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Original Article

ORIGINAL ARTICLE

# Maintained Frontal Activity Underlies High Memory Function Over 8 Years in Aging

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## Abstract

Aging is characterized by substantial average decline in memory performance. Yet contradictory explanations have been given for how the brains of high-performing older adults work: either by engagement of compensatory processes such as recruitment of additional networks or by maintaining young adults' patterns of activity. Distinguishing these components requires large experimental samples and longitudinal follow-up. Here, we investigate which features are key to high memory in aging, directly testing these hypotheses by studying a large sample of adult participants ($n > 300$) with fMRI during an episodic memory experiment where item-context relationships were implicitly encoded. The analyses revealed that low levels of activity in frontal networks—known to be involved in memory encoding—were associated with low memory performance in the older adults only. Importantly, older participants with low memory performance and low frontal activity exhibited a strong longitudinal memory decline in an independent verbal episodic memory task spanning 8 years back ($n = 52$). These participants were also characterized by lower hippocampal volumes and steeper rates of cortical atrophy. Altogether, maintenance of frontal brain function during encoding seems to be a primary characteristic of preservation of memory function in aging, likely reflecting intact ability to integrate information.

**Key words:** aging, brain maintenance, encoding, episodic memory, fMRI

## Introduction

Why do some individuals exhibit significant episodic memory decline with aging while others show preserved function (Wilson et al. 2002)? Experimental studies have shown substantial plasticity of the aging brain—that is, the brain's capacity for reactive change altering the individual's range of functioning (Pascual-Leone et al. 2005; Lövdén et al. 2010; Walhovd et al. 2016). In line with this, several studies have reported that compensatory mechanisms support successful episodic memory in aging, either by over-activation of existing networks or by recruitment of alternative circuits (Cabeza et al. 2002). In contrast, it has also been proposed that the primary determinant of successful memory aging is the relative lack of brain pathology and changes in brain function, the so-called "brain maintenance" view (Nyberg et al. 2012). A major challenge is that to test these opposing views, functional brain imaging of

participants at different ages needs to be combined with longitudinal data on memory change, preferably over many years. In the present study, we tested whether functional compensation or brain maintenance best characterized successful episodic memory function in aging in a large sample of 290 healthy adults from 19 to 81 years. Brain activity was assessed using functional magnetic resonance imaging (fMRI) during implicit encoding of item-source associations and linked to information about longitudinal memory function spanning back up to 8 years, hippocampal atrophy, cortical integrity and amyloid-beta (Aβ) positron emission tomography (PET) data.

Subsequent memory paradigms that segregate activity for trials associated with later successful memory versus forgetting permit the identification of activity associated with successful encoding processes. Research using this paradigm has commonly reported links between successful memory encoding and increased activity in widespread regions, including left-lateralized frontoparietal cortical networks and the hippocampus, and reduced activity (negative memory effects) in default-mode network (DMN) regions (Kim 2011; Sneve et al. 2015). Despite heterogeneity in the forms of memory tested, diminished posteromedial deactivation, decreased frontoparietal activity and recruitment of additional prefrontal regions—often contralateral to the dominant frontal activity patterns in young adults—emerge as recurrent features of memory encoding in older adults (Miller et al. 2008; Duverne et al. 2009; de Chastelaine et al. 2011; Düzel et al. 2011; Park et al. 2013; Maillet and Rajah 2014).

Increased brain activity in aging is often regarded as compensatory, especially if it correlates with better memory performance (Grady 2012). When age-specific patterns of activity are unrelated to performance or display negative associations, it is less clear whether this reflects compensatory activity, neural inefficiency, or dedifferentiation (Grady 2012; Nyberg et al. 2012; Rugg 2016). Paradoxically, higher prefrontal activity in older adults has been found to be both positively (Dennis et al. 2007; de Chastelaine et al. 2016) and negatively (Duverne et al. 2009; de Chastelaine et al. 2011) related to memory performance. In contrast, brain maintenance is more clearly endorsed when older participants with more pronounced decrements of brain function (applicable also to structural and neurochemical integrity) also exhibit worse memory performance (Nyberg et al. 2010). Regions associated with subsequent memory success in younger adults—that is, left inferior frontal gyrus and posteromedial regions—often show brain maintenance patterns of activity as the association between regional activity and memory function emerges only in higher ages (Miller et al. 2008; Duverne et al. 2009; Mattson et al. 2014; de Chastelaine et al. 2016).

In the present study, participants were tested for source-item associations in an unexpected memory test, approximately 90 min after incidental encoding in the MR scanner. The task was designed to test activity related to associative memory success, as the ability to form new associations is a crucial element in episodic memory and such memories are known to be particularly vulnerable to the effects of age (Old and Naveh-Benjamin 2008). We categorized each participant according to age and memory performance and estimated the activity associated with subsequent associative memory success. Evidence for brain maintenance will be considered if high-performing older participants exhibit similar levels of activity as younger adults—in regions consistently associated with later memory success—while decrements of activity are uniquely associated with poorer memory performance in higher ages. This pattern permits the identification of specific patterns supporting higher memory with higher ages. Higher activity in older adults—or in a subgroup of older adults—compared with younger participants will be interpreted as evidence for compensatory patterns. The role of this possible compensatory pattern will be determined by the specific association of these patterns with memory performance (successful, unsuccessful, attempted) (Cabeza and Dennis 2006). We hypothesized that "youth-like" patterns of brain activity, both in the frontal cortex and in the deactivated posteromedial regions, would be associated with high memory function in aging but not in younger adults, reflected in an age × performance interaction. Although cross-sectional studies are often employed to test brain maintenance (Düzel et al. 2011; Fandakova et al. 2015) and compensation (Davis et al. 2008) theories, they cannot easily separate the effects of aging from differences at baseline (Nyberg et al. 2010). Thus, we examined whether poor memory performance in the fMRI task was associated with steeper decline in memory function in an independent memory task tested 3 times over 8 years back in time. A positive relationship between longitudinal preservation of memory function, brain activity and task performance would strongly support the notion that older adults' in-scan performance reflects changes in memory function over time; that is, memory maintenance or decline. Finally, memory decline in higher ages is often associated with presence of neuropathological markers such as amyloid deposition as well as steeper structural decline. Here, we studied whether task performance was additionally explained by cortical and subcortical decline in the preceding years and/or accompanied by amyloid deposition by means of longitudinal MRI data and amyloid-PET scans. These analyses are not directly related to testing the maintenance versus compensation models.

## Materials and Methods

### Participants

A total of 290 participants (females = 196, age = 45.3 [17.3], age range = 19–81) were included in the main sample. Additionally, we draw a reference subsample that consisted of 55 young participants (females = 37, age = 28.4 [5.6], age range = 19–39) to define the core regions of the associative encoding network. The samples were independent as a participant was included either in the main or in the reference sample. The participants were recruited from ongoing projects coordinated by the Centre for Lifespan Changes in Brain and Cognition (LCBC), University of Oslo. All participants completed the experimental design and were screened through health and neuropsychological interviews. Participants were screened for neurologic or psychiatric disorders, chronic illness, premature birth, learning disabilities, handedness, or current use of medicines known to affect nervous system functioning. Participants were also excluded based on neuropsychological evaluation criteria: score <26 on the Mini Mental State Examination (MMSE; Folstein et al. 1975), score of ≥16 in the Beck Depression Inventory (BDI; Beck 1987), score <85 on the Wechsler Abbreviated Scale of Intelligence (Wechsler 1999), and a *T*-score of ≤30 on the California Verbal Learning Test II—Alternative Version (CVLT II; Delis et al. 2000) immediate delay and long delay. All participants gave written informed consent and the study was approved by the Regional Ethical Committee of South Norway. See SI methods for detailed information on exclusion criteria and project details. See Table S1 for main demographic and neuropsychological stats across the age × performance groups.

Participants were categorized according to the age group (young, middle-aged or old) with breakpoints at age 40 and 60, and according to the behavioral performance. Memory performance in the task was regressed against chronological age—as a continuous variable—and the residuals were used to classify participants in the high or the low-performing groups. That is, participants were categorized as having high or low memory according to their age, corresponding to residualized memory performance above or below 0. We modeled a linear relationship between age and memory performance as the Bayesian information criterion (BIC) did not yield much support for nonlinear relationships between age and memory performance (up to the fifth polynomial). The number of participants included in each low and high-performing subgroup was 62:62, 42:50, and 39:35 for the young, middle-aged, and older groups, respectively.

Longitudinal and Aβ information was available only for a subsample of the older participants ($n = 51$ and $n = 52$, respectively; Table 1) that were initially recruited from the "Cognition and Plasticity Through the Life-span" project coordinated by the Centre for LCBC, University of Oslo. The Aβ and the longitudinal subsamples did not differ from the pool of older adults in any sociodemographic or neuropsychological variables ($P > 0.3$ for all tests; Table 1).

## Experimental Design

The experiment consisted of an incidental encoding task and a surprise memory test after ≈90 min, both inside the scanner. The stimulus material consisted of black and white line drawings of items. The encoding and the retrieval tasks consisted of 2 and 4 runs, respectively, that included 50 trials each and three 11 s baseline periods. In the encoding runs, a trial started asking into the participant's headphones, either "Can you eat it?" or "Can you lift it?" (Fig. 1*a*). After 1 s, a picture of an item appeared on the screen together with a "Yes/No" response indicator. After 2 s a fixation cross appeared, and remained throughout the intertrial interval, that lasted between 1 and 7 s (exponential distribution; duration = 2.98 [2.49] s).

