The Effects of Age, Memory Performance, and Callosal Integrity on the Neural Correlates of Successful Associative Encoding

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This functional magnetic resonance imaging study investigated the relationship between the neural correlates of associative memory encoding, callosal integrity, and memory performance in older adults. Thirty-six older and 18 young subjects were scanned while making relational judgments on word pairs. Neural correlates of successful encoding (subsequent memory effects) were identified by contrasting the activity elicited by study pairs that were correctly identified as having been studied together with the activity elicited by pairs wrongly judged to have come from different study trials. Subsequent memory effects common to the 2 age groups were identified in several regions, including left inferior frontal gyrus and bilateral hippocampus. Negative effects (greater activity for forgotten than for remembered items) in default network regions in young subjects were reversed in the older group, and the amount of reversal correlated negatively with memory performance. Additionally, older subjects' subsequent memory effects in right frontal cortex correlated positively with anterior callosal integrity and negatively with memory performance. It is suggested that recruitment of right frontal cortex during verbal memory encoding may reflect the engagement of processes that compensate only partially for age-related neural degradation.

Keywords: cognitive aging, compensation, episodic memory, fMRI, verbal encoding

Introduction

Episodic memory—memory for unique events and their contexts—declines markedly with age (Nilsson 2003). This observation has motivated research aimed at elucidating the cognitive and neural bases of age-related episodic memory decline, much of it employing functional neuroimaging. A consistent finding from functional neuroimaging studies is that cortical activation associated with both episodic memory encoding and retrieval tends to be greater in older (>60 years) than in young (<30 years) individuals (for recent reviews, see Park and Reuter-Lorenz 2009; Spreng et al. 2010). "Age-related over-recruitment" can take the form of additional activation both in regions engaged in young subjects and in regions not activated in the young, often in the opposite cerebral hemisphere (Cabeza 2002). Some authors have proposed that over-recruitment reflects the engagement of compensatory processes that help maintain performance in the face of age-related decline in neural function (Cabeza et al. 2002; Park and Reuter-Lorenz 2009). Others, however, have suggested that over-recruitment may be a consequence of a breakdown in cortical functional specialization (Li et al. 2006) or in the regulation of cortical activation (Logan et al. 2002), and thus that over-recruitment may reflect age-related changes in neural function that are detrimental to cognitive function (Buckner and Logan 2002; Logan et al. 2002; see also Grady 2008).

In an early event-related functional magnetic resonance imaging (fMRI) study of the effects of age on the neural correlates of successful memory encoding, Morcom et al. (2003) segregated the fMRI responses elicited by study words according to whether or not the words were recognized on a later memory test. Subsequent memory effects—greater study activity elicited by later recognized than by later forgotten items (Paller and Wagner 2002)—were equally evident in the left lateral frontal cortex of young and older subjects but were present in right frontal cortex in the older group only. This result was replicated in a second study (Duverne et al. 2009), although, in this case, right frontal subsequent memory effects were statistically significant only for a subgroup of older adults in whom performance on the subsequent memory task was poor relative to the young subjects (see also Miller et al. 2008). This finding suggests that the emergence of right frontal effects in older individuals does not reflect the engagement of compensatory processes that preserve memory function at or near the level of young adults. Duverne et al. (2009) noted that right frontal over-recruitment might be adaptive nonetheless, reflecting processes that compensate partially, rather than fully, for impairment of the neural systems that support encoding in young and high-performing older adults. As Duverne et al. further noted, however, their findings are also consistent with the possibility that right frontal over-recruitment is detrimental to memory performance.

Duverne et al. (2009) also investigated the effects of age and performance on "negative" subsequent memory effects—when later remembered study items elicit less activity than items that are later forgotten (Otten and Rugg 2001; Wagner and Davachi 2001; Daselaar et al. 2004). They identified a medial parietal region where negative effects were prominent in young subjects but demonstrated a reliable effect in the opposite direction in the older group (attenuation or reversal of negative subsequent memory effects with age was also reported in 4 prior studies: Morcom et al. 2003; Gutchess et al. 2005; Kukolja et al. 2007; Miller et al. 2008). When the older subjects in Duverne et al. (2009) were segregated according to performance on the later memory test, negative effects were nonsignificant in relatively good performers but remained significant in the opposite direction (i.e., greater activity for later remembered items or positive effects) in relatively poor performers (for similar findings, see Miller et al. 2008). These results suggest that the negative relationship between memory performance and cortical "over-recruitment" during memory encoding in older subjects extends to regions where successful...
encoding is associated with relative decrements in activity in young individuals.

