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The relationships between age, associative memory performance and the neural correlates of successful associative memory encoding

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Abstract

Using fMRI, subsequent memory effects (greater activity for later remembered than later forgotten study items) predictive of associative encoding were compared across samples of young, middle-aged and older adults (total n = 136). During scanning, participants studied visually presented word pairs. In a later test phase, they discriminated between studied pairs, 'rearranged' pairs (items studied on different trials) and new pairs. Subsequent memory effects were identified by contrasting activity elicited by study pairs that went on to be correctly judged intact or incorrectly judged rearranged. Effects in the hippocampus were age-invariant and positively correlated across participants with associative memory performance. Subsequent memory effects in the right IFG were greater in the older than the young group. In older participants only, both left and, in contrast to prior reports, right IFG subsequent memory effects correlated positively with memory performance. We suggest that the IFG is especially vulnerable to age-related decline in functional integrity, and that the relationship between encoding-related activity in right IFG and memory performance depends on the experimental context.

Keywords

fMRI; Aging; Associative recognition; Episodic memory; Hippocampus; Over-recruitment

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[2]Although not reported in detail here, semi-automated analysis (http://surfer.nmr.mgh.harvard.edu/) of the T1-weighted structural images revealed that thickness and volume of the left and right IFG were significantly lower in the middle-aged and older samples than in the young participants, while hippocampal volume was reduced in the older group relative to either of the other two groups, which did not significantly differ on this measure. Controlling for the effects of these different structural measures did not however alter the outcomes of any of the ANOVA or regression analyses described in this section.

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1. Introduction

Episodic memory – memory for unique events – is one of several cognitive domains in which performance declines with increasing age (Koen & Yonelinas, 2014; Old & Naveh-Benjamin, 2008; Nilsson, 2003; Rönnlund et al., 2005). A significant fraction of age-related variance in episodic memory performance is attributable to differences in the efficacy with which events are encoded into memory (see Craik & Rose, 2012, for review), and numerous studies have utilized functional neuroimaging in an effort to elucidate the neural underpinnings of the effects of age on episodic memory encoding. The majority of these studies have employed event-related fMRI in concert with the 'subsequent memory procedure' (Paller & Wagner, 2002), examining age-related differences in neural activity predictive of successful or unsuccessful performance on a later memory test (e.g., de Chastelaine et al., 2011; Dennis et al., 2008; Duverne et al., 2009; Gutchess et al., 2005; Mattson et al., 2014; Miller et al., 2008; Morcom et al., 2003; Mormino et al., 2012; Park et al., 2013; see Maillet & Rajah, 2014, for review).

The findings from these studies are somewhat mixed, but show some consistent trends. There is converging evidence for example that 'negative' subsequent memory effects – where later remembered study items elicit relatively less activity than later forgotten items – are attenuated, and sometimes reversed, in older individuals (e.g., de Chastelaine et al. 2011; Duverne et al., 2009; Gutchess et al., 2005; Mattson et al., 2014; Miller et al. 2008; Mormino et al. 2012; Park et al., 2013). Consistent with these findings, in a recent published analysis of the present data set (de Chastelaine et al., 2015) we reported that while negative subsequent memory effects were reliable in young, middle-aged and older age groups, there was a graded attenuation in the size of the effects with increasing age (young > middle-aged > older). We do not discuss these findings further here, however; instead, we focus on 'positive' subsequent memory effects (henceforth, just 'subsequent memory effects' or 'encoding-related activity'), where study items that go on to be remembered on a later memory test elicit greater neural activity than items that are later forgotten (see Kim, 2011 for a review of relevant research in young adults).

Two fairly consistent trends emerge from studies examining the effects of age on subsequent memory effects: first, despite the vulnerability of the hippocampus to age-related volume reduction (see Raz & Rodrigue, 2006, for review), the weight of the evidence suggests that encoding-related activity in this region does not differ with age (e.g., de Chastelaine et al., 2011; Duverne et al., 2009; Miller et al., 2008; but see for example Dennis et al., 2008 for contrasting findings, and see Maillet & Rajah, 2014, for a review). Second, whereas the magnitude of subsequent memory effects in left lateral prefrontal cortex (PFC) also appear to differ little with age, the effects in homotopic regions of the right PFC have been reported to be greater in older than in young individuals (e.g., Morcom et al., 2003; Duverne et al., 2009), an example of age-related, right-frontal 'over-recruitment' (Grady, 2012).

Findings of right frontal over-recruitment are open to multiple interpretations (Grady, 2012). According to one set of proposals, for example, the findings reflect engagement of neural regions that help to compensate for age-related decline in processing efficiency in other regions sufficient to support task performance in younger individuals (e.g., Cabeza et al.,

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2002; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2014). A second set of proposals suggests that, rather than facilitating task performance, over-recruitment harms it, reflecting age-related de-differentiation of cortical specialization and an attendant decline in processing efficiency (e.g., Li et al., 2006). Another, related, proposal is that right frontal over-recruitment reflects age-related decline in the transcallosal inhibitory drive from the left hemisphere that suppresses activation of, and hence interference from, homotopic task-irrelevant cortical regions (e.g., Logan et al., 2002). Finally, it has been proposed that right frontal over-recruitment, at least as it is expressed in item-related activity (that is, in the BOLD response elicited by study items relative to the inter-item baseline) is a consequence of age-related sampling bias (Nyberg et al., 2010; see also Pudas et al., 2013).

One possible way of arbitrating between these different proposals is to assess the relationship between right prefrontal activity and task performance. In studies of episodic memory encoding, this amounts to asking whether, as would be predicted by the simplest form of the ‘compensation hypothesis’ described above, memory performance in older individuals is positively correlated with the magnitude of right frontal subsequent memory effects. Three studies in which this question was addressed (de Chastelaine et al., 2011; Duverne et al., 2009; Miller et al., 2008; but see also Bangen et al., 2012) reported consistent findings: in each case, a reliable correlation between right frontal subsequent memory effects and memory performance was observed, but the direction was negative. That is, right frontal encoding-related activity was greater in those individuals with the poorest memories for the study items.

These findings are inconsistent with the most straightforward prediction of the compensation hypothesis of age-related right frontal over-recruitment and, on the face of it, are more supportive of the proposal that over-recruitment is detrimental for memory encoding. As was discussed by, among others, de Chastelaine et al. (2011) and Grady (2012; see also Duverne et al., 2009), the findings are however compatible with other conceptualizations of age-related neural compensation. By one account (e.g., Düzel et al., 2012), it is those individuals most affected by aging, and hence with the lowest levels of performance, who engage compensatory mechanisms to the greatest extent. By an alternative account (de Chastelaine et al., 2011), right frontal over-recruitment reflects ‘partial’ compensation – sufficient to support performance on the study task, but not to boost memory encoding. We return to this issue in the Discussion.

The aim of the present study was to gain further insight into the relationship between age, encoding-related neural activity, and memory performance. We employed the same associative memory procedure as in our prior study of episodic encoding (de Chastelaine et al., 2011). Associative memory is well suited to studies such as the present one because it is strongly dependent on the recollection of qualitative information (e.g., Mickes et al., 2010) and is highly sensitive to age (Old & Naveh-Benjamin, 2008). In our prior study, we investigated subsequent memory effects in samples of young (N=18) and older (n=36) individuals. We found that the magnitude of the effects in several regions, including left inferior frontal gyrus (IFG) and hippocampus, did not differ according to age group. In the older participants, we also found that subsequent memory effects in left and right IFG demonstrated reliable but opposite relationships with memory performance, such that there

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was a positive correlation for the left IFG, and a negative correlation for the right IFG. We further reported that the integrity of the anterior corpus callosum, as this was indexed by fractional anisotropy (FA) estimated from diffusion tensor imaging (DTI), was both strongly age-dependent (replicating numerous prior reports, e.g., Head et al. 2004; Kochunov et al., 2012; O'Sullivan et al. 2001; Pfefferbaum et al. 2000), and positively correlated with the magnitude of subsequent memory effects in the right IFG. This latter finding is arguably inconsistent with the proposal that right frontal over-recruitment reflects age-related disruption of trans-callosal inhibition (e.g., Logan et al. 2002).

The present study extends this prior work in two important ways. First, we employed substantially larger samples of young and older participants than in the prior study (Ns of 36 and 64 respectively), affording greater statistical power with which to detect age-related differences in subsequent memory effects, and to examine the relationship between different facets of encoding-related activity and individual differences in subsequent memory performance. Thus, we were able to assess the generality of our prior finding that left and right frontal subsequent memory effects demonstrate opposite relationships with memory performance, and whether these or other relationships with performance differ with age. We were also able to assess the generality of a prior report that the magnitude of subsequent memory effects in the hippocampus is negatively correlated with subsequent associative memory accuracy in older individuals (Miller et al., 2008), and to examine whether this finding extends to other age groups. Second, in addition to samples of young and older individuals, here we also employed a sample of middle-aged individuals (N=36). This age-range has been relatively neglected in studies examining the effects of age on the neural correlates of episodic memory (we are aware of only three prior papers describing encoding-related activity in this population: de Chastelaine et al., 2015; Kwon et al., 2015; Park et al., 2013). The inclusion of middle-aged individuals provides a more continuous sampling of encoding-related activity across the lifespan than can be achieved with an extreme age groups approach, and hence provides additional insight into the profile of any age-related differences.