Test trials started asking the participants (Question 1): "Have you seen this item before?" (Fig. 1*d*). Then, a picture of an item appeared, and participants had to press Yes (old) or No (new). In each run, the old/new item odds ratio was 1:1. Each object stayed on the screen for 2 s; if the participant responded that the item was new or did not respond, the trial ended. Else, a new question followed (Question 2): "Can you remember what you were supposed to do with the item?". A No response ended the trial, whereas a Yes response, was followed by a 2-alternative forced choice question (Question 3): "Were you supposed to eat it or lift it?". The main experimental design is thoroughly described elsewhere (SI Methods; Sneve et al. 2015; Vidal-Piñeiro et al. 2017).

## Behavioral Analysis

For behavioral analysis, test trial responses to old items were classified as follows: 1) source memory (Yes response to Question 1 and 2 and correct response to Question 3); 2) item memory (correct Yes response to Question 1 and either a No response to Question 2, or incorrect response to Question 3); or 3) miss (incorrect No response to Question 1). We also computed additional behavioral measures: recognition hits (correct Yes response to Question 1, regardless response to Question 2 and 3) and incorrect source judgments (incorrect eat/lift response to Question 3). New items were classified either as 4) correct rejections or 5) false alarms. Memory performance in the task was assessed with a corrected source memory performance index (correct answers to Question 3—incorrect answers to Question 3). This correction tentatively accounts for processes such as false memories, threshold criteria in Question 2 or guessing behavior that affects the raw estimates of source memory performance. fMRI conditions were modeled based on the subsequent trial responses (see MRI Preprocessing). All nonvertex wise statistical analyses were performed in R-environment (https://www.r-project.org/; v.3.2.5). Statistical significance was considered at $P < 0.05$ (2-sided) and error bars represent standard error of means (SEM). When specified, false-positive rate correction for multiple comparisons was performed with Bonferroni adjustment (*P*-adj.), in which the threshold was corrected for the mean correlation between dependent variables (Sankoh et al. 1997; Krogsrud et al. 2018).

## MRI Acquisition

Imaging data were collected using a 24-channel Siemens head coil on a 3 T MRI (Siemens Skyra Scanner, Siemens Medical Solutions, Germany) at Rikshospitalet, Oslo University Hospital. The functional imaging parameters were equivalent across all fMRI runs: 43 transversally oriented slices (no gap) were measured using a BOLD-sensitive T2*-weighted EPI sequence (TR = 2390 ms, TE = 30 ms, flip angle = 90°; voxel size = 3 × 3 × 3 $mm^3$; FOV = 224 × 224 $mm^2$; interleaved acquisition; generalized autocalibrating partially parallel acquisitions acceleration factor = 2). Each encoding run produced 134 volumes. At the start of each fMRI run, 3 dummy volumes were collected to avoid T1 saturation effects in the analyzed data. Anatomical T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) images consisting of 176 sagittally oriented slices were obtained using a turbo field echo pulse sequence (TR = 2300 ms, TE = 2.98 ms, flip

**Table 1** Old subsamples. Selected demographic and neuropsychological variables from the old subsamples used in the longitudinal and the Aβ analysis. One sample *t*-tests for quantitative and chi-square tests for binomial variables were performed to test sample differences against the main pool of older participants. Overall, 43 participants were included in both the longitudinal and the Aβ sample

| | Old sample ($n = 72$) | Longitudinal sample ($n = 52$) | $t/\chi$ (P) | Aβ sample ($n = 51$) | $t/\chi$ (P) |
|---|---|---|---|---|---|
| Performance | 35:39 | 23:29 | 0.0 (0.9) | 23:28 | 0.0 (1.0) |
| Sex | 33:41 | 25:27 | 0.0 (0.8) | 23:28 | 0.0 (1.0) |
| Age | 67.8 (5.3) | 68.5 (5.4) | 0.9 (0.4) | 68.3 (5.6) | 0.6 (0.5) |
| Source memory | 0.3 (0.2) | 0.3 (0.2) | −0.5 (0.6) | 0.3 (0.2) | −0.7 (0.5) |
| WASI vocabulary | 66.3 (6.9) | 66.2 (7.0) | −0.1 (0.9) | 66.3 (7.5) | 0.0 (1.0) |
| WASI matrices | 25.2 (4.8) | 25.1 (5.2) | −0.2 (0.9) | 25.1 (5.4) | −0.2 (0.9) |
| CVLT learning | 51.6 (9.5) | 52.3 (9.1) | 0.5 (0.6) | 53.2 (9.8) | 1.2 (0.3) |
| CVLT 30' recall | 11.3 (2.8) | 11.4 (2.7) | 0.3 (0.8) | 11.5 (2.9) | 0.5 (0.6) |

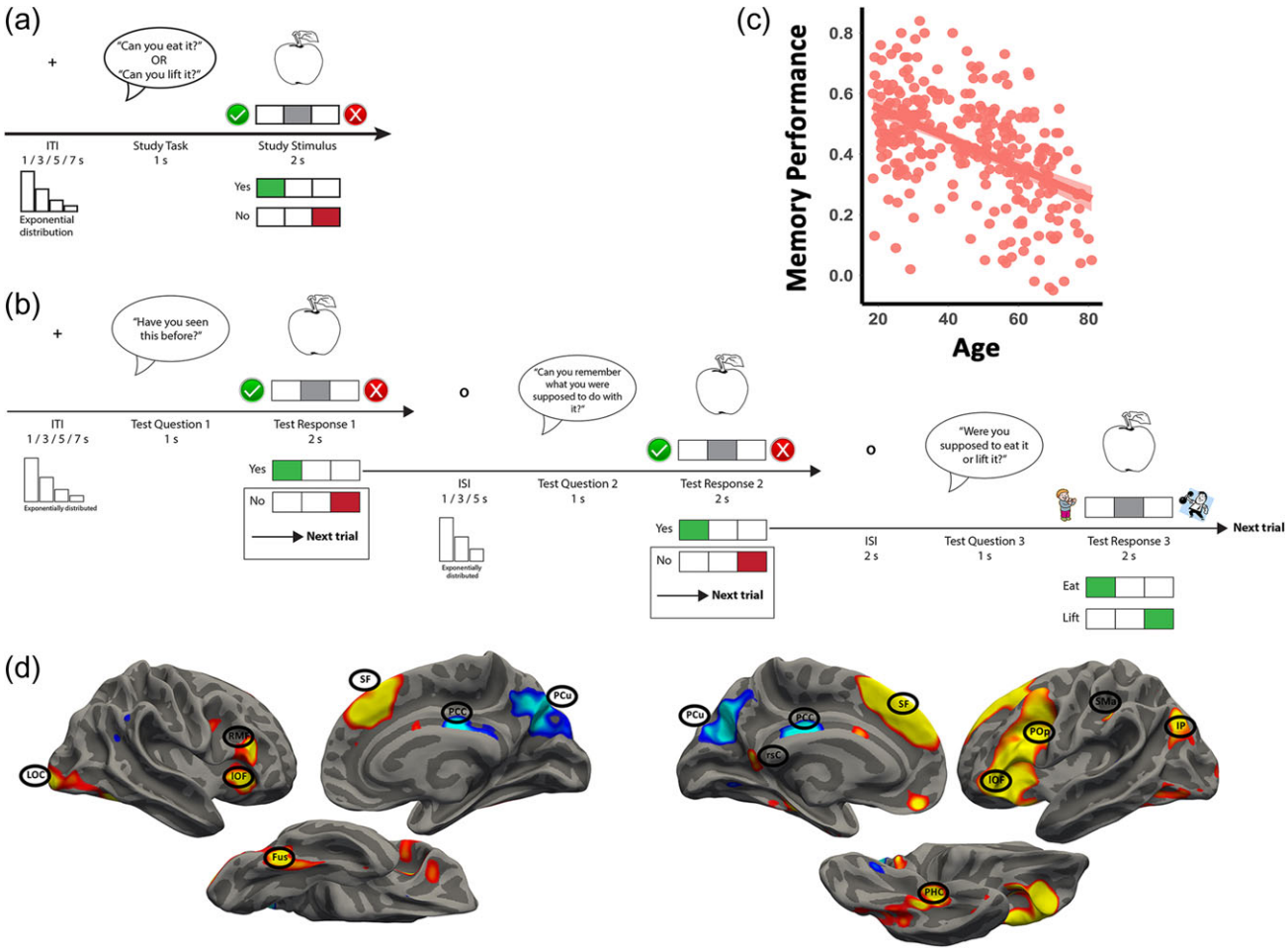


**Figure 1.** Experimental paradigm. (*a*) Schematic outline of an encoding trial. (*b*) Schematic outline of a retrieval trial. Test Questions 1 and 2 required a Yes/No response, whereas Question 3 consisted of a 2-alternative forced choice task. The trial ended if the participant responded No to either 1 of the 2 first questions. Adapted from Sneve et al. (2015). (*c*) Relationship between age and memory performance in the experimental task ($n = 290$). (*d*) Parameter estimates of subsequent memory effects (source vs. item memory contrast) in the young reference sample (FDR corrected; $P < 0.005$). Black circles indicate nearby ROI locations. SF = left/right superior frontal; IOF = left/right lateral orbitofrontal; PCC = left/right precuneus; PCC = left/right posterior cingulate; POp = left pars opercularis; SMa = left supramarginal; IP = left inferior parietal; PHC = left parahippocampal; rsC = left retrosplenial cortex; RMF = right rostral middle frontal; LOC = right lateral occipital; Fus = right fusiform.

angle = 8°, voxel size = $1 \times 1 \times 1\,mm^3$, FOV = $256 \times 256\,mm^2$). Additionally, a standard double-echo gradient-echo field map sequence was acquired for distortion of the echo planar images. Visual stimuli were presented in the scanner environment with an NNL 32-inch LCD monitor while participants responded using the ResponseGrip device (both NordicNeuroLab, Norway). Auditory stimuli were presented to the participants' headphones through the scanner intercom.

