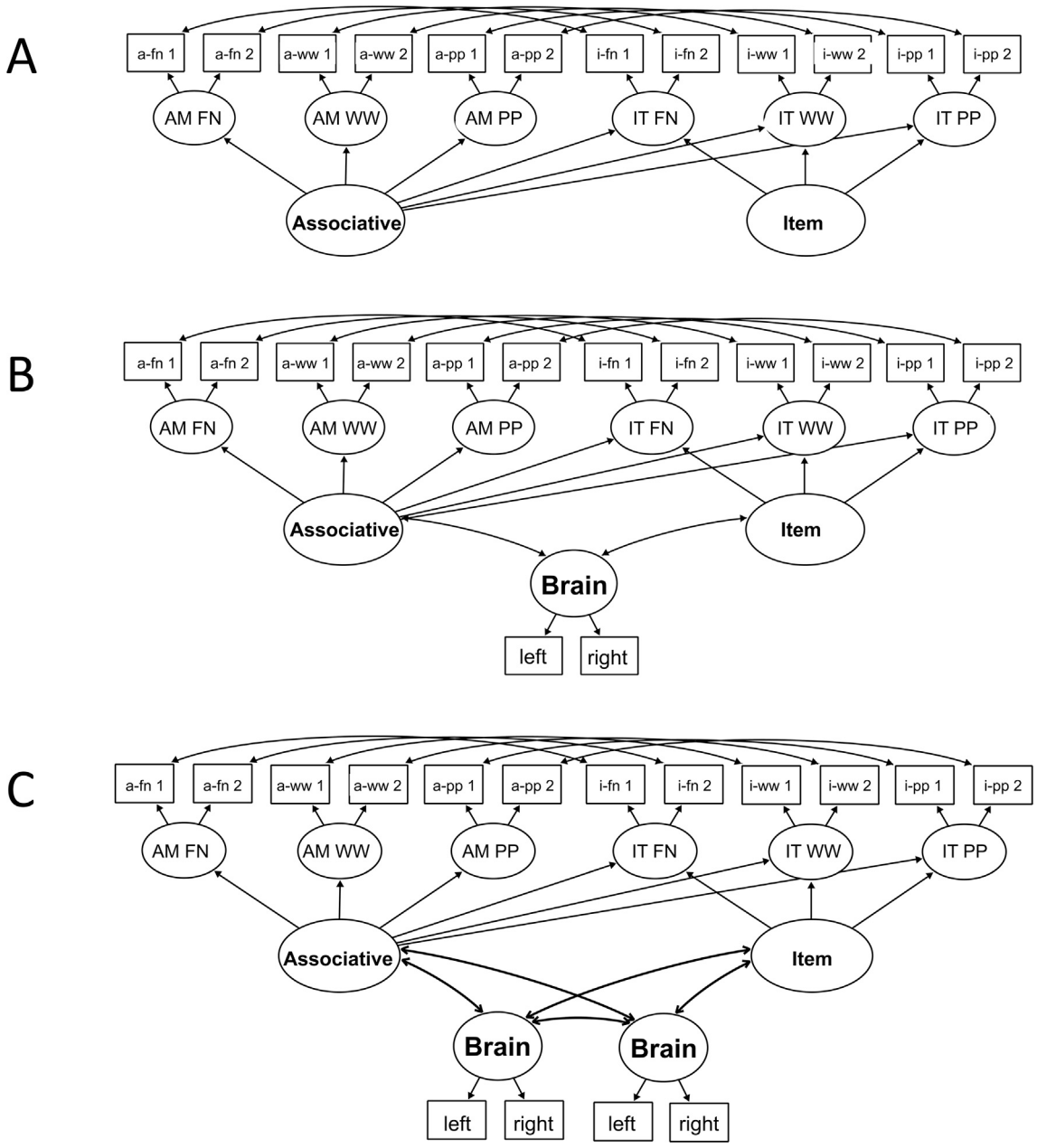


**Fig. 1.** SEMs testing the support for a distinction between item and associative memory (Cognitive model, A) and their differential relationships with brain structure in regions of interest (Brain model, B). The regional specificity of the relationships between item and associative memory and brain structure was tested by comparing relationships in PFC regions with relationships in MTL regions (Region specificity model, C). Regression weights are represented by single-headed arrows and covariances by double-headed arrows. The variances of all latent variables were fixed to unity and all factor loadings, intercepts, variances, and covariances were estimated. AM = associative memory tests, IT = item memory tests, FN = face-name, WW = word-word, PP = picture-picture, a-fn 1 = associative memory face-name measure 1, a-fn 2 = associative memory face-name measure 2, etc.