2. Materials and Methods

Additional methodological information can be found in de Chastelaine et al. (2015), where a complementary analysis of the present fMRI data set is reported (see Introduction).

2.1 Participants

Participants were 36 young (18–29 yrs; M = 22 yrs; SD = 3.0 yrs; 17 female), 36 middle-aged (43–55 yrs; M = 49 yrs; SD = 3.4 yrs; 17 female) and 64 older adults (63–76 yrs; M = 68 yrs; SD = 3.6 yrs; 35 female). The participants were recruited from the city of Dallas and surrounding communities, and comprised samples wholly independent of those participating in our previous study (de Chastelaine et al., 2011). All participants were in good health, had no history of cardiovascular, neurological or psychiatric disease, and were not taking central nervous system-active medication. The participants were right-handed, had learned English before age 5, and had normal or corrected-to-normal vision. Exclusion criteria based on neuropsychological test scores are described below. Informed consent was given by all

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participants according to the procedures approved by the UT Dallas and University of Texas Southwestern Institutional Review Boards. Participants were compensated at the rate of $30 per hour.

2.2 Neuropsychological testing

Standardized neuropsychological tests were administered in a separate experimental session. Participants were screened for dementia with the Mini-Mental State Examination (MMSE), for which a nominal cutoff score of 27/30 was adopted. Other tests included the California Verbal Learning Test-II (CVLT; Delis et al. 2000), the Wechsler Memory Scale (WMS-IV), the Digit Span Forward and Backward test of the Wechsler Adult Intelligence Scale Revised (WAIS-R) (Wechsler, 2001), the Digit/Symbol Coding test of the WAIS-R, Trail Making Tests A and B, letter and category fluency tests, the Wechsler Test of Adult Reading (WTAR; Wechsler 2001) and the Raven's Progressive Matrices (short version).

Potential participants were excluded if they scored >1.5 standard deviations (SDs) below their age-appropriate norm on either of the long-term memory tests (CVLT or the WMS), had an estimated full-scale IQ < 100 as indexed by performance on the WTAR, or scored >1.5 SDs below the age-appropriate norm on any two of the other neuropsychological tests. A composite CVLT recall score was calculated by averaging across the 4 recall tests (immediate and delayed free and cued recall, see Results: section 3.1 Neuropsychological data). Similarly, a composite WMS score was computed by averaging scores on the WMS 1 and WMS 2.

2.3 Experimental materials

The experimental materials comprised 320 semantically unrelated, visually presented word pairs. The words were concrete nouns ranging in length from 3 to 9 letters, selected from the word association norms compiled by Nelson et al. (2004). They were randomly divided into 4 lists of 80 pairs. For each set of yoked participants (1 young, 1 middle-aged and 1 or 2 older participants), the 4 lists were rotated such that each list provided stimuli for all 3 of the experimental word-pair categories: intact, rearranged and new (see below), and word pairs from 3 of the lists were pseudo-randomly ordered to form the study list. The test list included all 320 critical word pairs; 160 of the pairs had been presented at study (intact pairs), 80 comprised studied items that had been re-paired between study and test (rearranged pairs), and 80 were unstudied pairs (new pairs). Critical study pairs were intermixed with 80 null trials, and critical test pairs were intermixed with 106 null trials. Two buffer pairs were placed at the start and in the middle of each of the two study blocks and the test blocks (see below). Word pairs in the study and test lists were pseudo-randomly ordered such that the same word pair category did not occur more than three times consecutively. Practice study and test lists, comprising items not employed in the experimental lists proper, were also constructed.

2.4 Procedure

Prior to entering the MR scanner participants were given instructions and practice sessions for both the study task and the memory test. Thus, encoding was intentional. The study and test phases were conducted in separate scanning sessions. During the first scanning session,

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study pairs were presented in two consecutive blocks separated by a short rest interval. The study task required participants to indicate with a button press which of the two objects denoted by the words was more likely to fit into the other. Study task accuracy was indexed as the proportion of study pairs attracting the response considered the most plausible by consensus of three experimenters. After completing the study task, participants were removed from the scanner for 15 mins, and then returned to complete an associative memory test. Test pairs were presented in three consecutive blocks separated by short rest intervals. One of three button press responses was required to indicate whether each test pair was intact, rearranged or new. Participants were required to respond 'intact' when they recognized both words and had a specific memory of the two words having been presented together at study. They were instructed to make this judgment only when they were confident that the words had been studied together. A 'rearranged' response was required when both words were recognized from the study phase but there was no specific memory of the words being paired together previously. A 'new' response was required when neither word, or only one word, was recognized. DTI and structural scans were acquired after participants had completed the test phase. Study and test instructions emphasized the need for both accuracy and speed.

At both study and test, words were presented for a duration of 2 s just above and below central fixation in white uppercase Helvetica 30 point font against a black background. The word pairs subtended an approximate vertical visual angle of 1.8 deg. and a maximum horizontal visual angle of 5.1 deg. They were viewed via a mirror fixed to the head coil directly above the participants' eyes. Study and test pairs were preceded by a red fixation cross that was presented for 0.5 s and were followed by a white fixation cross for 1 s at study, and for 2 s at test. Null trials consisted of the presentation of a white fixation cross against a black background for 3.5 s or 4.5 s at study and test respectively. A 30 s rest break occurred halfway through each study and test block. Inter-block intervals lasted approximately 2 mins. Experimental control, including stimulus display, was implemented in the 'Cogent' software package (http://www.vislab.ucl.ac.uk/cogent.php).

2.5 MRI data acquisition

Functional and anatomical images were acquired with a Philips Achieva 3T MR scanner (Philips Medical System, Andover, MA USA) equipped with a 32 channel parallel imaging head coil. A T1-weighted anatomical image was acquired with a 3D magnetization-prepared rapid gradient echo (MP-RAGE) pulse sequence (FOV= 256×224, voxel size 1×1×1 mm, 160 slices, sagittal acquisition). DTI acquisition involved a single-shot EPI sequence (30 directions, 50 transverse slices, 2 mm thick, 1 mm gap, matrix size 112 × 110, TR 4410 ms, TE 51 ms; flip angle 90°, b 1000 s/mm^2, 1 × b = 0). Functional scans were acquired with a T2*–weighted echo-planar image (EPI) (TR 2 s, TE 30 ms, flip angle 70°, FOV 240×240, matrix size 80×78). Each EPI volume comprised 33 × 3 mm slices (1 mm inter-slice gap) with an in-plane resolution of 3 × 3 mm. Slices were acquired in ascending order, oriented parallel to the AC–PC line and positioned for full coverage of the cerebrum and most of the cerebellum. The functional data were acquired using a sensitivity encoding (SENSE) reduction factor of 2. fMRI data were acquired during both study and test phases (311 and 351 volumes for each study and test block, respectively). The first 5 volumes of each block

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were discarded to allow tissue magnetization to achieve a steady state. For the GLM analyses, study sessions were concatenated to form a single time-series.

2.6 DTI analysis

Computation of the diffusion tensor was performed using DTIstudio (Jiang et al. 2006). The program used non-rigid registration to correct for motion and eddy current related deformations. A first order tensor model was then fit to the DTI data on a voxel by voxel basis. The FA maps were calculated from the tensor parameters, which were used in the analysis. Voxel-wise FA values were scaled from 0 to 1, 0 representing isotropic diffusion and 1 maximum anisotropy. Before processing, images were reoriented parallel to the AC-PC line but were not spatially normalized. For each participant, regions-of-interest (ROIs) were drawn directly onto axial slices of the FA maps to cover the full extent of the anterior corpus callosum and, separately, the posterior corpus callosum. FA values were averaged across all slices in each of the ROIs to yield single values for the anterior and posterior regions of the corpus callosum for each participant.

2.7 MRI analyses

Here, we report analyses for the study phase only; the fMRI findings for the test phase will be described elsewhere. Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK), run under Matlab R2008a (MathWorks) was employed for MRI data analysis. Functional images were motion and slice-time corrected, realigned, and spatially normalized using a sample-specific template. The template was created by first normalizing (Ashburner and Friston 1999) the mean volume of each participant's functional time series (separately for study and test) with reference to a standard EPI template based on the Montreal Neurological Institute (MNI) reference brain (Cocosco et al. 1997). The normalized images were separately averaged within each age group and the resulting 3 mean images were then averaged to generate a template that was equally weighted with respect to the 3 age groups. Normalized volumes were resampled into 3 mm isotropic voxels and smoothed with an isotropic 8 mm full-width half-maximum Gaussian kernel. T1 anatomical images were normalized with a procedure analogous to that applied to the functional images.