A potential criticism of the study of Duverne et al. (2009) arises from their choice of memory test, which required recognition memory of single items. There is a wealth of evidence to suggest that item recognition is supported by 2 distinct processes, termed "recollection" and "familiarity" (Yonelinas 2002). Recollection involves the retrieval of qualitative information about a prior episode, whereas familiarity-based recognition depends upon an acontextual sense of prior occurrence that is devoid of episodic information. There is evidence that recollection is more vulnerable to advancing age than is familiarity (e.g., Howard et al. 2006). Thus, in the study of Duverne et al. (2009), the subjects exhibiting relatively poor performance on the subsequent recognition task may have been more reliant on familiarity than were the good performers. If this was the case, then the finding of differential patterns of subsequent memory effects according to memory performance in older subjects may merely reflect a difference in the neural correlates of encoding processes that support familiarity- versus recollection-based recognition memory.

The present study further investigated the relationship between encoding-related cortical activity and memory performance in older adults. In contrast to the item recognition memory test employed by Duverne et al. 2009 (and Morcom et al. 2003), here we employed a test of associative recognition. Associative recognition depends upon the ability to form new associations between preexperimentally unrelated items and is supported almost exclusively by episodic memory (recollection), receiving little contribution from familiarity (Parks and Yonelinas 2009). Thus, employment of this task minimizes the potential confound between the memory performance and the relative contributions of recollection and familiarity as noted above. Additionally, previous studies in young adults (e.g., Jackson and Schacter 2004; Park and Rugg 2008) have reported that subsequent memory effects for associative recognition in lateral frontal cortex are strongly left lateralized, making the procedure ideal for investigating factors that might influence age-related right frontal over-recruitment.

In addition to acquiring fMRI data, we also obtained diffusion tensor images (DTI) of the brain in order to assess the microstructural integrity of the corpus callosum. Age-related reductions in axonal and white matter integrity (as assessed by fractional anisotropy or FA) have been reported in a number of brain regions but particularly in the anterior corpus callosum (e.g., Pfefferbaum et al. 2000; O’Sullivan et al. 2001; Head et al. 2004; Kochunov et al. forthcoming). It has been proposed that one consequence of reduced callosal integrity is a weakening of transcallosal inhibition, and hence a tendency toward unilateral rather than unilateral cortical recruitment in response to cognitive challenge (Logan et al. 2002; Persson et al. 2006; Sullivan and Pfefferbaum 2006). According to this proposal, in circumstances where optimal processing is supported by lateralized neural populations (such as those supporting language), reduced callosal integrity facilitates the (maladaptive) coactivation of homotopic cortex. By this account, therefore, right frontal over-recruitment during verbal memory encoding is deleterious, reflecting the failure to selectively recruit cortical regions that are functionally specialized for verbal processing (Logan et al. 2002). On the basis of this hypothesis and the findings of Duverne et al. (2009), we predicted that right frontal subsequent memory effects in older adults would be negatively correlated with both associative recognition performance (pR) and anterior callosal FA.

### Materials and Methods

#### Participants

Eighteen young adults (11 females), aged between 18 and 29 years, and 36 older adults (23 females), aged between 63 and 77 years, participated. Data collected from 3 additional older adults were excluded because of inadequate behavioral performance, either during the study phase and/or during the test phase. All were healthy, right-handed fluent English speakers with normal or corrected-to-normal vision. They had no history of cardiovascular, neurological, or psychiatric disease and were not taking central nervous system-active medication. However, 10 of the included older subjects were taking antihypertensive medication. Young adults were students from the University of California, Irvine and older adults were local community members recruited mainly via newspaper advertisements. The study was approved by the Institutional Review Board of the University of California, Irvine. Informed consent was obtained before proceeding with the experiment.

#### Neuropsychological Testing

A battery of standardized neuropsychological tests was administered to all subjects in a separate experimental session (see Table 1). This battery assessed a range of cognitive functions known to either decline or be maintained with age. The Mini-Mental State Examination was employed to screen subjects for dementia. For this, a nominal cutoff score of 26/30 was adopted. Long-term memory was assessed with the California Verbal Learning Test-II (CVLT; Delis et al. 2000) and the Immediate and Delayed New York University (NYU) paragraph test (Kluger et al. 1999). As CVLT recall scores were highly correlated with each other, a composite recall score was calculated by averaging across the 4 tests (immediate and delayed free and cued recall) for the purpose of further analysis (see Results). For the same reason, a composite recall score was also computed by averaging Immediate and Delayed NYU scores. Short-term memory was assessed with the Digit Span Forward and Backward test of the Wechsler Adult Intelligence Scale Revised (WAIS-R) (Wechsler 2001). Executive functions were assessed with the Digit/Symbol Coding test of the WAIS-R, Trail Making Tests A and B, and letter and category fluency tests. An estimate of crystallized intelligence was obtained from the Wechsler Test of Adult Reading (WTAR; Wechsler 2001). The Beck Depression Inventory was also administered (Beck et al. 1961).
**Experimental Stimuli**