and item memory factors was furthermore tested by contrasting the cognitive model, in which the factors were assumed to be independent, to a model in which the covariance term between AM and ITEM was freely estimated.

To investigate relationships with structural brain variables, a latent brain factor was added to the cognitive model, allowing it to correlate with both ITEM and AM (brain model; Fig. 1B). These analyses were conducted using a region of interest approach, to test for the relative importance of specific task-relevant regions (lateral PFC and MTL) for inter-individual differences in associative over item memory, see description above (Fig. 2 A).

Given the high pre-post correlations for the brain measures (all Pearson's $rs > 0.90$), a pre-post average was calculated for each region of interest. Each region of interest was subsequently modelled as the shared variance (i.e., latent factor) of measures in the left and right hemisphere (brain model; Fig. 1B). Loadings of the left and right hemisphere indicators on the latent brain factor were constrained to be equal. Cortical thickness (volume for hippocampus) was evaluated for each region of interest in separate models. Statistical significance of the correlations was tested by comparing a model in which the correlation to be tested (e.g., AM-brain) was fixed to zero, while the other (e.g., ITEM-brain) was freely estimated, with a model in which both correlations were freely estimated. To test whether the AM-brain correlation differed significantly from the ITEM-brain correlation, the correlations were constrained to be equal in a model, which was compared to a model in which the correlations were freely estimated.

Regional specificity was subsequently tested for all regions showing a significantly differential relationship to AM performance or ITEM performance. This analysis was inspired by previous work proposing a distinction between the contributions of different MTL regions for item and associative memory and the relative importance of prefrontal brain volume for intentional associative recognition memory in older adults