For each participant, item-elicited neural activity was modeled by a delta function and convolved with 2 hemodynamic response functions (HRFs) using a GLM. These functions consisted of a canonical (Friston et al. 1998) and an orthogonalized, delayed HRF (Andrade et al. 1999), the latter generated by shifting the canonical HRF one TR (2 s) later in time. As the results obtained with the late HRF added little of theoretical significance to the findings obtained with the canonical function, they are not reported here. The fMRI data were analyzed in two stages. In the first stage, separate GLMs were constructed for each participant. Two events of interest were included in the design matrix: study pairs that went on to be correctly endorsed as intact (subsequent associative hits) and pairs that were later incorrectly identified as rearranged (subsequent associative misses) on the subsequent associative recognition test. Study pairs later incorrectly identified as new, those that became rearranged at test or were not responded to, buffer pairs and the two 30 s breaks interposed during the study list were also modeled, along with 6 regressors representing motion-related variance and 2 constants representing means across each scan session. The time series in

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each voxel were high-pass filtered to 1/128 Hz to remove low-frequency noise and scaled within session to a grand mean of 100 across voxels and scans.

In the second stage of the analysis, the participant-specific parameter estimates for subsequent associative hits and misses were taken forward to a 3 × 2 mixed-design analyses of variance (ANOVA) with factors of age group (young, middle-aged, older) and subsequent memory (associative hits, associative misses) using ANOVA models implemented within SPM8 (and hence employing single pooled error terms). Subsequent memory effects were operationalized as greater BOLD activity for subsequent associative hits than for subsequent associative misses. Whole brain analyses were conducted to identify subsequent memory effects that were common to the 3 age groups as well as effects that differed between groups using contrasts derived from the ANOVA models. Regions where subsequent memory effects did not differ according to age group (common effects) were identified by exclusively masking the across-group, main effect of subsequent memory (associative hit > associative miss, thresholded at $p < 0.001$, see below) with the two-sided age group x subsequent memory interaction contrast, liberally thresholded at $p < .05$ (two-sided). Regions demonstrating age-related differences in subsequent memory effects were identified by the age group x subsequent memory interaction contrast (2-sided), exclusively masked with each group's negative subsequent memory effect (associative misses > associative hits; thresholded at $p < .05$ one-sided) to restrict the findings to group-wise differences in positive effects (as noted in the Introduction, findings for negative subsequent memory effects have previously been reported, de Chastelaine et al., 2015). Following our prior practice (de Chastelaine at al., 2011; Duverne et al., 2009) parameter estimates for pre-experimentally selected regions of interest (ROI) (specifically, left and right IFG and hippocampus) were extracted from the unmasked across-participant main effect of subsequent memory. Whole brain subsequent memory and subsequent memory x age group interaction effects exceeding a height threshold of $p < 0.001$ and comprising clusters of 21 or more contiguous voxels were considered reliable. The cluster extent threshold was determined by a Monte Carlo simulation implemented in AlphaSim (http://afni.nimh.nih.gov/afni) to give a corrected cluster-wise significance level of $p < 0.05$.

Turning to the ROI analyses, we first determined if we could replicate our prior findings in older participants concerning the relationships between left and right frontal subsequent memory effects, anterior callosal FA and associative memory performance (de Chastelaine et al., 2011). For each participant, mean parameter estimates were extracted across all voxels within a 5 mm radius of the peak of the left IFG subsequent memory effect identified in the whole brain analysis described above, and from the homotopic ROI in the right hemisphere. For the older participants only, we conducted two partial correlation analyses identical to the ones employed in our previous analyses (de Chastelaine et al., 2011). The first investigated the relationship between the magnitude of right IFG subsequent memory effects and memory performance, controlling for the magnitude of left IFG subsequent memory effects. The second analysis investigated the correlation between the size of right IFG subsequent memory and anterior callosal FA, again controlling for left IFG effects.

Next, using the data from all 3 age groups, we assessed the effects of age on subsequent memory effects in the left and right IFG, as well as the relationship between these variables

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and associative memory performance. Parameter estimates from left and right IFG ROIs were subjected to a 3 (group) x 2 (hemisphere) x 2 (subsequent memory) ANOVA. We also examined the relationships between age group, IFG subsequent memory effects and memory performance with multiple regression analyses. The first regression model included memory performance as the dependent variable, and age group, left IFG subsequent memory effects and the age group x left IFG effect interaction term as predictor variables. The second model was identical except subsequent memory effects in the left IFG were replaced as a predictor variable with those in the right IFG. For the reasons outlined in the Results section (3.4.2 ROI analyses – IFG subsequent memory effects), these two regression analyses were followed up by a third analysis that employed the mean of the left and right IFG effects as the fMRI predictor variable.

We also used an ROI approach to investigate whether the magnitude of hippocampal subsequent memory effects, and any relationship between these effects and memory performance, varied across age groups. Mean parameter estimates were extracted across all voxels within a 3 mm radius of the peak of the hippocampal subsequent memory effect identified in the unmasked subsequent memory contrast and subjected to a 3 (group) x 2 (subsequent memory) ANOVA. In addition, we employed multiple regression to examine whether hippocampal effects were related to memory performance, and whether any such relationship differed according to age. The regression model included memory performance as the dependent variable, along with age group, the left hippocampal subsequent memory effect, and the age group x hippocampal effect interaction term as predictor variables.

Finally, for the older participants only, we conducted between-experiment analyses by combining the data from the current experiment with those from our previous study (de Chastelaine et al., 2011). This allowed us to directly compare the two sets of findings. The IFG data for the previous experiment were those reported previously (see de Chastelaine et al., 2011). Parameter estimates were also extracted from voxels in the left hippocampal region that demonstrated a significant subsequent memory effect in that study. This region was identified by the whole brain, across-group main effect of subsequent memory (MNI co-ordinates −27, −9, −15; see Figure 2B and Table 4 of de Chastelaine et al., 2011). We first contrasted the magnitudes of the subsequent memory effects in left IFG and right IFG and, separately, the left hippocampus according to experiment. For the IFG data, we used a 2 (experiment) x 2 (hemisphere) x 2 (subsequent memory) ANOVA and, for the hippocampal data, a 2 (experiment) x 2 (subsequent memory) ANOVA. We also performed 3 regression analyses, one for each ROI (left IFG, right IFG and left hippocampus), in which memory performance was the dependent variable, and the variables of experiment, age, the subsequent memory effect in the ROI in question, and the subsequent memory effect by experiment interaction term, were the predictor variables.

For the purposes of visualizing the fMRI findings, Caret software (Van Essen et al., 2001) was used to map fMRI effects of interest on to inflated fiducial brains derived from the PALS-B12 atlas (Van Essen 2002, 2005) in SPM5 space. Results were also visualized using sections from the across-group averaged T1 structural image.

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3. Results

See de Chastelaine et al. (2015) for additional description and discussion of the neuropsychological and behavioral findings.

3.1 Neuropsychological data

Table 1 summarizes demographic and neuropsychological data for the three age groups. To briefly summarize, the 3 age groups showed equivalent performance on tests that are typically preserved with age, while composite recall of word lists was significantly lower in the older, but not in the middle-aged group, compared to the younger participants. Older participants also demonstrated poorer performance on tests of speeded cognition relative to both the younger and middle-aged groups. Performance of both older and middle-aged participants was lower than that for younger participants on a test of fluid intelligence (Raven's Matrices), while performance on a test of crystallized intelligence (WTAR) was age-invariant.

3.2 Behavior

3.2.1 Study phase—Accuracy on the study task was high and did not differ significantly between age groups: means (standard deviations (SDs)) of 0.81 (0.09), 0.82 (0.07) and 0.80 (0.09) for the young, middle-aged and older groups, respectively. Reaction times (RTs) to study items also did not differ significantly between the groups: mean RT (SDs) of 1913 (290) ms, 1805 (310) ms and 1849 (243) ms for young, middle-aged and older groups, respectively.

In parallel to the later fMRI analyses, study RTs for word pairs presented in the same pairing at test (intact pairs) were segregated according to subsequent memory (associative hits versus associative misses). A 3 (group) x 2 (subsequent memory) ANOVA revealed a main effect of subsequent memory ($F1, 133 = 38.25$, $p < 0.001$), reflecting faster study RTs for associative hits than for associative misses (collapsed across age-group, 1835 (279) ms and 1883 (285) ms respectively). There was no effect of age, and no group by subsequent memory interaction.

3.2.2 Test phase—Table 2 summarizes performance on the associative recognition test. Associative recognition accuracy (hereafter referred to as 'pR') was indexed as the difference between the proportion of intact test pairs correctly endorsed as intact (associative hits) and the proportion of rearranged test pairs incorrectly endorsed as intact (associative false alarms). A one-way ANOVA of these data indicated a graded decline in pR with age ($F2, 135 = 12.80$, $p < 0.001$), with means (SDs) of 0.48 (0.19), 0.39 (0.14) and 0.31 (0.15) for the young, middle-aged and older groups, respectively. Pair-wise t-tests revealed that young participants were more accurate than both middle-aged ($t64 = 2.25$, $p < 0.05$) and older participants ($t59 = 4.50$, $p < 0.001$), and that middle-aged participants were more accurate than the older participants ($t76 = 2.60$, $p < 0.025$).