## MRI Preprocessing

Cortical reconstruction and volumetric segmentation of the T1-weighted scans were performed with the FreeSurfer v.5.3 pipeline (http://surfer.nmr.mgh.harvard.edu/fswiki; Dale et al. 1999; Fischl et al. 1999; Fischl and Dale 2000). Briefly, the automatized processing pipeline includes removal of nonbrain tissue, Talairach transformation, intensity correction, tissue and volumetric segmentation, cortical surface reconstruction, and cortical parcellation. All volumes were visually inspected and minor manual edits were performed when necessary. Hippocampal volumes at native space were further extracted to study the association between hippocampal activity and memory performance (SI Methods: fMRI Analysis).

Functional imaging data from the memory task was preprocessed using the Freesurfer Functional Analysis Stream (FSFAST; https://surfer.nmr.mgh.harvard.edu/fswiki/FsFast) and components from the FSL toolbox (http://fsl.fmrib.ox.ac.uk/fsl/). For each run, fMRI images were corrected for distortions caused by B0 inhomogeneities in EPI scans, motion corrected respect the mid-volume, slice timing corrected to the middle of a volume's TR and, intensity normalized. fMRI images were further registered to each participant's anatomical volume, slightly smoothed (at 5 mm full width at half maximum [FWHM]) at volume space and, denoised through an independent component analysis (ICA)-based approach (FIX v1.062; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIX) (Griffanti et al. 2014; Salimi-Khorshidi et al. 2014). fMRI data were decomposed into independent components that were automatically classified as "good" or "bad," so that bad component-associated signal could be removed from the data. To optimize the approach, we supplied FIX with a classifier weight-file trained with the study data. A classifier was trained based on manually labeled

components from 32 datasets, which were randomly chosen from the young and old pool of participants. On average, FIX removed 55.3% (9.2) of the BOLD signal variance. An age × performance ANCOVA (sex was introduced as a covariate of no-interest) revealed that FIX removed a greater proportion of the BOLD signal in older ages ($F[1,283] = 25.1$, $P < 0.001$). No differences were found neither with performance nor with the age × performance interaction terms ($P > 0.5$). See Table S2 for additional information on the variance removed by FIX in each age × performance group.

A first-level general linear model (GLM) consisting of the conditions of interest with onsets and durations corresponding to the experimental trial period was set up for each encoding run and was convolved with a double-gamma canonical hemodynamic response function (HRF). GLMs were estimated both in the cortical surfaces and in the subcortical structures of interest. Each event was assigned to a condition based on the participant's response to a given item during the test sessions. The conditions of interest were source and item memory conditions as defined in the behavioral analysis. Two additional regressors were included to soak up BOLD variance associated with miss memory trials and with trials in which the participant did not emit a response. Data were high-pass filtered at 0.01 Hz, and temporal autocorrelations were prewhitened. For each individual, parameter estimates from the source versus item contrast were computed for further statistical analysis. Cortical maps of parameter estimates were resampled to a common space using a surface-based intersubject registration and smoothed at 8 mm FWHM.

The associative contrast of interest was the source vs. item memory as it better isolates the processes of interest and controls for unattended items that would likely be classified as miss memory trials. Equivalent contrasts are commonly—albeit not unanimously—used in the literature (Miller et al. 2008; de Chastelaine et al. 2011, 2015, 2016; Kim and Giovanello 2011; Leshikar and Duarte 2014). The main disadvantage of the source versus item contrast is that possible differences in activity might be associated with item memory effects. This effect is limited in the current study, as source versus item memory and source versus miss memory spatial maps exhibited almost identical spatial correlations ($r = 0.92$; Fig. S1) and shared all the positive and negative subsequent memory cluster effects.

## fMRI Analysis

### *ROI Analysis*

ROIs were independently defined using the "reference" subsample ($n = 55$). A total of 16 surface ROIs were generated on cortical coordinates with "maxima" and "minima" subsequent memory effects (source versus item memory contrast). Briefly, cortical ROIs were expanded by 12 iterations encompassing up to 721 vertices (mean area = 364 $mm^2$). Each iteration included the neighboring vertices while respecting the reference subsample activation maps. The set of ROIs can be downloaded as supplementary material. See Table S3 for additional information on ROIs. The ROIs were distributed across the cortical surfaces, bilaterally, representing core regions of the encoding network (SI Methods, Fig. 1*d*). In each ROI, we ran an ANOVA on mean subsequent memory activity, with age, performance and, age × performance interaction as factors (sex was also included as a covariate of no-interest). Post hoc Tukey (HSD) tests served to test differences across pairs of means. For the frontal ROIs, the analyses were repeated in a subsample of participants with "absolute" low memory scores (SI Methods and Results; Fig. S2). For the frontal and posteromedial ROIs, the analyses were repeated based on different operationalizations of memory performance (SI Methods and Results) and with the additional introduction of covariates of no-interest.

### *Vertexwise Analysis*

To explore whether age, performance, and age × performance effects on activity were present outside the core regions of the encoding network, we carried a GLM vertexwise analysis—with sex also included as a covariate of no interest. Individual contrasts of parameter estimates, that is, source versus item memory maps, resampled in a common cortical "fsaverage" space, were fed to a GLM analysis. Statistical significance was tested at each cortical vertex and the resulting maps were corrected for multiple comparisons using a cluster-based approach; vertices were thresholded at $P < 0.01$ and the remaining clusters were tested through permutation inference across 10.000 iterations using PALM scripts (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM; Winkler et al. 2014). Cluster significance was considered at a family-wise error (FWE)-corrected level of $P < 0.05$. Mean estimates for each subject were extracted from the surviving clusters and post hoc Tukey (HSD) tests were applied to examine differences across pairs of means.

### *Activity Gradient Analysis*

We carried an activity gradient analysis with Matlab® (v.R2016a) in-house scripts to explore the spatial association between age, performance, and age × performance effects and activity. This descriptive analysis allows the detection of age and performance effects patterns along the memory effects continuum. Based on the reference sample we sorted and binned ($n = 50$) all the cortical vertices, bihemispherically, as a function of the estimated mean signal change in the source versus item memory contrast. As a result, cortical vertices were classified along an activity gradient such as vertices with negative memory effects were grouped in the lower part of the gradient while vertices with the highest memory effects were clustered in the high-end of the distribution. We then computed, for each bin of the gradient, the proportion of vertices in which activity significantly related to age, performance, and age × performance. The distribution of effects along the continuum may additionally inform about the presence of compensatory and maintenance effects. In presence of compensatory patterns of activity, we would expect effects of age or age × performance outside the end sections of the activity gradient. Age × performance effects in the end sections exclusively—and subsequent post hoc tests pointing-out reduced activity in low-performing older adults- would be considered as evidence for brain maintenance patterns.

## Hippocampal Analyses

For each participant, the hippocampal volume was defined through the semi-automatized FreeSurfer preprocessing pipeline (SI Methods: MRI Preprocessing). Mean hippocampal activity contrast estimates were extracted per participant and hemisphere and fed to a higher-order GLM analysis. Subsequent memory effects in the hippocampus were tested with a 3 × 2 × 2 mixed-effects ANOVA with age, performance, and hemisphere as factors (Fig. S3).

### Longitudinal Memory Decline

Preceding longitudinal decline in an off-scan memory test was computed in a subsample of older participants with available longitudinal observations. These participants had 3 completed measurements, obtained in 3.9 (0.6) years intervals ($n$ = 52; Table 1, SI Methods), that included neuropsychological testing and MRI scanning. The third observation corresponded in time with the current experimental task. By regressing each participants' California Verbal Learning Test II (CVLT II; Delis et al. 2000) long delay free recall scores against time, we estimated an intercept and a linear slope that represented memory at baseline and decline, respectively (Josefsson et al. 2012). The relationship between memory decline and memory performance in the fMRI task was tested with an ANCOVA that also included memory at baseline as a covariate.

### Beta-Amyloid and Structural Integrity Analysis

Aβ status for the subsample of older participants was derived using [18F]-Flutemetamol-PET (Table 1). Large cortical aggregate were computed and introduced in a Gaussian mixture model approach that assigned to each participant a probability of belonging to the high and low Aβ distribution (SI Methods; Fig. S4; Mormino et al. 2014; Hedden et al. 2016). Chi-squared tests were used to test the relationship between Aβ status and memory performance group in the subsample of older participants.