Stimuli comprised 320 visually presented semantically unrelated word pairs. Each word denoted a common object and ranged in length from 3 to 9 letters. The words were selected from the word association norms compiled by Nelson et al. (2004). Stimuli were randomly divided into 4 lists of 80 word pairs. Lists were rotated so that, across subjects, each list provided the stimuli for all 3 of the experimental word pair categories: intact, rearranged, and new pairs (see below). For each set of yoked subjects (1 young and 2 older subjects), word pairs from 3 of the lists were pseudorandomly ordered to form the study list. Critical word pairs in the study list were intermixed with 80 null events. Two buffer pairs were placed at the start and 2 in the middle of each of 2 study blocks (see below). The test list comprised 320 critical word pairs and 2 buffer pairs placed at the start of the list. One hundred and sixty of the test pairs had been presented at study (intact pairs), 80 of the pairs were studied items that had been repaired from study (rearranged pairs) and 80 were unstudied pairs (new pairs). The sequence of events in the study and test lists were pseudorandomly ordered such that the same type of event did not occur more than 3 times in succession. Practice study and test lists were formed from items additional to those used to create the experimental lists.

**Procedure**

Subjects were given instructions and practice sessions for both the study task and the memory test prior to scanning, thus, they were aware that their memory for the study items would be tested. DTI were then acquired over a period of 12 min followed by a 7-min structural scan. Subjects were instructed to respond as quickly as possible without sacrificing accuracy. Subjects were able to view the experimental stimuli via a mirror placed directly above their eyes. Words were presented one above the other in white uppercase Helvetica 30 point font against a black background in the center of the screen for 2 s. Word pairs subtended an approximate vertical visual angle of 1.72° and a maximum horizontal visual angle of 4.58° at a 1-m viewing distance. Each pair was preceded by a red fixation cross for 0.5 s and replaced with a white fixation cross for 1 s. Null trials consisted of the presentation of a white fixation cross against a black background for 3.5 s. Thus, for all trials, stimulus onset asynchrony was 3.5 s. A 30 s break occurred halfway through each study block, and the interblock interval was approximately 2 min.

Approximately 25 min after the scanning session, subjects completed an associative recognition memory test. Test pairs were presented on the screen in the same format as at study. Each test trial consisted of a red fixation cross for 0.5 s, followed by the word pair which stayed on the screen until subjects made a response. One of 3 key press responses was required to indicate whether each pair was intact, rearranged, or new. Subjects were required to respond "intact" when they recognized both words and had a specific memory of the 2 words being presented together previously. A "rearranged" response was required when both words were recognized from study 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. Although the test was self-paced, subjects were instructed to respond as quickly as possible without sacrificing accuracy. Word pairs were replaced by a white fixation cross for 1 s once a response was made. Experimental control, including stimulus display, was implemented in the "Cogent" software package (http://www.vislab.ucl.ac.uk/cogent.php).

**MRI Acquisition**

Functional and anatomical images were acquired on a Philips Achieva 3T MR scanner equipped with a transmit/receive radio frequency head coil. Functional scans were acquired with a T2*-weighted echo-planar image (EPI) sequence with the following parameters: time repetition (TR) 2 s, time echo (TE) 30 ms, flip angle 70°, field of view (FOV) 240 × 240, and matrix size 80 × 79. Each EPI volume consisted of 30 slices, 3 mm thick with 1 mm interslice gap, acquired in ascending order, oriented parallel to the AC–PC line, and positioned for full coverage of the cerebrum and most of the cerebellum. Functional data were acquired during each study block (311 volumes each) and concatenated across the 2 sessions prior to model estimation. The first 5 volumes of each session were discarded to allow tissue magnetization to achieve a steady state.

A T1-weighted anatomical image was acquired using a 3D magnetization prepared rapid gradient echo pulse sequence (FOV = 240 × 240, matrix size 220 × 195, voxel size 1 mm3, 150 slices, sagittal acquisition). DTI acquisition involved a single-shot EPI sequence (48 directions, 60 transverse slices, 2 mm thick, no gap, matrix size 112 × 109, TR 12350 ms, TE 71 ms; flip angle 70°, b 1000 s/mm2, 1 × b = 0).