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3.3 DTI data

Mean FA values from the ROIs in anterior and posterior portions of the corpus callosum (see Table 3) were subjected to a 3 (group) x 2 (region) ANOVA. This revealed a main effect of group ($F_{1,133} = 9.56$, $p < 0.001$), a main effect of region ($F_{1,133} = 623.22$, $p < 0.001$) and a group by region interaction ($F_{2,133} = 21.83$, $p < 0.001$). The interaction largely reflected the typical finding of greater age-related decline for anterior, relative to posterior, callosal FA (see Introduction: section 1). Follow-up t-tests indicated that anterior callosal FA was higher in the young group compared to both the middle-aged ($t_{70} = 5.05$, $p < 0.001$) and older ($t_{78} = 7.47$, $p < 0.001$) groups (between which FA did not differ), while posterior callosal FA did not differ between the young and either the middle-aged or older groups (both $ps > 0.1$), although (inexplicably) it was reliably higher in the older than the middle-aged group ($t_{94} = 2.73$, $p < .01$).

3.4 fMRI data

3.4.1 Whole brain analyses—Subsequent memory effects common to the three age groups were identified at the whole-brain level by the across-group main effect of subsequent memory (associative hits > associative misses) exclusively masked with the group x subsequent memory interaction thresholded at $p < .05$ two-sided (see Materials and Methods: section 2.7 MRI analyses). As is summarized in Table 4 and depicted in Figure 1, the outcome of this contrast revealed age-invariant subsequent memory effects in a left-lateralized cortical network that included the ventral IFG and hippocampus.

We were unable to identify any clusters demonstrating a group by subsequent memory interaction (when this was exclusively masked with each group's negative subsequent memory effect; cf. de Chastelaine et al., 2015) at our pre-experimentally determined whole-brain threshold of $p < 0.001$.

3.4.2 ROI analyses – IFG subsequent memory effects—Mean parameter estimates from the ventral left IFG and homotopic right hemisphere ROI are depicted for each group in Figure 2 (these estimates were extracted from the peaks of the main effect of subsequent memory described above, but without the application of the exclusive mask, see Materials and Methods: section 2.7 MRI analyses. In no case did the removal of the mask change the loci of the peak co-ordinates detailed in Table 4). For the older participants only, we conducted two correlational analyses that mirrored those employed in our previous analyses (de Chastelaine et al., 2011). The first, investigating the relationship between the magnitude of right IFG subsequent memory effects and pR (controlling for the magnitude of left IFG subsequent memory effects), failed to demonstrate a significant correlation between the two variables ($p > 0.1$). The second correlational analysis, investigating the relationship between the size of right IFG subsequent memory effects and anterior callosal FA, also failed to demonstrate a significant relationship ($p > 0.8$).

The ANOVA conducted on the IFG data from all 3 age groups, with levels of group (3), hemisphere (2) and subsequent memory (2), revealed a main effect of hemisphere ($F_{1,132} = 136.63$, $p < 0.001$), a subsequent memory by hemisphere interaction ($F_{1,132} = 49.94$, $p < 0.001$), and an age group by subsequent memory by hemisphere interaction ($F_{2,132} = 5.84$,

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$p < 0.005$). Follow-up paired samples t-tests indicated that while each age group showed robust subsequent memory effects in the left IFG (as expected, given the whole brain results reported above), subsequent memory effects in the right IFG were evident in the older group only ($t63 = 2.29$, $p = 0.025$). Moreover, the magnitude of the right IFG subsequent memory effects in the older group was significantly greater than that in the young group ($t67 = 2.22$, $p < 0.05$), and showed a non-significant trend in the same direction relative to the middle-aged group ($t70 = 1.89$, $p < 0.07$). The effects for the young and the middle age groups did not significantly differ ($p > .8$). These findings suggest that IFG subsequent memory effects were less asymmetric in the older group than in the two younger groups. To directly test for group differences in the asymmetry of IFG effects, we conducted a between-groups one-way ANOVA on the difference scores between the left and right IFG subsequent memory effects (i.e., left IFG minus right IFG). The ANOVA revealed a main effect of group ($F2,135 = 5.84$, $p < 0.005$), which is unsurprising given that this effect is synonymous with the three-way interaction effect reported above. More importantly, follow-up pairwise tests (independent t-tests) indicated greater asymmetry in the young group relative to the older group ($t67 = 3.12$, $p < 0.005$), a trend for greater asymmetry in the young compared to the middle-aged group ($t63 = 1.96$, $p < 0.06$), and no significant difference in asymmetry between the middle-aged and older groups ($p > 0.1$).

Repeating the foregoing analyses using ANCOVAs to control for any effects of memory performance resulted in the identical pattern of findings. Thus, the reported age effects are not a consequence of a confound between age group and level of subsequent memory performance (for discussion of the implications of such a confound see Rugg and Morcom, 2005; Rugg, in press).

Regression analyses were conducted to assess whether the magnitude of subsequent memory effects in either the left or right IFG were predictive of pR, and whether any such relationship differed with age. As is evident from Table 5, in both models age group was, unsurprisingly, a reliable predictor of pR[1]. In the regression model for the left IFG, the interaction term was significant (see Table 5), indicating that the regression slopes for the relationship between pR and left IFG subsequent memory effects differed reliably between age groups. Correlation analyses were conducted to assess the relationship between left IFG subsequent memory effects and pR separately for each group. These analyses revealed a positive relationship between pR and left IFG subsequent memory effects for the older participants ($r = 0.269$, $p < 0.05$), but no significant correlations between these two variables for the middle-aged or young participants (both $ps > 0.1$; the low correlations in these two age groups were not a consequence of restricted variance in the left IFG subsequent memory effects. SDs of these effects were 0.78, 0.52 and 0.65 in the young, middle-aged and older groups respectively. Corresponding SDs for the right IFG effects were 0.58, 0.56 and 0.53). By contrast, the regression model for the right IFG failed to identify either the magnitude of the subsequent memory effect, or its interaction with age group, as a reliable predictor of pR. In light of our *a priori* interest in the relationship between the magnitude of right IFG

[1]Age and pR were significantly correlated across the older participants, $r = -0.260$, $p < 0.05$. Accordingly, correlation and regression analyses conducted on this age group alone either controlled for the effects of age (correlation), or included it as a predictor variable (regression).

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subsequent memory effects and memory performance in older individuals (see Introduction: section 1), we calculated the correlation between these variables in the older group only. The correlation was .275 ($p < .05$) after controlling for age.

The analyses of the relationships between subsequent memory performance and left and right IFG subsequent memory effects suggests that, in striking contrast to our prior findings (de Chastelaine et al., 2011), both effects in older participants were positively correlated with performance. Accordingly, in a third regression analysis (conducted for the older participants only), we employed the mean of the two IFG subsequent memory effects as a predictor variable, along with the continuous variable of age. Age again accounted for a significant proportion of the variance in memory performance. Importantly, so too did the averaged left and right IFG subsequent memory effects (partial $r = .328$, $p < 0.01$). The partial plot of this relationship is illustrated in Figure 3.

3.4.3 ROI analyses – hippocampus—Unsurprisingly, given the findings for the whole brain analyses described previously, the ANOVA of left hippocampal activity revealed a reliable main effect of subsequent memory, in the absence of an interaction between this factor and age group. Importantly, the same results were obtained when the analysis was repeated with an ANCOVA that controlled for individual differences in pR (age group x subsequent memory interaction, $p > 0.1$). Thus, there was no evidence that the relationship between subsequent memory performance and hippocampal subsequent memory effects reported below was sufficiently strong to have led to a spurious null effect of age group on these effects.

Turning to the regression model assessing the relationship between left hippocampal subsequent memory effects and associative memory performance (Table 6), both age group and left hippocampal subsequent memory effects, but not the age group by subsequent memory effect interaction term, were reliable predictors of pR (left hippocampal effect: partial $r = 0.212$). After dropping the interaction term from the model, the across-group partial correlation (controlling for age group) between the left hippocampal effect and pR was 0.223 ($p < 0.01$; see Figure 4 for the partial plot of this relationship).

3.4.4 Between-experiment analyses (older participants)—Independent t-tests indicated that pR did not differ between the two experiments ($p > 0.4$). A 2 (experiment) x 2 (subsequent memory) ANOVA conducted on study RTs revealed a main effect of subsequent memory ($F1, 98 = 6.69$, $p < .025$), indicating that RTs were longer for subsequent associative misses than for subsequent associative hits, a main effect of experiment ($F1, 98 = 8.01$, $p < .01$), indicating that RTs were longer for the present relative to the previous experiment, and a trend for the interaction between these factors' RTs ($p < 0.07$). Paired samples t-tests conducted for each experiment separately revealed that, as was the case for the entire sample, RTs for subsequent associative misses were longer than those for subsequent associative hits in the present experiment ($t64 = 3.42$, $p < 0.005$). The RTs did not however differ significantly in our prior study ($p > 0.5$).