The imaging data used in the longitudinal structural integrity analysis were collected using a 12-channel head coil on a 1.5 T Siemens Avanto scanner (Siemens Medical Solutions, Germany) at Rikshospitalet, Oslo University Hospital and consisted on 2 repeated 160-slice sagittal T1-weighted MPRAGE per participant per time point. The anatomical images were preprocessed with the longitudinal FreeSurfer stream (SI Methods: MRI Preprocessing), brought to fsaverage average space, and smoothed at 15 mm FWHM. By regressing each participants' cortical volumes against time, we obtained a linear slope representing decline in cortical volume with time (Josefsson et al. 2012), which was used as the measure of interest. To explore whether decline in cortical integrity was associated with memory function in older adults, we carried a GLM vertexwise analysis that included performance level and vertexwise cortical volume at baseline as predictors of longitudinal decline in cortical volume. Statistical significance was tested at each cortical vertex and the resulting maps were corrected for multiple comparisons using a cluster-based approach; where vertices were initially thresholded at $P < 0.01$ and cluster-significance tested at $P < 0.05$ through permutation inference (Winkler et al. 2014). In addition, we specifically explored the effect of hippocampal and entorhinal atrophy on memory performance in older adults. Decline in hippocampal and entorhinal volume was estimated for each participant with linear fittings (Josefsson et al. 2012). Both analyses consisted on 2 × 2 performance × hemisphere mixed-models that included intracranial volume (ICV) and volume at baseline as covariates of no interest. See SI Methods for additional analysis and details on the structural integrity analyses.

## Results

The fMRI task (Fig. 1*a*,*b*) allowed us to isolate encoding activity associated with later associative memory success, defined as source memory activity versus activity associated with item memory only. Sex was included as a covariate of no interest in all the analysis.

**Table 2** Experimental statistics. Age effects on experimental variables were tested with GLMs that included sex as a covariate. All means represent proportions or seconds. $n$ = 290

| | All mean (SD) | Age $t$ ($P$) |
|---|---|---|
| Source hits (corrected) | 0.43 (0.18) | **−9.3 (<0.001)** |
| Recognition hits | 0.75 (0.11) | **−3.3 (0.001)** |
| Correct rejections | 0.91 (0.07) | **−5.1 (<0.001)** |
| Misses | 0.22 (0.11) | 2.2 (0.03)* |
| False alarms | 0.06 (0.05) | **4.0 (<0.001)** |
| Source hits | 0.52 (0.14) | **−6.6 (<0.001)** |
| Incorrect source judgments | 0.09 (0.07) | **9.7 (<0.001)** |
| Item memory | 0.19 (0.08) | **3.0 (<0.001)** |
| Reaction time (encoding) | 1.02 (0.14) | **7.9 (<0.001)** |
| Reaction time (Q1 retrieval)[a] | 1.03 (0.11) | **12.0 (<0.001)** |

[a]Only correct responses to old items are considered.
*Denotes uncorrected significance while bold statistics denotes significance after adjustment for multiple comparisons ($P < 0.01$). See Behavioral Analysis for the definition of the variables.

### Behavioral Classification

Mean memory performance—assessed with a corrected source memory index—was 0.43 (standard deviation [SD] = 0.18). A GLM revealed a strong negative relationship between memory performance and chronological age ($t[287] = -9.4$, $P < 0.001$; Fig. 1*c*, see additional behavioral stats derived from the fMRI task in Table 2) but not with sex ($t[287] = -1.0$; $P = 0.3$). Memory performance in the task was regressed against age (as a continuous variable) and the residuals were used to classify participants in the high or the low performance groups. See Table S2 for behavioral measures derived from the fMRI task across the age × performance groups; note that all age × performance groups exhibited above-chance memory performance.

### Brain Activity

#### *ROI Analysis*

We identified 16 ROIs that represented core regions of the memory network using an independent reference sample of young participants (Fig. 1*d*; $n$ = 55, SI Methods and Results). For each ROI, we ran an ANOVA to test the effects of age, performance, and age × performance interaction on subsequent memory activity. See Table S4 for complete ROI analysis statistics. Two frontal ROIs, in the left superior frontal ($F[2,283] = 4.9$, $P = 0.008$) and the left lateral orbitofrontal ($F[2,283] = 5.1$, $P = 0.007$) cortices exhibited Bonferroni corrected ($P$-adj. = 0.008) age × performance interactions (Fig. 2). In addition, the right superior frontal ($F[2,283] = 3.7$, $P = 0.03$) and the left pars opercularis ($F[2,283] = 3.0$, $P = 0.05$) ROIs showed significant age × performance unadjusted by multiple-comparisons ($P < 0.05$; Fig. 2). Post hoc tests (Tukey HSD) revealed differences specifically in the older participants, as low-performing participants showed significantly lower frontal encoding-activity for trials later successfully recalled with source memory. To rule out the possibility that low activity in the low-performing elderly was a result of their poorer memory accuracy per se, a group of participants were selected based on absolute low memory performance, that is, age not covaried out, and thus exhibiting comparable levels of performance (SI Methods and Results, Fig. S2). Age differences in frontal activity remained evident, supporting the view that lower frontal encoding activity is characteristic of low-performing older participants only and do not reflect low levels of performance per se.

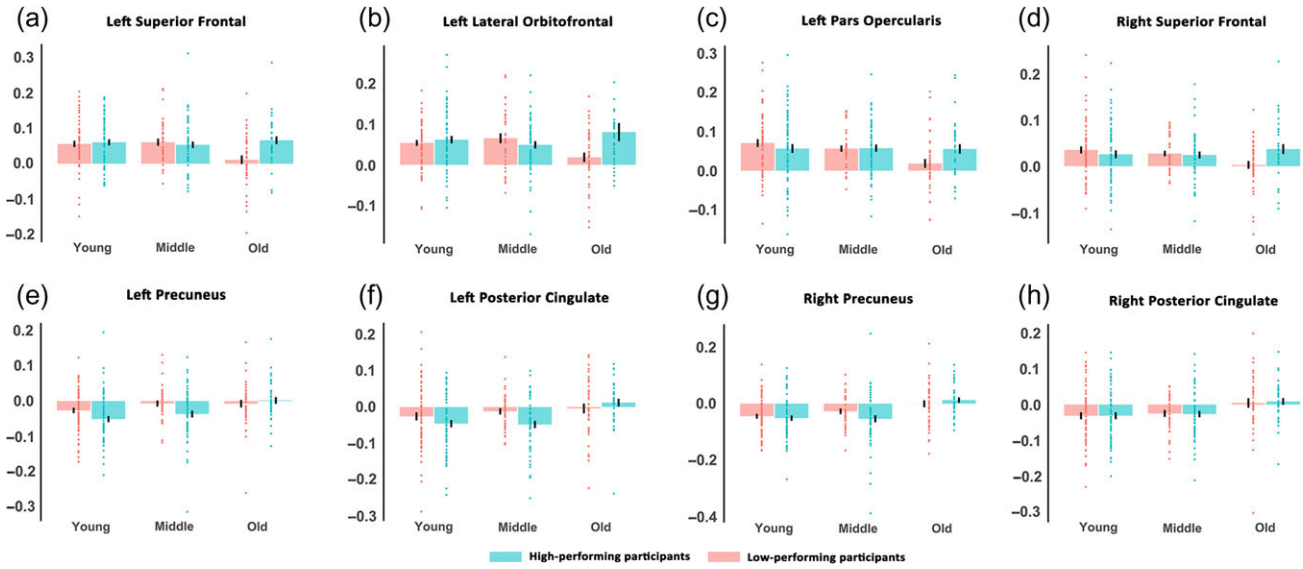


**Figure 2.** ROI analysis. Selected barplots from the ROI analysis. Each barplot represents mean subsequent memory effects in each age × performance subgroup ($n$ = 290). The upper row displays frontal ROIs that exhibited unadjusted ($P < 0.05$) age × performance interaction. The left superior frontal and the left orbitofrontal ROIs remained significant when the threshold was adjusted by multiple-comparisons ($P$-adj. = 0.008). The lower row displays posteromedial ROIs that showed age effects. An outlier data point is not represented in the left lateral orbitofrontal plot (old high-performing group).

The absence of age × performance interactions in the posteromedial cortex was somewhat surprising (Miller et al. 2008; Duverne et al. 2009; Mattson et al. 2014). Nonetheless strong main effects of age were found in these ROIs—left and right posterior cingulate ($F$[1,283] = 7.0, $P$ = 001; $F$[1,283] = 13.4, $P < 0.001$) and precuneus ($F$[1,283] = 7.1, $P < 0.001$; $F$[1,283] = 6.9, $P$ = 0.001; $P$-adj. = 0.008; Fig. 2). Older adults showed less negative memory effects so that posteromedial activity was not a predictor of subsequent memory success in this group. Age effects in the posteromedial ROIs remained significant when corrected by source memory performance across the entire sample ($F \geq 6.9$ and $P \leq 0.001$ in any test; SI Methods and Results). Thus, differences in brain activity with age in the posteromedial cortex were not attributable to age-related decrements in performance. Neither age nor performance was clearly associated with the remaining ROIs.

The age effects in the posteromedial ROIs and the age × performance effects in the frontal ROIs remained significant in a series of control analyses that included exclusion of participants with corrected source memory ≤0 ($n$ = 4), use of residualized memory performance without categorization, use of the uncorrected source memory index as the performance measure of interest, and the inclusion of matrix-reasoning scores as a covariate of no interest (as matrix scores showed age × performance effects (see Table S2)). See SI Methods and Results for the additional analyses. ROI activity was unrelated to underlying cortical thickness (SI Results).