**MRI Data Analysis**

Functional images were preprocessed and analyzed with Statistical Parametric Mapping (SPM5; Wellcome Department of Cognitive Neurology. http://www.fil.ion.ucl.ac.uk/spm5.html). Volumes were motion and time-slice corrected, realigned, and then spatially normalized using a sample-specific template. The template was created by first normalizing (Ashburner and Friston 1999) the initial volume of each subject’s functional time series with reference to a standard EPI template based on the Montreal Neurological Institute (MINI) reference brain (Cocosco et al. 1997). The normalized volumes were separately averaged within each age group and the resulting 2 mean images were then averaged to generate a template that was equally weighted with respect to the 2 age groups. Normalized volumes were resampled into 3 mm isotropic voxels and smoothed with an isotropic 10 mm full-width half-maximum Gaussian kernel. T1 anatomical images were normalized with a procedure analogous to that applied to the functional images. Normalized T1 images were resampled into 2 mm isotropic voxels.

For each subject, stimulus-elicited neural activity was modeled by a delta function and convolved with 2 hemodynamic response functions (HRFs) using a general linear model (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. We report here the effects detected with the canonical HRF only as results from the late HRF did not add to these findings.

The design matrix of the GLM modeled the blood oxygen level-dependent responses elicited by 2 events of interest: study pairs correctly endorsed as intact (i.e., hits) and study pairs incorrectly identified as rearranged pairs (i.e., misses) on the subsequent test. Study pairs incorrectly identified as new and the two 30 s breaks interposed during the study list were also modeled. The time series in 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. These contrasts were carried forward to a second stage in which subjects were treated as a random effect.

**DTI Analysis**

Computation of the diffusion tensor was performed using DTIstudio (Jiang et al. 2006). The program reads the DTI image series and applies nonrigid registration to correct for motion and eddy current related deformations. Then a first order tensor model is fit to the DTI data on a voxel by voxel basis. Finally, the FA maps are calculated from the tensor parameters, which are 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 subject, 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 subject. The mean number (and range) of slices used was 9 (7–12) for the young group and 10 (8–13) for the older group; the means did not significantly differ between groups (P > 1).
Results

Neuropsychological Data
Demographic and neuropsychological data for the 2 age groups are summarized in Table 1. The older adults showed the typical pattern of age-related reduction and preservation of scores on the neuropsychological test battery (Salishouse 2010). Notably, they performed worse than the young group on tests of long-term memory (CVLT) and speeded cognition, but consistent with some previous studies (Morcom et al. 2003; Li et al. 2004), they outperformed the young subjects on the word-reading test employed to estimate crystallized intelligence.

Behavioral Performance

Study Phase
Accuracy on the study task (indexed by the proportion of study pairs attracting the response determined to be the most plausible by the experimenter) was high in both age groups, with means (standard deviations [SDs]) of 0.83 (0.07) and 0.85 (0.07) for the young and older groups, respectively. Neither accuracy nor reaction time (RT: 1641 (253) ms and 1689 (280) ms for young and old, respectively) differed significantly between the groups. In a further analysis, study RTs for word pairs represented as intact pairs at test were segregated according to whether the pairs were correctly endorsed as intact or incorrectly endorsed as rearranged (paralleling the fMRI subsequent memory analyses described later). Analysis of variance (ANOVA) revealed no effects of age or subsequent memory on the RTs, and no evidence for an interaction between the 2 factors. Analogous to our analyses of the fMRI subsequent memory effects, we also computed the correlation across our older subjects between the magnitude of any subsequent memory effect on study RT and later associative recognition memory. The correlation did not approach significance (P > 0.3).

Test Phase
Performance on the associative recognition task is summarized in Table 2. Associative recognition accuracy was indexed as the proportion of intact, rearranged, and new pairs given intact, henceforth referred to as pR. Accuracy was markedly higher in the young than in the older incorrectly judged intact, and pairs incorrectly identified as rearranged (associative misses) on the later memory test.

Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young adults</th>
<th>Older adults</th>
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<tbody>
<tr>
<td>Intact responses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact pairs</td>
<td>0.63 (0.11)</td>
<td>0.52 (0.14)</td>
</tr>
<tr>
<td>Rearranged pairs</td>
<td>0.09 (0.09)</td>
<td>0.23 (0.14)</td>
</tr>
<tr>
<td>New pairs</td>
<td>0.02 (0.05)</td>
<td>0.06 (0.07)</td>
</tr>
<tr>
<td>Rearranged responses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact responses</td>
<td>0.30 (0.08)</td>
<td>0.34 (0.11)</td>
</tr>
<tr>
<td>Rearranged pairs</td>
<td>0.77 (0.09)</td>
<td>0.56 (0.16)</td>
</tr>
<tr>
<td>New pairs</td>
<td>0.23 (0.13)</td>
<td>0.29 (0.13)</td>
</tr>
<tr>
<td>New responses</td>
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<td></td>
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<tr>
<td>Intact pairs</td>
<td>0.07 (0.06)</td>
<td>0.13 (0.08)</td>
</tr>
<tr>
<td>Rearranged pairs</td>
<td>0.14 (0.05)</td>
<td>0.21 (0.10)</td>
</tr>
<tr>
<td>New pairs</td>
<td>0.75 (0.14)</td>
<td>0.64 (0.16)</td>
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</tbody>
</table>

Note: The table shows the proportion of intact, rearranged, and new pairs given intact, rearranged, and new responses.