A 2 (experiment) x 2 (hemisphere) x 2 (subsequent memory) ANOVA of the data from the left and right IFG revealed, as would be expected given the outcomes of the independent

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analyses of the data from the two studies, a main effect of subsequent memory ($F1, 98 = 25.82$, $p < .001$) and a hemisphere by subsequent memory interaction ($F1, 98 = 21.58$, $p < 0.001$). There were, however, no significant interactions involving both the factors of experiment and subsequent memory ($ps > 0.1$). A 2 (experiment) by 2 (subsequent memory) ANOVA of the left hippocampal data also revealed (again unsurprisingly) a main effect of subsequent memory ($F1, 98 = 21.32$, $p < 0.001$), which, like the effects for the IFG, did not significantly interact with experiment ($p > 0.06$).

The regression analyses employed to assess the relationships between pR and the subsequent memory effects in left IFG, right IFG and left hippocampus each accounted for significant proportions of the variance in pR (left IFG: $F4, 99 = 3.53$, $p < .01$, $R^2 = 0.093$; right IFG: $F4, 99 = 4.66$, $p < .005$, $R^2 = 0.129$; left hippocampus: $F4, 99 = 4.12$, $p < .005$, $R^2 = 0.112$). In each case, age was a significant predictor of pR. For the models employing as predictors subsequent memory effects in the left IFG and the left hippocampus, the experiment by subsequent memory effect interaction terms were not significant and, in both cases, the subsequent memory effects were positively correlated with pR across participants (left IFG: $r = 0.220$, $p < 0.05$; left hippocampus: $r = 0.240$, $p < 0.025$). After dropping the interaction term from each of the models, the partial correlation (controlling for age and experiment) between pR and hippocampal subsequent memory effects was 0.260 ($p < 0.01$; see Figure 5), but the partial correlation between pR and left IFG effects was no longer significant. For the model with right IFG subsequent memory effects as a predictor variable, the experiment by subsequent memory effect interaction term was significant ($p < 0.005$). Partial correlations (controlling for age) for each experiment separately revealed a significant negative relationship between pR and right IFG effects in the prior experiment ($r = -0.342$, $p < 0.05$), consistent with what was previously reported using a somewhat different regression model and, of course, the significant positive relationship between pR and right IFG effects already described for the current experiment (see Results: section 3.4.2 ROI analyses – IFG subsequent memory effects). The partial plots of each of these relationships are illustrated in Figure 6.

3. Discussion

The present findings significantly extend those of our prior study of the effects of age on the neural correlates of associative encoding (de Chastelaine et al., 2011). Several of the findings reported in that study were replicated here. These include age-invariance in the magnitude of subsequent memory effects in left IFG, posterior cortical regions and the hippocampus and, in older participants, a positive correlation between the magnitude of left IFG subsequent memory effects and later associative recognition performance. A new finding to emerge from the present study was an age-invariant correlation between the magnitude of hippocampal subsequent memory effects and subsequent memory performance. A striking disparity between our present and prior findings was evident in respect of right IFG subsequent memory effects in older individuals. Whereas we previously reported a negative correlation between these effects and later memory performance, the correlation in the present experiment was positive. Below, we discuss the relevance of these and related findings to the understanding of the effects of age on the neural correlates of episodic memory encoding, and to individual differences in memory performance.

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3.1 Behavioral data

The demographic and neuropsychological test profiles of the present young and older samples were highly comparable to those of our prior study, as was associative recognition performance. Therefore there is little reason to suppose that any of the disparities in the respective fMRI findings reflect differences in the characteristics of the young and older samples employed in the two studies.

Whereas the present study largely followed the experimental procedures employed previously, it differed from our prior experiment in one potentially important way. While in both of the experiments participants performed the study task in the MRI scanner, in our prior experiment the subsequent associative recognition test was undertaken outside of the scanner on a laptop computer and was unpaced. In the present study, by contrast, participants re-entered the scanner and performed a paced version of the memory test while further fMRI data were acquired. Thus, the two experiments differed in respect of both the amount of overlap between the study and test contexts, and the time constraints imposed on the test judgments. Given that subsequent memory effects can qualitatively differ depending on the nature of the later memory test (Otten, 2007; Park et al., 2008; Rugg et al., 2008; Wong et al., 2013), it might not be surprising if some of the fMRI findings diverged between our present and prior studies.

We return to this issue later, but note here that the procedural differences between the test phases of the two studies seem likely to account for why study RTs differed according to subsequent memory performance in the present study (when they were some 50 ms faster for study pairs correctly endorsed as intact), but did not do so previously. We conjecture that the different test conditions in the two studies resulted in participants processing what were ostensibly the same retrieval cues in partially different ways (that is, they adopted different ‘retrieval orientations’ (Rugg, 2004; Rugg & Wilding, 2000), such that successful retrieval depended upon overlap between different combinations of the features of the retrieval cues and stored memory representations in the two studies. For example, the high perceptual overlap between the study and test pairs in the present experiment might have led participants to base their memory judgments on retrieved perceptual information to a greater extent than in the prior experiment, when study-test overlap at the perceptual level was lower.

3.2 fMRI findings

The present findings converge with the majority of prior studies to suggest that, in sharp contrast to what is typically reported for ‘negative’ subsequent memory effects, positive effects differ little in their magnitudes across much of the healthy human lifespan (Maillet & Rajah, 2014). This is the case even for regions such as the hippocampus and IFG, where age-related reductions in volume and cortical thickness are consistently reported (Raz & Rodrigue, 2006). As noted in Footnote 2, such reductions were also evident in the present participants. The right IFG is an exception to this general conclusion. Consistent with some prior reports (e.g., Duverne et al., 2009; Morcom et al., 2003), subsequent memory effects in this region were greater in older than in young participants, causing an age-related attenuation of the lateralization of the effects. In contrast to our prior study of associative

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memory encoding (de Chastelaine et al., 2011), however, there was no evidence in the present older sample of a correlation across participants between the strength of the lateralization of the IFG subsequent memory effects (as indexed by left – right difference scores) and subsequent memory performance.

Unlike in the case of our older participants, the magnitude and lateralization of frontal subsequent memory effects in the middle-aged sample did not significantly differ from those of the young participants. The similarity of the frontal subsequent memory effects between these two age groups is consistent with the findings of two previous studies in which encoding-related activity in PFC was compared between young and middle-aged individuals (Kwon et al., 2015; Park et al., 2013). The present findings suggest that, at least in relatively high-functioning individuals such as those comprising the present participant samples, right frontal over-recruitment of subsequent memory effects might not be evident until fairly late in the adult lifespan. A caveat to this conclusion arises from the finding that the right frontal subsequent memory effects in our middle-aged group did not significantly differ from the effects in either the young *or* the older participants. This raises the possibility that the magnitude of these effects varies continuously with age.

It is worth noting that, regardless of whether right frontal over-recruitment of subsequent memory effects varies continuously or discontinuously over the lifespan, it does not follow that it is a consequence of aging. An alternative possibility, for which there is indirect empirical support (Nyberg et al., 2010), is that the influence of age on the magnitude of right frontal subsequent memory effects reflects the differential sampling biases inherent in the recruitment of healthy participants at different points of the lifespan (see Rugg, in press, for further discussion of this issue). Arbitrating between these different accounts is not possible in the absence of relevant longitudinal data.

Although there was no evidence in the present older group of a relationship between over-recruitment of right frontal subsequent memory effects (as indexed by inter-hemispheric asymmetry of left and right frontal effects) and later memory performance, this is not to say the magnitude of the effects was independent of performance. Rather, asymmetry of the older participants' effects failed to predict later memory performance because both left and right IFG effects were positively correlated with performance. The finding for the left IFG is reminiscent of the results reported for this region in our prior study, and converges with the previous finding to suggest that encoding-related activity in the left IFG of older individuals is a determinant of associative memory performance. Presumably, this reflects the benefit to associative encoding that comes with relatively high engagement during the study task of the semantic control processes held to be supported by this region (Badre and Wagner, 2007; Wong et al., 2013). By itself, however, this account does not explain why left IFG subsequent memory effects were correlated with later memory performance in older participants only. One possibility is that it is only in older individuals that the functional capacity of the left IFG is so limited that it acts as a mediator of encoding efficacy. By this account, processes supporting effective encoding are more sensitive to the amount of IFG engagement in older than in young or middle-aged individuals because of the high level of neural resources required to overcome limitations in processing efficiency caused by age-related synaptic or neuronal loss (cf. Grady, 2012; Motes et al., 2011; Reuter-Lorenz &

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Cappell, 2008). There seems little reason to suppose that a similar account would not extend to the analogous findings reported here for the right IFG, to which we now turn.