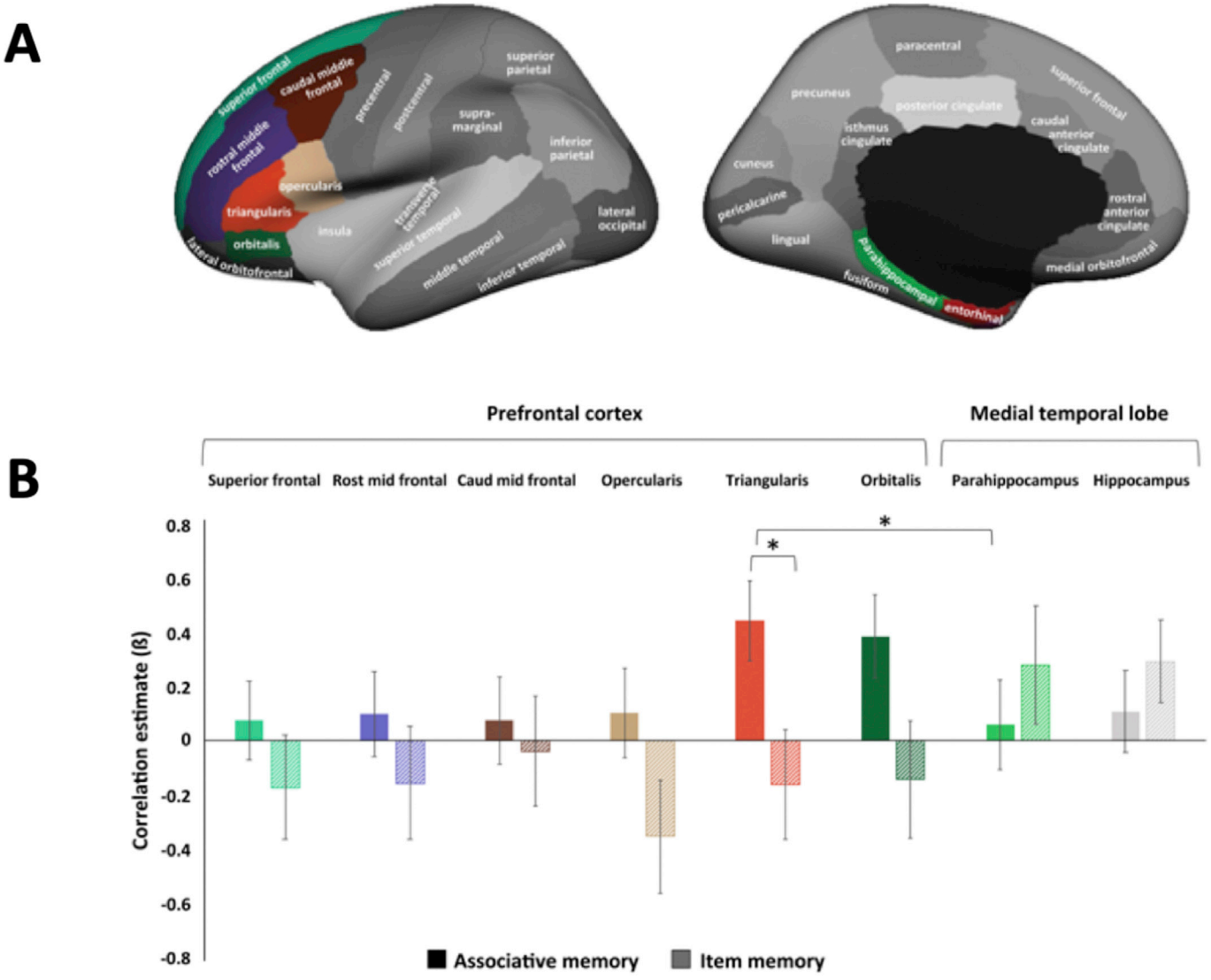


**Fig. 2.** (A) Results from the brain model for the different regions of interest, as indicated by the colored parcels in the Desikan-Killiany parcellation map (image modified with permission from Desikan et al., 2006). The hippocampus was also included as a region of interest in the brain model but as a subcortical region is not depicted here. (B) Bar chart of the standardized β estimates for the correlations between the regions of interest and performance in item and associative memory, directly derived from the results presented in Table 1. The colors of the bars correspond to the colors of the region parcels in Table 1. Estimation of the model for the entorhinal cortex resulted in an improper solution and results for this region is therefore not included. The error bars represent the standard errors for the correlation estimates, but note that all significance testing was performed by model comparison using $\chi^2$ tests. Significant correlation estimates are indicated with *($p < 0.05$) overlaid on the bars. Significant differences in correlation strength between AM-brain and ITEM-brain associations and between AM-PFC and AM-MTL associations are indicated with *($p < 0.05$) above the relevant bars. Rost mid frontal = rostral middle frontal, Caud mid frontal = caudal middle frontal.

(Becker et al., 2015). To this end, prefrontal and medio-temporal regions that were identified as selectively important for associative memory or item memory were pitched against medio-temporal regions and prefrontal regions, respectively. For all brain regions showing a significantly different relationship to AM performance or ITEM performance, one prefrontal region of interest (PFC) and one medial temporal region of interest (MTL) were included simultaneously in the model, and were allowed to correlate with each other and with AM or ITEM (region specificity model, Fig. 1C). Each combination of PFC and MTL regions were entered into separate models. To test whether the correlation with performance differed between the PFC and the MTL regions, a model in which the PFC-performance and MTL-performance correlations were constrained to be equal was compared to a model in which they were freely estimated. Like in the basic brain model, loadings of the left and right hemisphere indicators on the latent brain variables were constrained to be equal.