DTI Data
Mean FA values from the ROIs in the anterior and posterior corpus callosum are presented in Figure 1. ANOVA (factors of age and callosal region) revealed a main effect of age (F_1,52 = 35.41, P < 0.001) that was modified by an age × region interaction (F_1,52 = 15.85, P < 0.001). The main effect reflected higher FA (and hence higher microstructural integrity) in the young subjects. The interaction arose because the age effect was greater in the anterior (mean FA of 0.53 vs. 0.60 for older and young subjects, respectively) than in the posterior (means of 0.62 vs. 0.65) corpus callosum, consistent with numerous prior reports (Sullivan and Pfefferbaum 2006).

fMRI Data
Subsequent memory analyses were based on the contrasts between activity elicited by study pairs correctly endorsed as intact (associative hits) and pairs incorrectly identified as rearranged (associative misses) on the later memory test. Analyses of subsequent memory effects were conducted in 3

![Table 3](https://academic.oup.com/cercor/article-abstract/21/9/2166/384553/2169)

Table 3

<table>
<thead>
<tr>
<th>Variables</th>
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<th>5</th>
<th>6</th>
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| a. Older group (n = 36) | 1. Right front effect — 2. Left front effect 0.83** — 3. pH –0.27 –0.01 — 4. Anterior callosal FA 0.50** 0.34* 0.11 — 5. Posterior callosal FA 0.10 0.11 0.06 0.55** — 6. Default region effect 0.81** 0.70** –0.27 0.47** 0.27 — b. Young group (n = 18) 1. Right front effect — 2. Left front effect 0.64** — 3. pH –0.24 –0.28 — 4. Anterior callosal FA 0.40 0.16 0.00 — 5. Posterior callosal FA 0.31 0.26 0.08 0.31 — 6. Default region effect 0.56* 0.37 0.10 0.05 –0.12 —

*P < 0.05, **P < 0.01, 2-tailed t-tests.
stages. First, regions demonstrating memory effects common to the 2 age groups were identified. Second, we identified regions where effects differed according to age. Third, a region-of-interest (ROI) approach was employed to investigate the relative magnitudes of subsequent memory effects in left and right lateral frontal cortex, focusing on the extent to which the magnitude of right frontal effects was modulated by the variables of age, callosal integrity, and memory performance. The rationale for this last set of analyses is described in the Introduction.

**Age-Invariant Subsequent Memory Effects**

Subsequent memory effects and negative subsequent memory effects common to the 2 age groups were identified by the 2 sides of the main effect of subsequent memory (associative hits > associative misses and vice versa). Each contrast was thresholded at $P < 0.0005$ (uncorrected) with a cluster extent threshold of 9 contiguous voxels. The contrasts were exclusively masked by the age × subsequent memory interaction effect (thresholded at $P < 0.1$, 2-sided) to remove any voxels where the effects differed reliably according to age. This procedure (the results of which are summarized in Table 4) identified age-invariant subsequent memory effects in a left-lateralized cortical network that included the inferior frontal gyrus and temporal and occipital regions, as well as in bilateral hippocampus (see Fig. 2). Age-invariant negative subsequent memory effects were limited to a small region of right prefrontal cortex (Table 4).

**Age-Related Differences in Subsequent Memory Effects**

We searched for regions where subsequent memory effects differed according to age by computing each side of the age × subsequent memory interaction, thresholding each contrast at $P < 0.0005$ (uncorrected) with a 9 voxel cluster extent threshold. No voxels were identified where subsequent memory effects were greater in the young subjects than in the older group. The complementary contrast revealed 7 clusters, localized mainly to midline and right lateral cortical regions, where subsequent memory effects (i.e., associative hits > associative misses) were greater in the older subjects than in the young group (Table 5 and Fig. 3). To characterize the nature of this interaction, we extracted parameter estimates from the peak voxel from each of the clusters listed in Table 5 and subjected the estimates from the 2 groups to separate ANOVAs, employing the factors of region and subsequent memory (associative hit vs. associative miss). ANOVA of the parameter estimates from the older subjects also revealed a main effect of subsequent memory ($F_{1,39} = 5.21, P < 0.05$). In this case, however, the effect reflected larger estimates for later remembered study pairs, that is, reliable “positive” subsequent memory effects. Thus, consistent with the impression given by Figure 4, and in line with prior findings (Miller et al. 2008; Duverne et al. 2009), the age × subsequent memory interaction effects illustrated in Figure 3 reflect a cross-over between negative subsequent memory effects in the young group and positive effects in the older subjects.