As already noted, the present findings for the right IFG differed qualitatively from our previous results[3], sufficiently so that there was a statistically significant cross-over interaction in the relationship between memory performance and the magnitude of right IFG subsequent memory effects in the two experiments (Figure 6). Also unlike in our prior study, while FA of the anterior corpus callosum demonstrated the expected pattern of age-related decline (see Introduction: section 1), it did not predict the magnitude of right IFG subsequent memory effects in our older participants. Thus, both the structural and behavioral correlates of these effects differed between the two studies. As we alluded to previously, we conjecture that these disparate findings reflect the different circumstances under which memory was tested in the two experiments and, consequently, differences in the nature of the retrieved information that supported the associative recognition judgments in each case. We explained our prior findings (de Chastelaine et al., 2011; see also Duverne et al., 2009) by proposing a 'partial compensation' account of right frontal subsequent memory effects. According to this account, the effects reflect recruitment of right frontal cortical regions in individuals in whom the functional integrity of the left IFG is insufficient to support the demands of the study task. The account further proposed that whereas right frontal recruitment benefits on-line processing of the study items, it makes little or no contribution to encoding, which remains dependent on the processing supported by left IFG. Hence, we argued, the negative relationship between the magnitude of right frontal subsequent memory effects and memory performance that we reported came about because the effects serve as a proxy for the functional integrity of left frontal cortex.

The present finding of a positive relationship in older individuals between right frontal subsequent memory effects and performance can, perhaps, be accommodated by a simple (albeit, *ad hoc*) modification to the partial compensation account outlined above. According to this modified account, recruitment of the right IFG continues to reflect a compensatory response to the failure of the left IFG to fully meet the demands of the study task. Rather than contributing solely to study processing, however, recruitment of the right IFG in the present experiment also contributed to the formation of a memory representation that was potentially accessible on the later memory test. As was discussed earlier, this may have arisen because the high level of contextual and perceptual overlap between the study and test tasks encouraged a retrieval strategy that weighted perceptual features, or other features of the study items preferentially processed by right IFG, more heavily than was the case in our previous study. Obviously, additional research will be needed to examine the validity of this and alternate accounts. Irrespective of the precise reasons for the disparity between the

[3]A reviewer noted that right frontal subsequent memory effects might have lower reliability than left frontal effects, and that this could have contributed to the differential relationship with performance observed for the right frontal effects in the present and prior experiments. To examine this possibility, we re-ran the subsequent memory analyses in the present older group treating odd- and even-numbered remembered and forgotten trials as separate conditions, allowing us to assess the internal reliability of subsequent memory effects. This analysis yielded 4 IFG subsequent memory effects for each hemisphere: (1) hit (odd) – miss (odd); (2) hit (odd) – miss (even); (3) hit (even) – miss (odd); (4) hit (even) – miss (even). The mean across-participant correlations between the magnitudes of these effects were .40 and .35 for the left IFG and right IFG respectively (ranges were .61 to .072 on the left and .73 to −.002 on the right). Thus, there was minimal, if any, evidence for a difference in the internal reliability of IFG effects between the two hemispheres. It remains to be established whether this conclusion extends to measures of test-retest reliability.

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present and previous findings (de Chastelaine et al., 2011; see also Duverne et al., 2009; Miller et al., 2008), it seems clear that the functional significance of right frontal subsequent memory effects in older adults depends upon poorly understood but seemingly subtle variations in experimental context. Importantly, the present findings are inconsistent with the notion that these effects invariably reflect processing that confers no mnemonic benefit.

A reviewer suggested that our proposal that recruitment of the right IFG in older adults in support of memory encoding is driven by degradation of the functional integrity of the left IFG leads to a testable prediction. Specifically, the relationship between right IFG subsequent memory effects and memory performance should be stronger in participants with relatively small rather than relatively large left IFG effects (on the assumption that the size of subsequent memory effects in the left IFG is a reflection of the functional integrity of the region). To examine this prediction, we dichotomized our older group by a median split based on the size of left IFG subsequent memory effects, and then computed the correlations between memory performance and right IFG effects. Consistent with the reviewer's prediction, the correlation in the sub-group with the smaller left IFG effects was sizeable and significant ($r = .513$, $p < .005$), while the correlation in the sub-group with the larger effects was negligible ($r = -.087$). These correlations differed significantly ($p < .025$).

In agreement with our prior findings (de Chastelaine et al., 2011; see also Miller et al., 2008, and Maillet & Rajah, 2014, for review), we identified robust, age-invariant subsequent memory effects in the left hippocampus. The present effects were age-invariant not only in their magnitudes, but also with respect to the across-participants relationship that they demonstrated with subsequent memory performance. We conducted an across-experiment regression analysis (using subsequent memory data from the left anterior hippocampal peak reported by de Chastelaine et al., 2011; MNI coordinates −27, −9, 15) to examine whether we might have missed a similar age-invariant relationship in our prior study. As is illustrated in Figure 7, the analysis revealed a reliable relationship across participants between left hippocampal effects and memory performance in the combined young and older samples ($r = .259$, $p = .001$, after controlling for age group and experiment, with no hint of any interaction effects involving these variables, $ps > 0.4$). Therefore it seems that our failure to identify this relationship previously was a Type II error.

The finding that the relationship between encoding-related activity in the hippocampus and later memory performance is age-invariant stands in contrast to the findings for the left and right IFG subsequent memory effects, where relationships with performance were evident in older individuals only. Thus it would appear that, unlike in these frontal regions, encoding-related activity in the hippocampus predicts later memory performance to largely the same extent regardless of the amount of any age-related structural decline. The functional significance of this relationship is unclear. On the one hand, it might be a direct reflection of individual differences in hippocampal function, perhaps reflecting the capacity of the structure to bind disparate information about a study event into a durable memory representation (Eichenbaum et al., 2007). Thus, hippocampal subsequent memory effects might act as a marker for age-invariant individual differences in the efficiency with which the hippocampus can capture the products of on-line processing of a study event. Alternately, the relationship between hippocampal subsequent memory effects and memory

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performance might be indirect. For example, the relationship might reflect individual differences not in the functional capacity of the hippocampus, but in the amount or the quality of the information about a study event that it receives. There is evidence, for instance, that both subsequent memory performance and encoding-related activity in the hippocampus are modulated by the amount of attentional resources that are directed towards a study event or a sub-set of its features (Aly & Turk-Browne, 2015; Uncapher & Rugg, 2009). Therefore the present findings might be a reflection of individual differences in processing resources or attentional strategies deployed by participants in performing the study task.

Our finding of a positive relationship in older individuals between the magnitude of hippocampal subsequent memory effects and later memory performance stands in contrast to the findings of Miller et al. (2008). In a study of face-name encoding, these authors reported the opposite relationship, such that older adults who performed relatively poorly on the later memory test demonstrated greater encoding-related activity in the hippocampus than higher-performing individuals. The finding was interpreted as evidence for compensatory hippocampal 'hyper-activation' in the face of decline in the functional integrity of other brain regions (see also Mormino et al., 2012). There are a number of possible explanations for the divergence between the present findings and those of Miller at al. (2008), including the different sample sizes employed in the respective studies (Ns of 100 and 17 older participants), and the composition of the samples (mean age was some 5 years older in the sample of Miller et al., 2008 than in our studies, and the age range was markedly broader). The present results are however consistent with those from a large longitudinal study (Pudas et al., 2013). These authors reported that the magnitude of encoding-related hippocampal activity in older individuals (assessed in a blocked rather than an event-related design) correlated positively across participants with their memory performance, and was higher in individuals in whom episodic memory performance had remained stable over the preceding 15–20 years than in individuals who demonstrated a decline in performance over the same period (see Persson et al., 2012, and Pudas et al., 2014, for related findings from the same study). The present cross-sectional data provide little insight into the extent to which the age-related differences evident in associative recognition performance reflect effects of aging (within-participant decline over time) rather than age-correlated factors such as birth cohort effects (Rönnlund and Nilsson, 2009; Baxendale, 2010), and hence cannot be compared directly with the findings of Pudas et al. (2013). The data converge with those findings however to suggest that encoding-related activity in the hippocampus of healthy adults is more strongly predictive of memory performance than it is of chronological age.

We conclude by noting an important caveat to the interpretation of the present findings (and those of most prior studies where age-related differences in brain activity were examined with fMRI). Our conclusion that age has little impact on the magnitude of encoding-related activity in regions such as the left IFG and hippocampus rests on the assumption that the transfer function mediating between neural activity and the fMRI BOLD signal is age-invariant. There is evidence however that cerebrovascular reactivity (CVR) – an important non-neural determinant of BOLD signal magnitude – both varies across individuals of the same age, and declines monotonically with increasing age (Lu et al., 2011). This decline appears to be sufficient to lead to an underestimation of the size of at least some types of

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fMRI effects in older relative to young individuals when the effects are uncorrected for individual differences in CVR (e.g., Liu et al., 2013; Tsvetanov et al. 2015). Thus it is possible that the magnitude and regional extent of age-related 'over-recruitment' in encoding-related activity were underestimated in the present study. Importantly, it is unlikely that this caveat extends to our principal findings, which pertain to the relationships between individual, rather than group-wise, differences in the size of fMRI encoding effects and subsequent memory performance. Indeed, on the assumption that individual variation in CVR in our participants was largely uncorrelated with their memory performance, correcting for the variation would, if anything, lead to a strengthening of these relationships. That said, it will be important in future studies to incorporate methods (e.g., Ravi et al., 2015) that permit the influence of individual differences in CVR on the fMRI BOLD signal to be estimated and the signal corrected accordingly.