## 2. Results

The cognitive model (dual-process model; Fig. 1A) demonstrated good fit to the data ($\chi 2$ (39, $N = 160$) = 51.38, $CFI = 0.986$, $RMSEA = 0.045$; for factor loadings see SI-2). Removing the specific ITEM factor (single-process model) resulted in a significantly worse model fit ($\chi 2$ (42, $N = 160$) = 70.40, $CFI = 0.967$, $RMSEA = 0.065$), in support of a unique contribution of ITEM to the model, ($\chi 2$ (3, $N = 160$) = 19.02, $p < .05$). In support of the independence of the latent AM and ITEM factors, model fit did not differ between the cognitive model, which assumed independence between the latent AM and ITEM factors, and a model in which this covariance term was freely estimated ($\chi 2$ (1, N = 160) <0.01, p ≈ 1).

The brain model (Fig. 1B) converged with good model fit for all regions of interest (Table 1). However, the variance-covariance matrix was not positively definite for the entorhinal cortex, with improbable estimates for some loadings, which prevented further interpretation of results in this region. Among the remaining regions, AM was significantly correlated with cortical thickness in the pars triangularis and pars orbitalis whilst no significant correlations were detected for ITEM in any of the regions of interest (Table 1). For the pars triangularis, the correlation with AM was significantly higher than the correlation with ITEM and the same pattern was marginally significant in the pars orbitalis (Table 1). For illustrative purposes, the pattern of correlation estimates is visualized in Fig. 2B. The qualitative pattern in Fig. 2B shows that whilst all AM-brain correlations are numerically positive, the ITEM-brain correlations are numerically positive only in medial temporal regions and negative in all prefrontal regions, indicating a level of regional specificity. Whilst this qualitative pattern was not tested formally, it suggests that prefrontal regions (pars triangularis, pars orbitalis) may contribute more to associative memory than medial temporal regions, whilst the reverse pattern may be true for item memory.

To formally test for regional specificity of the contribution of the pars triangularis to associative memory demonstrated previously, the correlation between associative memory performance and pars triangularis was contrasted to the corresponding correlation with the HC and the

**Table 1**
Model fit indices ($\chi^2$, *CFI, RMSEA*) and standardized parameter estimates ($\beta$) for the correlations between the different regions of interest and item memory (ITEM) and associative memory (AM), as well as inferential statistics for the model comparisons that tested the significance of and between these correlations.

| | **Brain model fit** (df=61, n=160) | | | **AM correlation** | | | **ITEM correlation** | | | **AM vs ITEM correlation** | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Region of interest** | $\chi^2$ | *CFI* | *RMSEA* | $\beta$ | $\chi^2(1)$ | *p* | $\beta$ | $\chi^2(1)$ | *p* | $\chi^2(1)$ | *p* |
| Superior frontal | 83.60 | 0.98 | 0.05 | 0.07 | 0.24 | 0.62 | -0.17 | 0.81 | 0.37 | 0.99 | 0.32 |
| Rostral middle frontal | 69.45 | 0.99 | 0.03 | 0.09 | 0.36 | 0.55 | -0.16 | 0.81 | 0.45 | 0.90 | 0.34 |
| Caudal middle frontal | 70.63 | 0.99 | 0.03 | 0.07 | 0.21 | 0.65 | -0.04 | 0.81 | 0.84 | 0.20 | 0.66 |
| Pars opercularis | 76.30 | 0.98 | 0.04 | 0.10 | 0.35 | 0.55 | -0.35 | 0.81 | 0.10 | 2.69 | 0.10 |
| **Pars triangularis** | 71.28 | 0.99 | 0.03 | **0.43** | 7.08 | 0.01 | -0.16 | 0.81 | 0.43 | **4.81** | 0.03 |
| **Pars orbitalis** | 81.70 | 0.98 | 0.05 | **0.38** | 5.19 | 0.02 | -0.14 | 0.81 | 0.51 | 3.51 | 0.06 |
| Parahippocampus | 94.08 | 0.96 | 0.06 | 0.06 | 0.11 | 0.74 | 0.27 | 0.81 | 0.23 | 0.60 | 0.44 |
| Hippocampus | 66.61 | 0.99 | 0.02 | 0.10 | 0.48 | 0.49 | 0.29 | 0.81 | 0.35 | 0.40 | 0.53 |

*Note.* Significant results are highlighted in bold. Estimation of the brain model for the entorhinal cortex provided an improper solution and results for this region are therefore not included in the table.