As noted in the Introduction, there is prior evidence that the reversal of negative subsequent memory effects in older subjects is associated with relatively poor memory performance (Miller et al. 2008; Duverne et al. 2009). We therefore computed the correlation across our older subjects between their pR scores and the mean magnitude of their positive

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**Table 4**

Peak voxels of positive and negative subsequent memory effects common to young and older adults

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<tr>
<td>24</td>
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<td>27</td>
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**Table 5**

Peak voxels of age group × subsequent memory interaction effects

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**Figure 2.** Regions demonstrating subsequent memory effects common to young and older subjects. (A) Effects rendered onto the left hemisphere of the 3D single-subject MNI reference brain. (B) Bilateral hippocampal subsequent memory effects superimposed on the normalized T1-weighted image averaged across all subjects.

**Figure 3.** Interaction effects identifying regions where subsequent memory effects were greater in older than in young subjects. The effects are superimposed on normalized mean T1-weighted images.
resulting partial correlation coefficient was associative pR after controlling for anterior callosal FA. The memory effects and anterior callosal FA, we computed the correlation with posterior callosal FA was nonsignificant. In neuronal degradation (Kochunov et al. 2007). There was interaction (Fig. 3) and callosal FA, another putative index of subjects between the subsequent memory effects averaged their positive subsequent memory effects in a medial parietal region that demonstrated negative effects in young subjects correlated significantly with a putative index of neural dysfunction (amyloid deposition as measured by imaging of Pittsburgh Imaging Compound B or PiB; Sperling et al. 2009). In light of this finding, we computed the correlation in our older subjects between the subsequent memory effects averaged across the regions demonstrating an age x subsequent memory interaction (Fig. 3) and callosal FA, another putative index of neuronal degradation (Kochunov et al. 2007). There was a positive association between the subsequent memory effects and anterior callosal integrity (see Table 3a). By contrast, the correlation with posterior callosal FA was nonsignificant. In light of the association between the older subjects’ subsequent memory effects and anterior callosal FA, we computed the correlation between the magnitude of the effects and associative pR after controlling for anterior callosal FA. The resulting partial correlation coefficient was -0.367 (P < 0.05, 2-tailed). Thus, as reported previously (Miller et al. 2008; Duverne et al. 2009), the degree to which negative subsequent memory effects are attenuated or reversed in older subjects is inversely associated with performance on the later memory test.

**Effects of Age on Frontal Subsequent Memory Effects**

To permit an unbiased assessment of the influence of age on left and right lateral frontal subsequent memory effects, we used the same ROI approach adopted by Duverne et al. (2009).

First, the peak voxels demonstrating subsequent memory effects in ventral [-39 33 -9], middle [-51 27 9], and dorsal [-45 12 21] left inferior frontal gyrus were identified from the across-group main effect of subsequent memory. We then extracted the mean parameter estimates across all voxels within a 5 mm radius of each peak and from homotopic ROIs in the right hemisphere. Preliminary analyses demonstrated that the subsequent memory effects did not demonstrate ROI x age interactions. The parameter estimates were therefore collapsed across the ROIs to provide single estimates of the size of left and right frontal subsequent memory effects for each subject, and these data are shown in Figure 5. ANOVA employing the factors of age, subsequent memory (associative hit vs. associative miss), and hemisphere revealed main effects of subsequent memory (F(1,52) = 199.94, P < 0.001) and hemisphere (F(1,52) = 12.89, P < 0.01) and an interaction between these 2 factors (F(1,52) = 53.83, P < 0.001). Follow-up analyses revealed that, across the 2 age groups, left frontal subsequent memory effects were reliable (F(1,52) = 30.80, P < 0.001), whereas right frontal effects were not (F(1,52) < 1). The same patterns were evident when the data from each age group were subjected to separate ANOVAs. Thus, these analyses failed to demonstrate an influence of age on the magnitude of right frontal subsequent memory effects, contrary to the findings of Morcom et al. (2003) and Duverne et al. (2009).