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- Age-invariant hippocampal subsequent memory effects predicted memory performance
- Right IFG subsequent memory effects were evident only in older adults
- IFG subsequent memory effects predicted subsequent memory only in older adults

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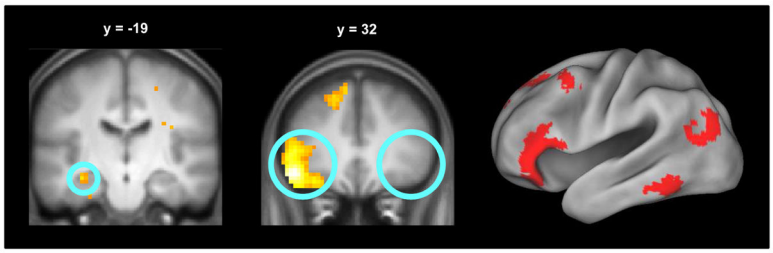

Figure 1.

Clusters demonstrating across-group subsequent memory effects. Effects are displayed on coronal sections of the across-groups mean T1-weighted structural image and the left lateral surface of a standardized brain (PALS-B12) atlas using Caret 5. The blue circles indicate the regions (left hippocampus, left and right IFG) from which parameter estimates were extracted for the ROI analyses.

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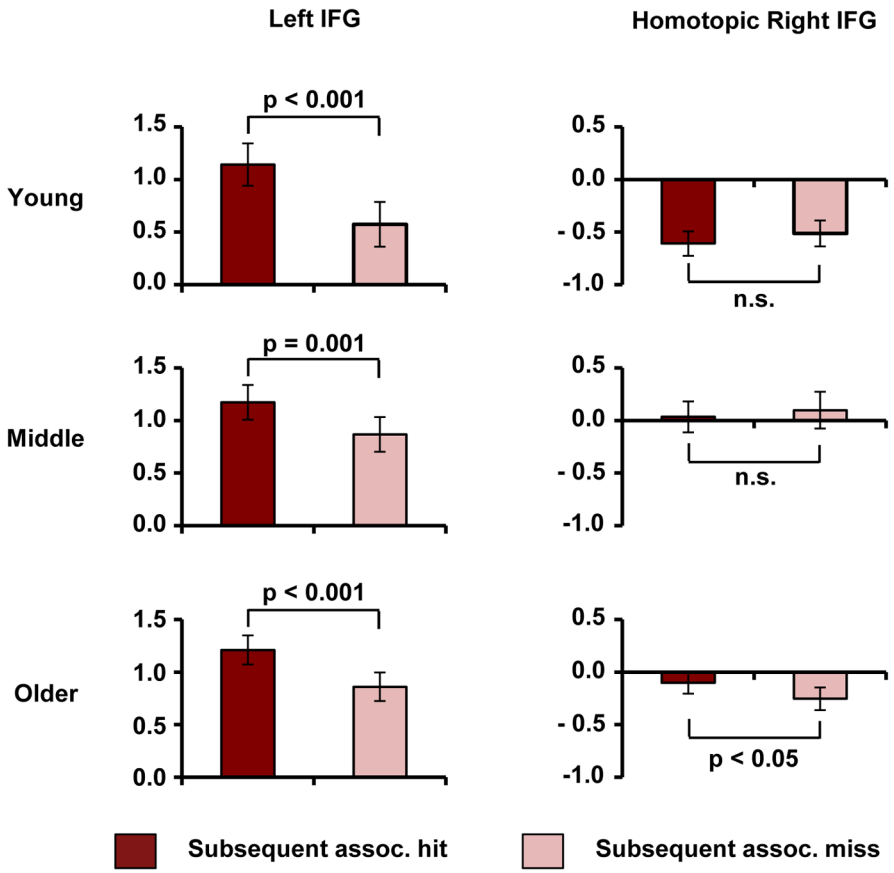

Figure 2.

Mean parameter estimates (arbitrary units) for the three age groups for subsequent associative hits and misses extracted from left and homotopic right IFG ROIs.

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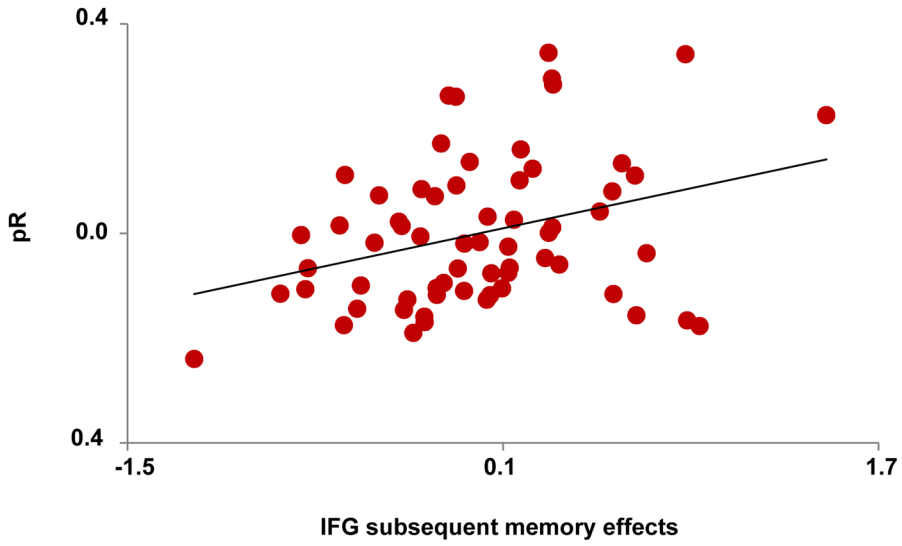

Figure 3.
Partial plot showing the relationship across older participants between IFG subsequent memory effects collapsed across hemisphere and pR, controlling for age.

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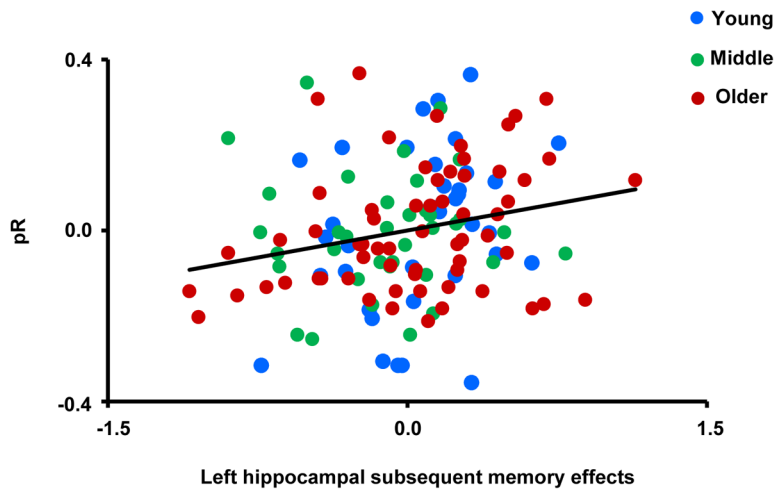

Figure 4.
Partial plot showing the relationship across participants between subsequent memory effects in the left hippocampus and pR after controlling for age group.

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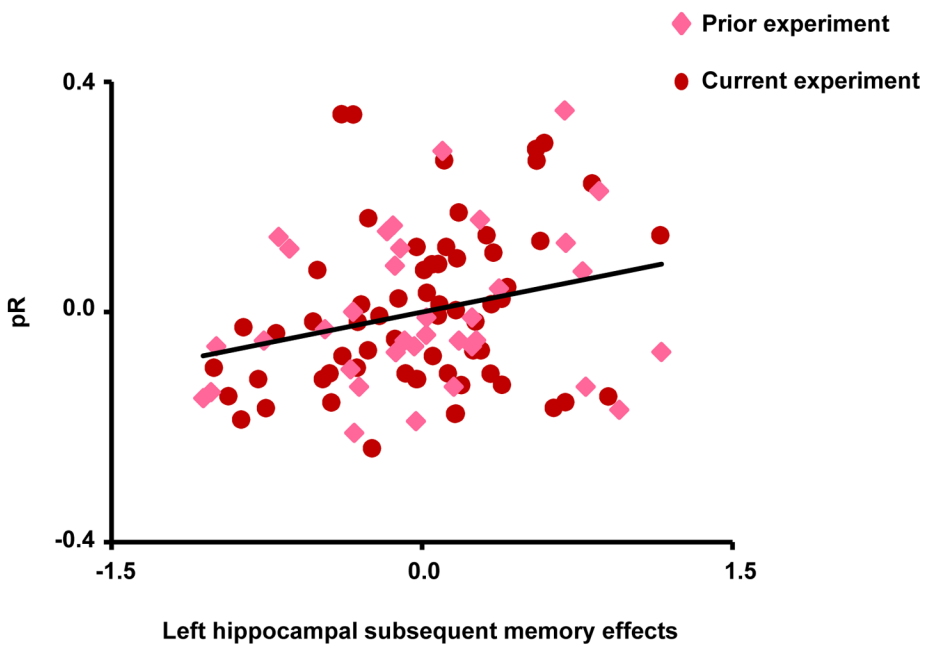

Figure 5.
Partial plot showing the relationship across older participants between subsequent memory effects in the left hippocampus and pR after controlling for age and experiment.