parahippocampal regions of the MTL, in two separate models (Fig. 1C). Model fit was good for the model that included the HC ($\chi^2$ (86, $N = 160$) = 89.18, *CFI* = 0.997, *RMSEA* = 0.015) as well as the model that included the parahippocampus ($\chi^2$ (120, $N = 160$) = 114.07, *CFI* = 0.97, *RMSEA* = 0.045). Fixing the AM-PFC and AM-HC correlations to be equal resulted in a significant decrease in model fit only when the pars triangularis was contrasted with the parahippocampus ($\chi^2$ (1, $N = 160$) = 4.05, $p < .05$), although a trending pattern was detected also for the pars triangularis and the hippocampus, ($\chi^2$ (1, $N = 160$) = 3.70, $p = 0.054$), supporting that the demonstrated relationship between the pars triangularis and associative memory is indeed specific to the frontal lobe.

A correlation matrix of all included measures and their means and standard deviations are available in the supplementary information (SI-1).

Follow-up analyses. Whilst the age range of the study sample is relatively narrow (age 65–75), age-related variation in cognition and brain structure is possible. Therefore, in a set of follow-up analyses, all models were re-run with age included as an observed variable.

In the cognitive model (Fig. 1A), age was regressed on the AM and ITEM latent factors. As in the original analysis, statistical support for a distinction between item and associative memory was evaluated by a comparison to a model that included a single memory factor, which Age was regressed on. Again, the cognitive model demonstrated good fit to the data ($\chi2$ (49, N = 160) = 61.88, CFI = 0.985, RMSEA = 0.041) and removing the specific ITEM factor resulted in a significant decrease in model fit ($\chi2$ (4, N = 160) = 19.02, p = 0.0006545). Thus, the empirical support for a separation between associative and item memory remained even after accounting for age. For more detailed output on the cognitive model with age included in the model, see SI-3.

In the brain model (Fig. 1B), age was regressed on the Brain, AM, and ITEM latent factors. As in the original analysis, statistical significance of the correlations was tested by comparing a model in which the correlation to be tested (e.g., AM-brain) was fixed to zero, while the other (e.g., ITEM-brain) was freely estimated, with a model in which both correlations were freely estimated. The AM-brain correlation remained significant in the pars triangularis, $\chi2$ (1, N = 160) = 7.224, p = 0.007, and in the pars orbitalis, $\chi2$ (1, N = 160) = 5.590, p = 0.018, when age was included in the model. However, the direct comparison of correlation strength between the AM-brain and the ITEM-brain correlations in the pars triangularis no longer reached significance when age was included in the model, $\chi2$ (1, N = 160) = 3.775, p = 0.052. For complete statistical output from the brain models with age included, see SI-4.

In the region specificity model (Fig. 1C), age was regressed on MTL, FC, AM and ITEM. As in the original analysis, a model in which the PFC-performance and MTL-performance correlations were constrained to be equal was compared to a model in which they were freely estimated. The model that contrasted the parahippocampus and the pars triangularis converged with good model fit ($\chi2$ (98, N = 160) = 126.045, CFI = 0.970, RMSEA = 0.042), but fixing the AM-PFC and AM-HC correlation did no longer result in a significant drop in model fit ($\chi2$ (1, N = 160) = 3.7039, p = 0.05428). The model that contrasted the pars trianglularis and the hippocampus did not converge when age was included in the model.

## 3. Discussion

The main findings of the present study are in line with our hypotheses showing (a) support for a distinction between recollection-based and familiarity-based performance in older adults at a behavioural level and (b) an association between recognition performance and cortical thickness in the ventromedial PFC that is specific to associative recollection-based processes (relative to familiarity-based item memory) and to the pars triangularis (relative to the parahippocampus in the MTL). Below we discuss each finding and its respective interpretation and limitations in detail.