The results fit well with the concept that brain preservation is the major characteristic behind good memory function in aging. The frontal specificity is congruent with the prominent role of the frontal cortex in associative memory (Murray and Ranganath 2007; Wong et al. 2013) and the vulnerability of both frontal structure and function to the effects of age (Nyberg et al. 2010; Fjell et al. 2014). Prominent effects of age, but no interaction with memory performance were observed in the posteromedial regions (see also de Chastelaine et al. 2015). Thus, it is not possible to elucidate whether the functional mechanisms behind posteromedial deactivation are central to later memory success or reflect more unspecific age-related changes, for example, reduced brain flexibility.

### *Hippocampal Analyses*

Both the left and the right hippocampus exhibited subsequent memory effects, as tested with one-sample $t$-tests ($t$[289] = 6.7, $P < 0.001$; $t$[289] = 2.8, $P$ = 0.006). Main effects of hemisphere ($F$[1,284] = 13.0, $P < 0.001$; left > right), but not of age, performance or age × performance interaction on hippocampal activity were found in a 3 × 2 × 2 mixed-effects ANOVA ($P > 0.05$; Fig. S3). In absence of age × performance effects, the remaining analyses were exclusively focused on the cortical mantle.

### *Vertexwise Analysis*

The same GLM model used in the ROI analysis was implemented vertexwise, with corrections for multiple comparisons to assess effects of age or age × performance outside the ROI regions (i.e., recruitment of additional areas). The results replicated the ROI analysis. Age × performance interactions were found bilaterally, in the superior frontal cortex. Post hoc tests (Tukey HSD) confirmed that group differences were caused by lower activity in the low-performing older adults. The posteromedial cortex exhibited significant effects of age due to diminished deactivation in the older group (Fig. 3, Table S5). No effects outside the core regions identified in the young reference sample (Fig. 1*d*) were observed. No main effects of performance survived the statistical threshold.

### *Activity Gradient Analysis*

To further test for possible evidence of compensatory activity outside core encoding regions—that could not we captured in the ROI analysis—we ran an activity gradient analysis that allowed us to test age and age × performance effects along a continuum. In the activity continuum, the lower and upper ends represented regions with low and high subsequent memory effects and the middle regions vertices whose activity was

not clearly associated with later memory in young adults. In presence of compensatory patterns of activity, we would expect effects of age or age × performance outside the end sections of the activity gradient. The analysis confirmed that effects of age and age × performance on subsequent memory activity were found exclusively in the core regions identified in the young reference sample (Fig. 4). As expected, age × performance effects were driven by reduced activity in the low-performing older adults as shown by post hoc tests (SI Results, Fig. S5). No evidence of age or age × performance effects was found in regions that were unrelated to memory success in the young. Thus, both, the vertexwise and the activity gradient analyses supported the notion that preserved frontal activity with aging, rather than compensatory activity, is a functional marker of memory maintenance.

## Longitudinal Memory Decline

The concept of brain maintenance implies that changes in cognitive function evolve over time and that cross-sectional analyses sometimes yield inaccurate conclusions (Nyberg et al. 2010). An association between preceding memory decline and memory performance in the task in older adults would support the notion that the cross-sectional memory scores represent—at least, partially aging processes. For a subsample of the older participants ($n$ = 52), longitudinal scores in a verbal recall memory task (Delis et al. 2000) for 3 time-points extending back on average 7.8 years were available (SI Methods and Table 1). Older participants in the low-performing group, characterized by lower frontal encoding activity, exhibited memory decline in this test of long delay free recall of words ($t$[1,28] = −3.2, $P$ = 0.004). In contrast, the high-performers, who had similar frontal activity to the young and middle-aged groups, showed longitudinal preservation of memory function ($t$[1,22] = −0.4; $P$ = 0.7). A direct comparison between both groups—that included memory at baseline as a covariate—revealed that the low-performing older participants exhibited a significantly steeper decline in memory function over time ($F$[1,49] = 4.4; $P$ = 0.04; Fig. 5). The results support the assumption that intersubject variability in older participants'

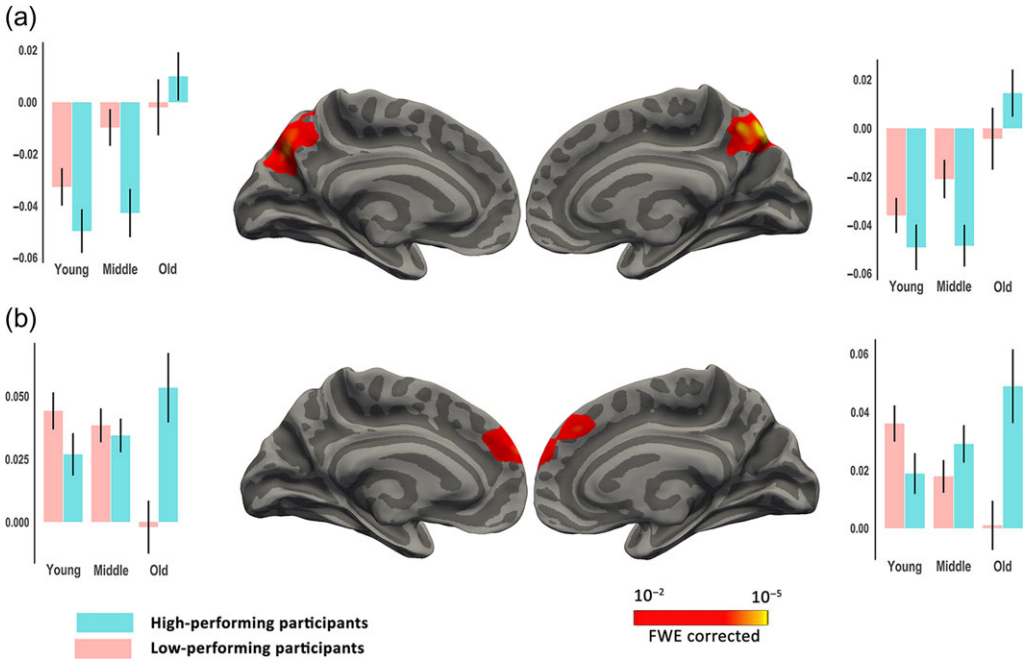


**Figure 3.** Vertexwise analysis. Cortical parameter estimates of subsequent memory activity associated with (*a*) age and (*b*) age × performance interaction ($n$ = 290). Vertex significance is displayed in FWE-corrected clusters (cluster-forming $P$ < 0.01; cluster-based $P$ < 0.05). See Table S5 for cluster stats. All plots display mean cluster activity arranged by age and performance groups.

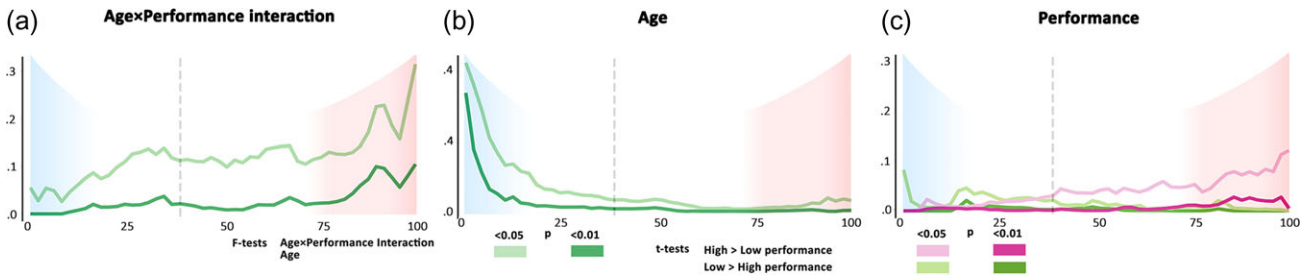


**Figure 4.** Activity gradient analysis. The colored lines represent the proportion of vertices that exhibited (*a*) age × performance interaction, (*b*) age, and (*c*) performance effects, along the activity gradient; that is, the subsequent memory effects exhibited by the young reference sample. The blue and red shadows represents percentages of the activity gradient with negative and positive subsequent memory effects ($P$ < 0.05). The dashed line represent the point with null mean signal change.

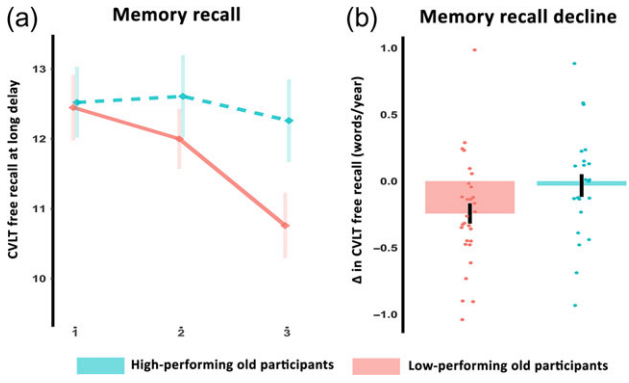


**Figure 5.** Longitudinal memory function. CVLT 30 min free recall in older participants with high and low memory performance in the experimental fMRI task. (*a*) Mean (SEM) memory recall at each time-point for high and low-performing older participants groups. (*b*) Dots represent the estimated memory decline for each participant as obtained by fitting time since the first observation in a linear model with each participants' 3 time-points ($n$ = 52). Bar plots represent mean (SEM) estimated memory decline for high and low-performing older participants groups.

performance is—at least, partially—driven by memory function decline over time.