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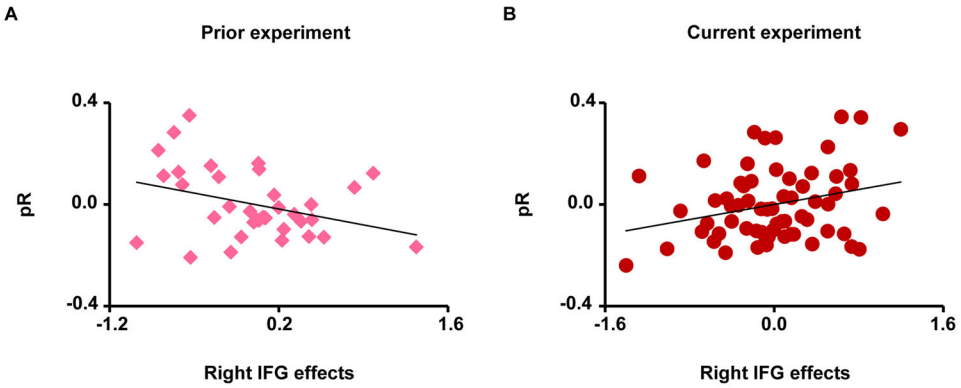

Figure 6.

Partial plots (controlling for age) showing the relationships between pR and right IFG subsequent memory effects across older participants from (A) the prior experiment; (B) the current experiment.

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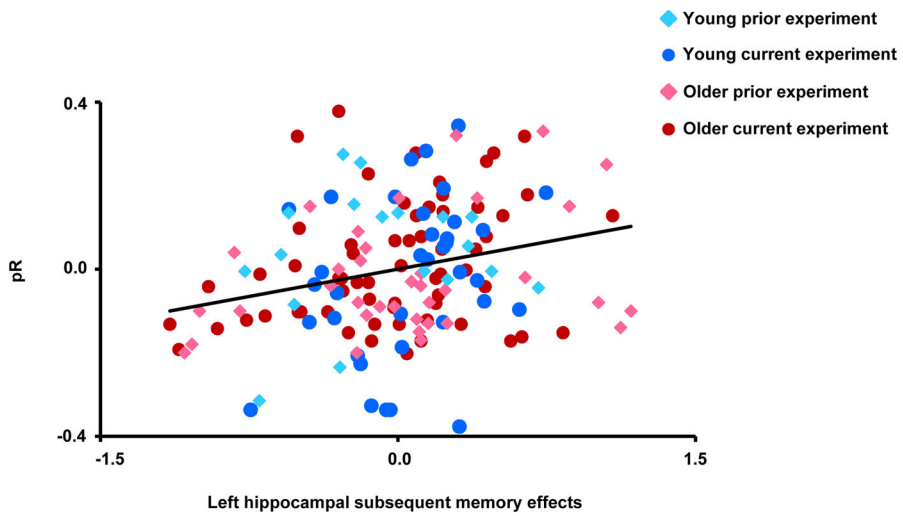

Figure 7.

Partial plot showing the relationship across young and older participants from the prior and current experiments between subsequent memory effects in the left hippocampus and pR after controlling for experiment and age group.

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Table 1

Demographic and neuropsychological data (mean, SD, and range) for young, middle-aged, and older adults.

	Young adults			Middle-aged adults			Older adults		
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
Age	22.2	3.0	18–29	49.4	3.4	43–55	68.4	3.6	63–76
Years of Education[a †]	15.5	2.4	11–22	16.3	2.6	10–22	17.1	2.3	12–22
Mini Mental State Exam	29.6	0.6	28–30	29.3	0.8	28–30	29.3	0.8	27–30
CVLT[1] **Composite Recall**[a †]	13.3	1.9	9.3–16	12.4	2.0	9–16	12.0	2.5	5.5–16
CVLT[1] **Recognition**[a ≠, b *]	15.6	0.6	14–16	15.2	0.9	13–16	14.8	1.3	12–16
CVLT[1] **False Positives**[a †, b *]	0.9	1.0	0–4	1.9	2.2	0–8	1.9	2.2	0–10
WMS[2] **Composite Score**	29.0	6.6	15.5–41	27.1	6.2	14–44.5	27.5	5.3	18.5–39.5
Forward/Backward Digit Span	18.0	3.9	11–26	18.2	3.5	13–26	18.3	4.4	12–27
Digit Symbol Substitution[a ≠, b †, c †]	61.4	10.1	39–83	55.2	7.8	41–70	49.7	8.5	31–74
Trail A[a ≠, c ≠]	20.9	7.3	11–47	24.1	6.7	14–39	32.5	11.4	15–88
Trail B[a ≠, c ≠]	46.7	17.3	23–108	51.7	16.9	27–95	74.8	46.7	31–360
Letter Fluency	43.6	11.8	23–65	47.5	12.0	28–69	45.3	12.6	21–81
Category Fluency	24.8	5.9	16–42	24.0	5.9	13–36	22.3	5.5	12–40
WTAR[3] **Raw Score**	112.3	5.0	102–119	111.1	5.1	101–118	112.5	5.5	101–119
Raven's Prog. Matrices[4] [a ≠, b **]	11.2	1.0	8–12	10.4	1.5	7–12	9.7	2.0	3–12

[1] California Verbal Learning Test.

[2] Wechsler Memory Scale (WMS-IV).

[3] Wechsler Test of Adult Reading Full Scale Intellectual Quotient.

[4] Short version of Raven's Progressive Matrices.

Note: Statistically significant difference between a) young and older adults, b) young and middle-aged adults, c) middle-aged and older adults.

* $p < 0.05$,

** $p < 0.01$,

† $p < 0.005$,

$^{\neq}p < 0.001$, 2-tailed t-tests.

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Table 2

Mean proportions (±SD) of intact, rearranged, and new test pairs given intact, rearranged, and new responses in each age group. Correct responses are highlighted in bold.

	Young	Middle-aged	Older
Intact responses			
Intact pairs	**0.63 (0.17)**	**0.63 (0.14)**	**0.56 (0.16)**
Rearranged pairs	0.15 (0.11)	0.24 (0.12)	0.25 (0.13)
New pairs	0.03 (0.06)	0.06 (0.07)	0.07 (0.07)
Rearranged responses			
Intact pairs	0.26 (0.12)	0.27 (0.11)	0.29 (0.13)
Rearranged pairs	**0.64 (0.16)**	**0.55 (0.15)**	**0.49 (0.16)**
New pairs	0.29 (0.15)	0.30 (0.16)	0.30 (0.16)
New responses			
Intact pairs	0.11 (0.09)	0.10 (0.09)	0.14 (0.09)
Rearranged pairs	0.20 (0.11)	0.21 (0.13)	0.26 (0.12)
New pairs	**0.68 (0.17)**	**0.64 (0.19)**	**0.63 (0.18)**

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Table 3

Mean FA values (SDs) from the anterior and posterior corpus callosum ROIs according to age group.

	Young	Middle-aged	Older
Anterior corpus callosum	0.73 (0.03)	0.70 (0.03)	0.69 (0.03)
Posterior corpus callosum	0.79 (0.03)	0.78 (0.03)	0.80 (0.04)

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Table 4

Peak voxels of the across-group main effect of subsequent memory, exclusively masked by the 2-sided group by subsequent memory contrast.

Coordinates			Peak *Z*	No. of above-threshold voxels	Region
x	*y*	*z*			
−48	32	−11	6.44	477	Left IFG
−12	26	58	5.03	227	Left superior medial frontal cortex
−30	17	55	4.05	79	Left superior frontal gyrus
−30	31	−23	5.34	194	Left fusiform gyrus
−33	−19	−14	4.11	sub-peak	Left hippocampus
−60	−52	−17	4.61	97	Left inferior temporal gyrus
−48	−70	22	4.46	240	Left angular gyrus
30	−13	1	3.73	26	Right putamen
33	−16	25	3.82	30	White matter
27	−31	−29	4.44	31	Right cerebellum
27	−34	61	3.55	26	Right post-central gyrus
21	−73	−35	4.79	124	Right cerebellum

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Table 5

Results of the across-group regression models investigating to what extent age group, IFG subsequent memory effects (left or right) and their interaction with age, predict subsequent associative memory performance.

Model	*b*	SE *b*	β	*P* value
Age group	−.107	.019	−.523	.000
LIFG subsequent memory effect	.004	.020	.015	.849
LIFG subsequent memory effect x Age group	.056	.022	.231	.013
Age group	−.084	.016	−.414	.000
RIFG subsequent memory effect	.007	.025	.024	.772
RIFG subsequent memory effect x Age group	.041	.029	.112	.166

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Table 6

Results of the across-group regression model investigating to what extent age group, left hippocampal subsequent memory effects, and the interaction between these variables, predict subsequent associative memory performance.

Model	*b*	SE *b*	β	*P* value
Age group	−.075	.018	−.370	.000
Left hippo subsequent memory effect	.090	.036	.219	.014
Left hippo subsequent memory effect x Age group	−.014	.042	−.033	.732