This is the first time that familiarity- and recollection-based recognition performance were investigated with SEM methods using IAMTs, which measure item and associative memory within the same task procedure, using the same stimulus material, encoding phase, and encoding instructions (but see Henson et al., 2016 for similar approach but different study goal). By using several independent indicators for item and for associative memory, derived from the IAMTs, the behavioral data could be modelled at the latent ability level. Specifically, the variance that was assumed to be shared among the item and associative recognition tests (recollection-based contributions to performance) was captured separately from the variance that was assumed to be shared amongst the three item memory indicators (familiarity-based processes), whilst disregarding task-specific effects and controlling for measurement error. The model that included such a distinction resulted in better model fit compared to a model that was limited to a single episodic memory factor, providing evidence for the relevance of the distinction between associative and item memory at the latent ability level in older adults.

Good associative recognition performance was found to be associated with greater cortical thickness in two lateral prefrontal regions of interest, the pars triangularis and the pars orbitalis. This is in line with a previous demonstration of a positive correlation between associative recognition performance and cortical thickness in dorso- and ventrolateral prefrontal brain regions in older adults, with no associations being detected for item memory with any other prefrontal or medio-temporal brain region (Becker et al., 2015). The correlation between recollection-based recognition and cortical thickness was significantly stronger than the corresponding correlation for familiarity-based recognition in the ventromedial PFC (i.e., pars triangularis). This finding provides support for a specific role of the pars triangularis for accounting interindividual differences in associative memory ability, with no such role for item memory, in older adults. Furthermore, the association between associative recognition and the pars triangularis appeared to be regionally specific to the lateral prefrontal lobe. Specifically, the correlation between associative memory ability and brain structure in the pars triangularis was significantly stronger than the corresponding association in the parahippocampus, with a trending effect also relative to the hippocampus. This provides preliminary support that the ventromedial prefrontal lobe is more important for the explanation of interindividual differences in associative memory performance than MTL regions in old age. The qualitative multivariate pattern of correlations furthermore appeared to support a broader distinction between the role of MTL regions in item memory over associative memory and the role of lateral PFC regions in associative memory over item memory. Whilst such a multivariate pattern awaits formal testing in future studies, the qualitative pattern of results is consistent with previous proposals of the functional separation between the MTL and the lateral PFC in item- and associative memory (Becker et al., 2015).

Becker et al. (2015) argued that the relative importance of the HC might have been underestimated in their study due to relatively small and young study sample (i.e., all individuals 60 years of age), in which age-related brain atrophy especially in the HC has not been so pronounced yet (see also Raz et al., 2005). Here, we tested a larger sample (n = 72) that covered a wider age range (65–75 years) and yet we demonstrated no significant contribution of MTL regions in accounting for interindividual differences in associative (recollection-based) memory. These findings suggest that the lateral PFC is more relevant for distinguishing older individuals with good and poor associative memory functioning than MTL regions. As previous functional and structural work especially in younger adults support the relative importance of the MTL (especially the hippocampus) for good associative memory functioning and recollection-based processes, age-comparative studies including younger and older adults and investigating the relative importance of MTL and lateral PFC for different age groups would be important to compare and even more longitudinal assessments of age-related changes of brain-behavior changes within individuals across the adult lifespan.

According to the dual-component model of episodic memory, its functionality relies on the interaction between strategic and associative

components (e.g., Shing et al., 2010). The strategic component of episodic memory refers to cognitive control processes that aid memory functioning during encoding and retrieval and are linked to the functionality and integrity of lateral PFC, while the associative component is engaged relatively automatically to aspects of relational binding (item--item, item-context) in long term memory (Chalfonte and Johnson, 1996; Naveh-Benjamin, 2000; Spencer and Raz, 1995), linked to intact MTL (H. Eichenbaum, 2004; Olsen et al., 2012). Functional MRI research has demonstrated that the dorsolateral PFC and the ventrolateral PFC is linked to strategic memory processes (e.g., information maintenance, inhibition, monitoring, and control processes) and self-initiated use of these strategies during encoding and retrieval of item pairs (Achim and Lepage, 2005; Bunge et al., 2004; Fletcher et al., 2003; Kirchhoff and Buckner, 2006; Kirchhoff et al., 2014; Qin et al., 2007; Wheeler and Stuss, 2003). Similarly, greater PFC volume has been found to be associated with better executive functions (Yuan and Raz, 2014), which are arguably important for strategic memory processes. In this context, the association between associative memory and cortical thickness in the ventromedial prefrontal cortex may therefore be accounted for by interindividual differences in strategic processes and not automatic binding processes. Related to this, the relative importance of brain structure in the PFC and MTL for associative memory have shown to be different under incidental and intentional encoding instructions (see Carr et al., 2017; Zamboni et al., 2013). Under incidental encoding instruction, participants were not aware of a subsequent memory test and did not self-initiate encoding strategies, Zamboni et al. (2013) for example found visuospatial associative memory performance of older adults to be linked to HC but not PFC volume. Intentional encoding instructions were used in the present study, allowing for intentional and effortful strategies, which may have further shifted the contribution towards PFC regions instead of towards MTL regions, which are more important for rapid formation of associations between relational information (see Becker et al., 2015).