### Structural Integrity and Amyloid Status

We considered the possibility that reduced performance in older adults could also be associated with brain structure decline and with Alzheimer's disease (AD) risk as determined by Aβ status. Based on [18F]-Flutemetamol-PET images, a subsample of older participants was classified as having either high or low levels of cortical Aβ ($n$ = 51; SI Methods: Fig. S4). The SUVR cut-off corresponded to a value of 1.62, in line with studies using $^{18}$F-flutemetamol and gray matter cerebellum as reference (Thurfjell et al. 2014). Overall, 10 older participants (19.6%; mean SUVR = 2.0 [0.40]) were categorized in the high Aβ group (6 high and 4 low-performing older participants). Aβ status was similar for high and low-performing older adults ($\chi^2_{(1,\ N\ =\ 51)}$ = 0.5, $P$ = 0.5). No difference of Aβ status among high and low-performing groups was observed when the cut-off values were modified (SI Results).

The rate of hippocampal volume decline was not associated with memory performance in older adults ($n$ = 52, 3 time-points, similar to the longitudinal neuropsychological measurements) when tested with a 2 × 2 performance × hemisphere model that ICV and hippocampal volume at baseline as covariates of no interest (main effect of performance, $F$[1,48] = 0.4, $P$ = 0.5). Yet, compared with high performers, low-performing older participants exhibited smaller hippocampi ($F$[1,71] = 4.2, $P$ = 0.04; SI Methods; Fig. S6). In parallel, low-performing older adults showed greater cortical atrophy (i.e., cortical volume loss) in left lateral parietal ($P$ < 0.01) and—with a less stringent significance threshold ($P$ < 0.05)—in the left inferior frontal cortex following a vertexwise analysis with rate of cortical atrophy as the predicted variable and performance and vertexwise cortical volume at baseline as regressors (SI Methods; Fig. S6). The results were comparable when cortical thinning was tested instead of volume. Performance level in older adults was unrelated to cortical volume and thickness when considered at the experimental task time point. As suggested by a reviewer, we restricted the cortical analysis in an entorhinal cortex ROI. The results were comparable to the cortical atrophy patterns. The rate of entorhinal volume decline in the preceding years was significantly associated with memory performance in older adults (main effect of performance, $F$[1,48] = 8.4, $P$ = 0.006). Yet, entorhinal volume was unrelated to performance at the experimental task time point ($F$[1,70] = 12, $P$ = 0.3) (Fig. S6).

## Discussion

The results indicate that brain maintenance of frontal function during encoding is a primary characteristic of memory preservation in aging. Only low-performing older participants, characterized by steeper longitudinal memory decline, as well as more cortical atrophy, over years preceding the scanning session, exhibited low frontal cortex activity. The findings are discussed further below.

### Frontal Maintenance

By combining large-scale fMRI data spanning the entire adulthood with longitudinal behavioral assessment, the current study provides evidence that memory maintenance in aging relies on preservation of frontal cortex function. This conclusion is supported by 3 interconnected findings. First, an age × performance interaction where specifically older adults, but neither young nor middle-aged participants, exhibited a relationship between memory and brain function. This finding suggests that the difference between high and low memory performers is evident only in older age, when—as predicted by the brain maintenance model—the task demands likely exceed to a greater extent the participants' cognitive resources. Second, older low performers also showed a steeper decline of memory function over years preceding the fMRI, suggesting that their performance relates to actual changes occurring with aging. Third, the low-performing older adults showed lower frontal function even when compared with younger and middle-aged participants with the same performance level, demonstrating that lower frontal function is not a result of the lower performance levels of these older adults per se.

The critical role of the frontal lobe during associative encoding in aging is in congruence with prior neuropsychological and neuroimaging findings. Compared with so-called item memory, associative memory declines with age (Spencer and Raz 1995). Putative mechanisms are a decline in cognitive control, efficiency of self-initiated processes, or lack of attentional resources (Luo and Craik 2008), which rely strongly on prefrontal cortex function (Murray and Ranganath 2007; Wong et al. 2013). A less elaborate, semantic processing of the encoding material represents an additional, complementary mechanism that might explain age-related deficits in memory and frontal activity during encoding (Craik 1977). Longitudinal neuroimaging evidence also points to maintenance of frontally based functions as a significant contributor to memory preservation with aging as older participants with significant memory decline exhibited the largest changes in brain encoding function over time (Nyberg et al. 2010; Pudas et al. 2018). When specifically considering associative memory success activity, age-related decrements in the left frontal hemisphere (Dennis et al. 2008; Kim and Giovanello 2011) have been associated with poorer performance in older adults (de Chastelaine et al. 2016).

Activity in the prefrontal cortex likely reflects engagement of diverse control processes that contribute to the associative encoding (Badre and Wagner 2007). It has been proposed that with aging, the functional capacity of the frontal cortex might be exceeded so it acts as a mediator of encoding efficacy (de

Chastelaine et al. 2016). Such an account fits with the view that frontal cortical structure appears particularly vulnerable to the effects of age (Fjell et al. 2014). Diminished frontal activity in older adults might reflect limited brain flexibility when performing tasks—such as associative memory encoding—that require a rapid and coordinated interplay amongst segregated brain regions, for example, hippocampal–neocortical interaction (Preston and Eichenbaum 2013). The frontal regions outlined in the present study are characterized by a high degree of flexibility likely serving as hubs that integrate information from more specialized regions (Yeo et al. 2015).

### Age-Related Changes in the Posteromedial Regions

As consistently reported, older adults exhibited reduced deactivations (i.e., less negative subsequent memory effects) in the posteromedial cortex (Miller et al. 2008; de Chastelaine et al. 2011, 2015; Park et al. 2013). It is often suggested that these findings reflect an increased difficulty to reallocate cognitive resources during encoding, echoing the lack of deactivation in most externally oriented tasks (Samu et al. 2017). The lack of association between deactivation and performance in older adults was somewhat surprising (Miller et al. 2008; de Chastelaine et al. 2011; Mattson et al. 2014). Yet, our result is in accordance with 2 recent well-powered studies that did not find a memory–brain function relationship in these regions (Park et al. 2013; de Chastelaine et al. 2015). The exact role of posteromedial deactivations during memory encoding is uncertain as older participants with preserved memory function seem to successfully remember associations without significant posteromedial recruitment (Rugg 2016). Lower deactivation might represent a general neural mechanism (Samu et al. 2017), reflecting inefficient reconfiguration of brain dynamics during cognitive demands but nonetheless unspecific to the task. It remains unclear, though, whether negative memory effects and the much-known task-related deactivations reflect similar or independent underlying processes (de Chastelaine and Rugg 2014; de Chastelaine et al. 2015).

### Lack of Compensatory Effects

Compensatory patterns of activity are often viewed as an attempt to minimize cognitive decline associated with the gradual loss of brain integrity that accompanies age. We did not find evidence for compensatory patterns of activity associated with successful memory in aging in contrast to several studies arguing that neural compensation is an essential feature of preserved memory and cognition with higher age. A distinct feature of subsequent memory paradigms is the within-subject contrast that presumably matches the memory condition in terms of task demands. In this light, it is relevant to highlight a distinction between different aspects of compensatory patterns of activity that might be reflected in the concepts of flexibility and plasticity (Lövdén et al. 2010). Subsequent memory paradigms might be better suited to test the later concept. In any case, our results cannot exclude the presence of different compensatory patterns of activity on an individual level nor the engagement of those in presence of specific burden and pathology such as structural decline or amyloidosis (Daselaar et al. 2013; Oh and Jagust 2013). Also, the finding of right frontal over-recruitment with higher age regardless of its association with memory performance (Miller et al. 2008; Duverne et al. 2009; de Chastelaine et al. 2016) does not easily reconcile with the present findings. Elusive variations in the experimental designs and differences in the methodological pipeline (such as the procedure followed to define contralateral activity in most studies) may constitute causes for the inconsistent findings. The inclusion of more older participants (age > 80) might be an additional factor, as mechanisms of preservation might differ at "older-old" ages. Thus the lack of compensatory processes in the present study are restricted to the present sample and the presently used associative episodic memory task, and thus does not necessarily support generalization to other samples and cognitive tasks. While caution is needed, this and other studies (Nyberg et al. 2010, 2012; Düzel et al. 2011) also suggest that compensatory patterns of activity not necessarily represent a dominant characteristic of memory maintenance into higher ages.

Patterns of brain activity remained stable until the older ages, with middle-aged participants recruiting encoding networks to a similar extent as younger participants. The scarce evidence in the literature report mixed results. Both similar patterns of activity, compared with young adults, and patterns in-between those presented by younger and older participants are reported in middle-aged participants (Park et al. 2013; de Chastelaine et al. 2015; Ankudowich et al. 2016). The age effects on brain activity in the present study mimics the longitudinal findings on memory function that shows preserved cognition until the 60s (Rönnlund et al. 2005). In contrast, subsequent memory effects in the hippocampus were age-invariant. Hippocampal recruitment appears as a key aspect of associative encoding success along the entire adulthood, likely reflecting the capacity to bind different pieces of information into a unique episode. This finding is in agreement with much of the previous literature on subsequent memory effects (Duverne et al. 2009; Park et al. 2013; de Chastelaine et al. 2016; cf. Salami et al. 2012). Note that activity in subsequent memory paradigms is usually associated with a regions' capacity of shaping later memory outcome—and thus with those encoding processes that are associated with memory formation—more than with absolute recruitment and thus needs to be interpreted accordingly (see, Rugg 2016; Wang and Cabeza 2016, for detailed discussions). Further, task-effects might be better suited to explore other prominent notions of cognitive neuroscience of aging that cannot be properly assessed in the current study such as dedifferentiation.