**Relationship between Right Frontal Subsequent Memory Effects and Memory Performance**

In light of our prior finding (Duverne et al. 2009) of a negative relationship in older subjects between the magnitude of right frontal subsequent memory effects and memory performance, we used partial correlation to control for variance in the size of the left frontal effect and investigated whether a similar relationship existed in the present data. Controlling for the magnitude of left frontal subsequent memory effects removes the influence of variables that modulate the magnitude of subsequent memory effects for functionally uninteresting reasons (e.g., individual differences in hemodynamic transfer functions) and also ensures that the correlation between right frontal effects and a variable of interest, such as callosal FA, reflects uniquely shared variance. The correlation was -0.468 (P < 0.005, 2-tailed) indicating that, as in our prior study, memory performance in the older subjects was negatively associated with the size of right frontal subsequent memory effects. The scatter plot of the adjusted values is illustrated in Figure 6. The degree of asymmetry in the older subjects’ frontal subsequent memory effects was also correlated with pR. This was the case for both the difference between the left and right frontal effects (Left - Right, r = 0.358, P < 0.05) and for an asymmetry index that corrected for the overall size of the effects [(Left - Right)/(Left + Right), r = 0.367, P < 0.05]. These findings indicate that the greater the size of right frontal effects relative to the effects on the left, the worse is the performance on the later memory test.

**Relationship between Right Frontal Subsequent Memory Effects and Callosal Integrity**

As was noted in the Introduction, it has been hypothesized that age-related right frontal over-recruitment is a consequence of...
weakened interhemispheric inhibition resulting from a reduction in callosal integrity (Logan et al. 2002; Persson et al. 2006; Sullivan and Pfefferbaum 2006). According to this hypothesis, therefore, the size of right frontal subsequent memory effects and anterior callosal FA should be negatively correlated. We investigated this prediction by using partial correlation to characterize the relationship in the older subjects between the magnitude of their right frontal subsequent memory effect and anterior callosal FA (again controlling for variance in left frontal effects). The correlation was positive (0.416, $P < 0.025$, 2-tailed), indicating that right frontal subsequent memory effects in older individuals are associated with relatively greater, and not relatively lower, anterior callosal integrity. By contrast, the correlation with posterior callosal FA was far from significant ($r = 0.007$). The scatter plot of the adjusted values for anterior callosal FA and right frontal subsequent memory effects is illustrated in Figure 7 (for the raw correlations, see Table 3a).

**Multiple Regression Analysis**

The foregoing analyses indicate that, after controlling for variance in the size of left frontal subsequent memory effects, callosal FA and memory performance in our older subjects are each correlated with the magnitude of their right frontal subsequent memory effects, albeit in opposite directions. Therefore, we used multiple regression to determine whether these 2 variables, along with the magnitude of left frontal subsequent memory effects, accounted for independent proportions of the variance in the right frontal effects of the older group (the raw correlations between the variables entered into the following regression analyses are given in Table 3 for the older and, for comparison, the younger subjects). The regression model was highly significant ($F_{3,55} = 51.80, P < 0.001, R^2 = 0.829$). The model is summarized in Table 6, where it can be seen that each of the 3 predictor variables accounts for a significant proportion of the variance. We expanded the model to include the data from the young subjects also, adding age as a fourth predictor variable. This model also was highly significant ($F_{4,53} = 30.80, P < 0.001, R^2 = 0.716$), with all variables other than age demonstrating significant effects (all $P < 0.005$). Whereas this result should be interpreted with caution in light of the size of the young sample (which is too small to allow a 3-predictor regression model to be fit to these data alone), it raises the possibility that the relationship between right frontal subsequent memory effects, performance, and callosal integrity is not confined to older individuals.

![Figure 6](Image)

**Figure 6.** Partial plot showing the relationship in older subjects between right frontal subsequent memory effects and $pR$ after controlling for the size of the left frontal effect.

![Figure 7](Image)

**Figure 7.** Partial plot showing the relationship in older subjects between right frontal subsequent memory effects and anterior callosal FA after controlling for the size of the left frontal effect.

**Predictors of Memory Performance**

In a final set of analyses, we used multiple regression to address the question of how well the combination of frontal subsequent memory effects and anterior callosal FA predicted memory performance in older subjects. Thus, we constructed a regression model with associative $pR$ as the dependent variable and with anterior callosal FA and left and right frontal subsequent memory effects as the predictor variables. The model accounted for a significant proportion of the variance in performance ($R^2 = 0.339, F_{3,55} = 5.47, P < 0.005$). As is evident from Table 7, the magnitude of right frontal subsequent memory effects was significantly and negatively associated with $pR$. Interestingly, the left frontal effect and callosal FA also explained significant proportions of the variance in memory performance, in each case demonstrating a positive relationship. When callosal FA was dropped from the model, leaving only left and right frontal subsequent memory effects as the predictor variables, the fit (and the contributions of each variable) remained significant ($R^2 = 0.219, F_{2,55} = 4.64, P < 0.025$).