Interestingly, the word-word item memory task (IT2) showed relatively lower loadings for the item memory latent factors than the item memory tasks containing faces and names or pictures. Item memory was modelled as the shared variance among the three item recognition tests to separate the variance assumed to be specific to the item tests, namely familiarity-based retrieval processes. Thus, the lower loading of IT2 on the item memory factor suggests that IT2 captures less familiarity-based variance than IT1 and IT3, possibly due to the stimuli type. Indeed, relative to IT1 and IT3, IT2 has a higher loading on the associative memory factor, which suggests that remembering single words engages more recollection-based processes than remembering single faces, names and pictures. Future work is needed to systematically investigate stimulus material effect when it comes to the relative contribution of familiarity and recollection processes in item and associative memory functioning.

The binding deficit hypothesis (Naveh-Benjamin, 2000) indicates that older adults show larger age-related decline in associative than in item memory functioning, which is based on deficient associative binding abilities in older adults. This study does not directly compare younger and older adults, nor includes longitudinal assessment of performance and structural brain changes across time. Hence, we cannot provide any interpretations regarding age-related differences or changes in associative in relation to item memory and related structural brain correlates. The interpretation of our findings is restricted to inter-individual differences within a group of well-functioning, healthy older adults.

Whilst the sample size of this study was large relative to most previous studies, it can be considered limited in the context of the complexity of the analysis. This limitation is particularly pertinent to the follow-up analyses, in which the inclusion of age further increased the complexity of the models, requiring estimation of additional associations based on the same number of data points. Whilst inferential statistics remained in favor of a separation between associative memory and item memory and of associations between associative memory and cortical thickness in the pars triangularis and pars orbitalis, support for a specific association with associative memory, above and beyond item memory, and with the pars triangularis, above and beyond medial-temporal regions, dropped just below the significance threshold. Such minor variations in estimates and p-values are to be expected given the reduced statistical power in the follow-up analyses but it is evident that the present findings will need to be replicated in larger samples. The need for replication in larger samples is also emphasized by the multiple models tested in the present study without statistical adjustment, which represents an important limitation of the reported findings.

Model convergence problems were encountered for the entorhinal cortex (non-positive-definite variance-covariance matrix), which may have not occurred with larger sample sizes. The present findings therefore need to be replicated with larger study samples. It will also be important to evaluate the influence of the intentional encoding on the relative contribution of lateral PFC and MTL regions in accounting for interindividual differences in associative memory in old age. Disentangling the contribution of strategic and more automatic binding processes of associative memory will be important in future research. Furthermore, as the current study assessed static estimates of brain structure (cross-sectional design), which does not exclude the possibility that individual differences in brain volume and thickness might be (party) related to differences in age-related decline or inter-individual differences in brain structure, which existed already at younger ages. It will be necessary to test these associations longitudinally in order to establish whether age-related associative memory decline co-vary with deterioration in the lateral PFC over time. Finally, since the maximum likelihood estimation methodology used here rested on an untested assumption that the MR data were missing at random, it will be important to replicate the results in datasets with complete brain data.

In summary, the present study provided support for a distinction between associative memory (i.e., recollection-based memory performance) and item memory (i.e., more familiarity-based memory performance) and for a specific role of the ventromedial prefrontal cortex (pars triangularis) in accounting for interindividual differences in associative memory performance in older adults. These findings support the idea that successful intentional associative recognition performance in older adults is highly supported by strategic functioning.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.116475.

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