As longitudinal fMRI data were not available, we cannot rule out the possibility that the relationship between performance and activity in older ages reflects aspects other than aging processes, such as individual differences emerging early in life (Nyberg et al. 2010; Rugg 2016). The study has inherent limitations of cross-sectional designs (Raz and Lindenberger 2011). Yet, we address some limitations of cross-sectional studies by including longitudinal neuropsychological data spanning years back. This tackles a fundamental limitation of cross-sectional studies, such as the incapacity to determine that older participants with the lowest memory are those whose memory has been more affected by age. Also, the observation of age effects on encoding activity for participants with similar levels of performance suggests that the brain activity is not likely a direct effect of performance, which allows separation of aging and performance effects. In the present study, the cognitive and physiological measures were derived from a unique fMRI task and contrast which were optimized to study associative memories. Further, the study was focused on encoding as it represents the first critical step in the formation of an episodic memory. It is yet unknown to which extent the present findings generalize to other subsequent episodic memory paradigms and activity contrasts (i.e., testing recollection, item

memory, and recognition). Large lifespan datasets that include memory tasks inside the scanner will facilitate cross-studies comparisons (Van Essen and Glasser 2016).

It is unlikely that the present results in the frontal cortex are explained by pathological changes related to preclinical AD as Aβ status did not differ between the low and high-performing groups. Due to the small number of Aβ+ participants, one should refrain from extracting further conclusions regarding its impact on brain function (Mormino et al. 2012; Oh and Jagust 2013; Marks et al. 2017) and cognitive change (Vemuri et al. 2015; Harrington et al. 2017; Clark et al. 2018). Besides maintenance of brain function, memory function in aging is supported by structural brain integrity. The structural results complement the main findings and suggest that cognition in higher age is sustained by maintenance of both brain structure and function. The structural results suggest that older adults' cognitive function is related to both the degree of structural brain maintenance (i.e., less cortical atrophy) (Nyberg et al. 2012) and to pre-existing individual differences (i.e., smaller hippocampi) that may fit with brain reserve predictions (Katzman et al. 1989). This pattern is evident in the medial temporal lobe where entorhinal rate of atrophy was related to memory performance while smaller hippocampi at the experimental time-point, regardless the rate of atrophy, was associated with poorer cognition. The relationship between integrity of both structures and memory preservation in aging is unsurprising (Rodrigue and Raz 2004; Ward et al. 2015; Hedden et al. 2016; Gorbach et al. 2017), as both structures have prominent roles in memory processes (Scoville and Milner 1957; Squire and Zola-Morgan 1991) and are highly vulnerable to the effects of age (suffering accelerated rates of atrophy/thinning with higher age) (Fjell et al. 2009, 2013, 2014). Yet, the distinct relationship of both structures with memory performance was unexpected. One possibility is that hippocampus atrophy impacts memory once a certain threshold is reached (Pudas et al. 2018). Other feasible models involve cascade-like relationships between both structures (Ward et al. 2015) or complex interactions between co-occurring neurodegenerative events (Fjell et al. 2013). The limitations of the present sample precluded a full multivariate analysis, which represents a promising method to reveal these mechanisms. Further large, multimodal, longitudinal designs are needed to elucidate how functional, structural, and neurochemical integrity relate to each other and determine memory preservation into higher ages (Hedden et al. 2016).

### Conclusions

We conclude that brain maintenance of frontal function during encoding is a primary characteristic of higher memory in aging. Reduced activity during successful encoding likely reflects functional deficits during the integration of information. In addition to preserved function, high-performing older adults were also characterized by reduced rates of cortical atrophy and higher hippocampi volume.

## Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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## Notes

*Conflict of Interest*: None declared.

## References

Ankudowich E, Pasvanis S, Rajah MN. 2016. Changes in the modulation of brain activity during context encoding vs. context retrieval across the adult lifespan. Neuroimage. 139: 103–113.

Badre D, Wagner AD. 2007. Left ventrolateral prefrontal cortex and the cognitive control of memory. Neuropsychologia. 45: 2883–2901.

Beck AT. 1987. Cognitive models of depression. J Cog Psychother. 1:5–37.

Cabeza R, Anderson ND, Locantore JK, McIntosh AR. 2002. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage. 17:1394–1402.

Cabeza R, Dennis NA. 2006. Frontal lobes and aging: deterioration and compensation. In: Stuss DT, Knight RT, editors. Principles of frontal lobe function. 2nd ed.. New York: Oxford University Press. p. 629–652.

Clark LR, Berman SE, Norton D, Koscik RL, Jonaitis E, Blennow K, Bendlin BB, Asthana S, Johnson SC, Zetterberg H, et al. 2018. Age-accelerated cognitive decline in asymptomatic adults with CSF β-amyloid. Neurology. 90:e1306–e1315.

Craik FIM. 1977. Age differences in human memory. In: Birren JE, Schaie KW, editors. Handbook of the psychology of aging. 1st ed.. New York: Van Nostrand Reinhold. p. 384–420.

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

Daselaar SM, Iyengar V, Davis SW, Eklund K, Hayes SM, Cabeza RE. 2013. Less wiring, more firing: low-performing older adults compensate for impaired white matter with greater neural activity. Cereb Cortex. 21:983–990.

Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R. 2008. Que PASA? The posterior-anterior shift in aging. Cereb Cortex. 18:1201–1209.

de Chastelaine M, Mattson JT, Wang TH, Donley BE, Rugg MD. 2015. Sensitivity of negative subsequent memory and task-negative effects to age and associative memory performance. Brain Res. 1612:16–29.

de Chastelaine M, Mattson JT, Wang TH, Donley BE, Rugg MD. 2016. The relationships between age, associative memory performance, and the neural correlates of successful associative memory encoding. Neurobiol Aging. 42:163–176.

de Chastelaine M, Rugg MD. 2014. The relationship between task-related and subsequent memory effects. Hum Brain Mapp. 35:3687–3700.

de Chastelaine M, Wang TH, Minton B, Muftuler LT, Rugg MD. 2011. The effects of age, memory performance, and callosal integrity on the neural correlates of successful associative encoding. Cereb Cortex. 21:2166–2176.

Delis D, Kramer J, Kaplan E, Ober B. 2000. California verbal learning test—second edition (CVLT-II). San Antonio, TX: Psychological.

Dennis NA, Hayes SM, Prince SE, Madden DJ, Huettel SA, Cabeza R. 2008. Effects of aging on the neural correlates of successful item and source memory encoding. J Exp Psychol Learn Mem Cogn. 34:791–808.

Dennis NA, Kim H, Cabeza R. 2007. Effects of aging on true and false memory formation: an fMRI study. Neuropsychologia. 45:3157–3166.

Duverne S, Motamedinia S, Rugg MD. 2009. The relationship between aging, performance, and the neural correlates of successful memory encoding. Cereb Cortex. 19:733–744.

Düzel E, Schütze H, Yonelinas AP, Heinze HJ. 2011. Functional phenotyping of successful aging in long-term memory: preserved performance in the absence of neural compensation. Hippocampus. 21:803–814.

Fandakova Y, Lindenberger U, Shing YL. 2015. Maintenance of youth-like processing protects against false memory in later adulthood. Neurobiol Aging. 36:933–941.

Fischl B, Dale AM. 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci USA. 97:11050–11055.

Fischl B, Sereno MI, Dale AM. 1999. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage. 9:195–207.

Fjell AM, Walhovd KB, Fennema-Notestine C, McEvoy LK, Hagler DJ, Holland D, Brewer JB, Dale AM. 2009. One-year brain atrophy evident in healthy aging. J Neurosci. 29: 15223–15231.

Fjell AM, Westlye LT, Grydeland H, Amlien I, Espeseth T, Reinvang I, Raz N, Dale AM, Walhovd KB. 2014. Accelerating cortical thinning: unique to dementia or universal in aging? Cereb Cortex. 24:919–934.

Fjell AM, Westlye LT, Grydeland H, Amlien I, Espeseth T, Reinvang I, Raz N, Holland D, Dale AM, Walhovd KB, Alzheimer Disease Neuroimaging Initiative. 2013. Critical ages in the life course of the adult brain: nonlinear subcortical aging. Neurobiol Aging. 34:2239–2247.

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 12:189–98.

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

Grady C. 2012. The cognitive neuroscience of ageing. Nat Rev Neurosci. 13:491–505.

Griffanti L, Salimi-Khorshidi G, Beckmann CF, Auerbach EJ, Douaud G, Sexton CE, Zsoldos E, Ebmeier KP, Filippini N, Mackay CE, et al. 2014. ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. Neuroimage. 95:232–247.

Harrington KD, Lim YY, Ames D, Hassenstab J, Laws SM, Martins RN, Rainey-Smith S, Robertson J, Rowe CC, Salvado O, et al. 2017. Amyloid β-associated cognitive decline in the absence of clinical disease progression and systemic illness. Alzheimers Dement (Amst). 8:156–164.

Hedden T, Schultz AP, Rieckmann A, Mormino EC, Johnson KA, Sperling RA, Buckner RL. 2016. Multiple brain markers are linked to age-related variation in cognition. Cereb Cortex. 26:1388–1400.

Josefsson M, de Luna X, Pudas S, Nilsson L-G, Nyberg L. 2012. Genetic and lifestyle predictors of 15-year longitudinal change in episodic memory. J Am Geriatr Soc. 60:2308–2312.

Katzman R, Aronson M, Fuld P, Kawas C, Brown T, Morgenstern H, Frishman W, Gidez L, Eder H, Ooi WL. 1989. Development of dementing illnesses in an 80-year-old volunteer cohort. Ann Neurol. 25:317–324.

Kim H. 2011. Neural activity that predicts subsequent memory and forgetting: a meta-analysis of 74 fMRI studies. Neuroimage. 54:2446–2461.

Kim S-, Giovanello KS. 2011. The effects of attention on age-related relational memory deficits: fMRI evidence from a novel attentional manipulation. J Cogn Neurosci. 23: 3637–3656.

Krogsrud SK, Fjell AM, Tamnes CK, Grydeland H, Due-Tønnessen P, Bjørnerud A, Sampaio-Baptista C, Andersson J, Johansen-Berg H, Walhovd KB. 2018. Development of white matter microstructure in relation to verbal and visuospatial working memory—a longitudinal study. PLoS One. 13: e0195540.

Leshikar ED, Duarte A. 2014. Medial prefrontal cortex supports source memory for self-referenced materials in young and older adults. Cogn Affect Behav Neurosci. 14:236–252.

Luo L, Craik FIM. 2008. Aging and memory: a cognitive approach. Can J Psychiatry. 53:346–353.

Lövdén M, Bäckman L, Lindenberger U, Schaefer S, Schmiedek F. 2010. A theoretical framework for the study of adult cognitive plasticity. Psychol Bull. 136:659–676.

Maillet D, Rajah MN. 2014. Age-related differences in brain activity in the subsequent memory paradigm: a meta-analysis. Neurosci Biobehav Rev. 45:246–257.

Marks SM, Lockhart SN, Baker SL, Jagust WJ. 2017. Tau and β-amyloid are associated with medial temporal lobe structure, function, and memory encoding in normal aging. J Neurosci. 37:3192–3201.

Mattson JT, Wang TH, de Chastelaine M, Rugg MD. 2014. Effects of age on negative subsequent memory effects associated with the encoding of item and item-context information. Cereb Cortex. 24:3322–3333.

Miller SL, Celone K, DePeau K, Diamond E, Dickerson BC, Rentz D, Pihlajamaki M, Sperling RA. 2008. Age-related memory impairment associated with loss of parietal deactivation but preserved hippocampal activation. Proc Natl Acad Sci U S A. 105:2181–2186.

Mormino EC, Betensky RA, Hedden T, Schultz AP, Ward A, Huijbers W, Rentz DM, Johnson KA, Sperling RA, Alzheimer's Disease Neuroimaging Initiative, Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing, Harvard Aging Brain Study. 2014. Amyloid and APOE ε4 interact to influence short-term decline in preclinical Alzheimer disease. Neurology. 82:1760–1767.

Mormino EC, Brandel MG, Madison CM, Marks S, Baker SL, Jagust WJ. 2012. Aβ deposition in aging is associated with increases in brain activation during successful memory encoding. Cereb Cortex. 22:1813–1823.

Murray LJ, Ranganath C. 2007. The dorsolateral prefrontal cortex contributes to successful relational memory encoding. J Neurosci. 27:5515–5522.

Nyberg L, Lövdén M, Riklund K, Lindenberger U, Bäckman L. 2012. Memory aging and brain maintenance. Trends Cogn Sci. 16:292–305.

Nyberg L, Salami A, Andersson M, Eriksson J, Kalpouzos G, Kauppi K, Lind J, Pudas S, Persson J, Nilsson LG. 2010. Longitudinal evidence for diminished frontal cortex function in aging. Proc Natl Acad Sci USA. 107: 22682–22686.

Oh H, Jagust WJ. 2013. Frontotemporal network connectivity during memory encoding is increased with aging and disrupted by beta-amyloid. J Neurosci. 33:18425–18437.

Old SR, Naveh-Benjamin M. 2008. Differential effects of age on item and associative measures of memory: a meta-analysis. Psychol Aging. 23:104–118.

Park H, Kennedy KM, Rodrigue KM, Hebrank A, Park DC. 2013. An fMRI study of episodic encoding across the lifespan: changes in subsequent memory effects are evident by middle-age. Neuropsychologia. 51:448–456.

Pascual-Leone A, Amedi A, Fregni F, Merabet LB. 2005. The plastic human brain cortex. Annu Rev Neurosci. 28:377–401.

Preston AR, Eichenbaum H. 2013. Interplay of hippocampus and prefrontal cortex in memory. Curr Biol. 23:R764–R773.

Pudas S, Josefsson M, Rieckmann A, Nyberg L. 2018. Longitudinal evidence for increased functional response in frontal cortex for older adults with hippocampal atrophy and memory decline. Cereb Cortex. 26:936–948.

Raz N, Lindenberger U. 2011. Only time will tell: cross-sectional studies offer no solution to the age-brain-cognition triangle: comment on Salthouse (2011). Psychol Bull. 137:790–795.

Rodrigue KM, Raz N. 2004. Shrinkage of the entorhinal cortex over five years predicts memory performance in healthy adults. J Neurosci. 24:956–963.

Rugg MD. 2016. Interpreting age-related differences in memory-related neural activity. In: Cabeza R, Nyberg L, Park DC, editors. Cognitive neuroscience of aging: linking cognitive and cerebral aging. 2nd ed.. New York: Oxford University Press. p. 183–207.

Rönnlund M, Nyberg L, Bäckman L, Nilsson LG. 2005. Stability, growth, and decline in adult life span development of declarative memory: cross-sectional and longitudinal data from a population-based study. Psychol Aging. 20:3–18.

Salami A, Eriksson J, Nyberg L. 2012. Opposing effects of aging on large-scale brain systems for memory encoding and cognitive control. J Neurosci. 32:10749–10757.

Salimi-Khorshidi G, Douaud G, Beckmann CF, Glasser MF, Griffanti L, Smith SM. 2014. Automatic denoising of functional MRI data: combining independent component analysis and hierarchical fusion of classifiers. Neuroimage. 90:449–468.

Samu D, Campbell KL, Tsvetanov KA, Shafto MA, Cam-CAN consortium, Tyler LK. 2017. Preserved cognitive functions with age are determined by domain-dependent shifts in network responsivity. Nat Commun. 8:14743.

Sankoh AJ, Huque MF, Dubey SD. 1997. Some comments on frequently used multiple endpoint adjustment methods in clinical trials. Stat Med. 16:2529–2542.

Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry. 20: 11–21.

Sneve MH, Grydeland H, Nyberg L, Bowles B, Amlien IK, Langnes E, Walhovd KB, Fjell AM. 2015. Mechanisms underlying encoding of short-lived versus durable episodic memories. J Neurosci. 35:5202–5212.

Spencer WD, Raz N. 1995. Differential effects of aging on memory for content and context: a meta-analysis. Psychol Aging. 10:527–539.

Squire LR, Zola-Morgan S. 1991. The medial temporal lobe memory system. Science. 253:1380–1386.

Thurfjell L, Lilja J, Lundqvist R, Buckley C, Smith A, Vandenberghe R, Sherwin P. 2014. Automated quantification of 18F-flutemetamol PET activity for categorizing scans as negative or positive for brain amyloid: concordance with visual image reads. J Nucl Med. 55:1623–1628.

Van Essen DC, Glasser MF. 2016. The human connectome project: progress and prospects. Cerebrum. cer-10-16.

Vemuri P, Lesnick TG, Przybelski SA, Knopman DS, Preboske GM, Kantarci K, Raman MR, Machulda MM, Mielke MM, Lowe VJ, et al. 2015. Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. Brain. 138:761–771.

Vidal-Piñeiro D, Sneve MH, Storsve AB, Roe JM, Walhovd KB, Fjell AM. 2017. Neural correlates of durable memories across the adult lifespan: brain activity at encoding and retrieval. Neurobiol Aging. 60:20–33.

Walhovd KB, Westerhausen R, de Lange A-MG, Bråthen ACS, Grydeland H, Engvig A, Fjell AM. 2016. Premises of plasticity - And the loneliness of the medial temporal lobe. Neuroimage. 131:48–54.

Wang WC, Cabeza R. 2016. Episodic memory encoding and retrieval in the aging brain. In: Cabeza R, Nyberg L, Park DC, editors. Cognitive neuroscience of aging: linking cognitive and cerebral aging. 2nd ed.. New York: Oxford University Press. p. 301–337.

Ward AM, Mormino EC, Huijbers W, Schultz AP, Hedden T, Sperling RA. 2015. Relationships between default-mode network connectivity, medial temporal lobe structure, and age-related memory deficits. Neurobiol Aging. 36:265–272.

Wechsler D. 1999. Wechsler abbreviated scale of intelligence. New York, NY: The Psychological Corporation: Harcourt Brace & Company.

Wilson RS, Beckett LA, Barnes LL, Schneider JA, Bach J, Evans DA, Bennett DA. 2002. Individual differences in rates of change in cognitive abilities of older persons. Psychol Aging. 17:179–193.

Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. 2014. Permutation inference for the general linear model. Neuroimage. 92:381–397.

Wong JX, de Chastelaine M, Rugg MD. 2013. Comparison of the neural correlates of encoding item-item and item-context associations. Front Hum Neurosci. 7:436.

Yeo BTT, Krienen FM, Eickhoff SB, Yaakub SN, Fox PT, Buckner RL, Asplund CL, Chee MWL. 2015. Functional specialization and flexibility in human association cortex. Cereb Cortex. 25:3654–3672.