To assess the generality of the ability of foregoing predictor variables to account for variance in older subjects’ memory function, we ran the above regression analysis using as dependent variables 2 composite measures of memory performance derived from our neuropsychological test battery, indexing recall on the CVLT and the NVU paragraph tests, respectively. In the case of the CVLT, the model was significant ($R^2 = 0.282, F_{2,55} = 4.20, P < 0.025$), with both left (positive relationship) and right (negative relationship) frontal subsequent memory effects accounting for significant proportions of the variance in CVLT scores. The model for NYU paragraph recall was not significant ($P > 0.2$).

**Table 6**

Results of the regression model investigating variables that predict the magnitude of the older subjects’ right frontal effects

<table>
<thead>
<tr>
<th>Model</th>
<th>$b$</th>
<th>SE $b$</th>
<th>$\beta$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(constant)</td>
<td>-1.998</td>
<td>0.585</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left frontal effect</td>
<td>0.571</td>
<td>0.060</td>
<td>0.734</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anterior callosal FA</td>
<td>4.038</td>
<td>1.119</td>
<td>0.282</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$pR$</td>
<td>-1.078</td>
<td>0.272</td>
<td>-0.292</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: $b$, unstandardized coefficient; SE $b$, standard error of the unstandardized coefficient; and $\beta$, standardized coefficient.
Discussion

As reported previously (Morcom et al. 2003; Duverne et al. 2009), age-invariant subsequent memory effects were evident in several cortical and MTI regions, including left inferior frontal, parietal and fusiform cortex, and bilateral hippocampus. Also in line with prior reports (Miller et al. 2008; Duverne et al. 2009), regions where negative subsequent memory effects were evident in young subjects demonstrated reliable positive effects in the older group. Crucially, we also replicated our prior finding (Duverne et al. 2009) of a negative relationship in older subjects between right frontal subsequent memory effects and memory performance. There was no support, however, for the prediction that right frontal subsequent memory effects would be negatively correlated with callosal FA. To the contrary, there was a reliable positive relationship between these variables. Finally, we used multiple regression to address the extent to which the variables of callosal FA and left and right frontal subsequent memory effects collectively accounted for variance in memory function among our older subjects. The regression model accounted for more than 30% of the variance not only in performance on the subsequent associative recognition test but also on a standardized neuropsychological memory test, the CVLT. Below, we discuss the implications of these findings for the understanding of age-related episodic memory decline.

Behavioral Results

Performance on the study task did not differ according to age or accuracy on the later memory test. Thus, neither the between-group nor the memory performance-related differences that were observed in fMRI subsequent memory effects are likely to have arisen because of a confound with differential study performance. By contrast, young subjects markedly outperformed the older group on the associative recognition test, consistent with prior findings (for a review, see Old and Naveh-Benjamin 2008).

A reviewer noted that the contrast used to assess associative recognition performance—the difference between the proportion of intact judgments given to intact versus rearranged test pairs (pR)—and the contrast used to identify fMRI subsequent memory effects—the difference in activity elicited by study pairs later judged as intact versus rearranged—are discrepant, raising the question of how the performance and fMRI measures are related. We assume that the memory test differentiated intact pairs according to whether the strength of their memory representation was sufficient to exceed the response criterion for an intact response. Thus, fMRI subsequent memory effects reflect differences in the encoding-related activity elicited by study items that, at retrieval, on average gave rise to a relatively strong versus a relatively weak recollection signal. If the variance in the memory strength of studied test items is largely determined by factors other than those operating at encoding (e.g., factors such as forgetting rate or retrieval cue processing), then a subsequent memory contrast will reveal null effects. By contrast, if processes operating at encoding do influence later memory strength, subsequent memory effects should be evident in regions that support these processes. By investigating the relationship across subjects between subsequent memory effects and an appropriate measure of memory strength (pR in the present case), it is possible to determine whether the magnitude of the effects in different regions covaries with strength, and if so in which direction.

DTI Findings

As has been reported previously (O'Sullivan et al. 2001; Head et al. 2004; Pfefferbaum et al. 2005; Kochunov et al. forthcoming), callosal FA was lower in the older group, and this age effect was reliably greater for the anterior than the posterior callosum. Why there should be a posterior–anterior gradient in age-related loss of callosal integrity is not clear (for discussion, see Kochunov et al. forthcoming), but an obvious implication of this phenomenon is that interhemispheric communication between the frontal cortices should be especially susceptible to increasing age (Logan et al. 2002; Persson et al. 2006; Sullivan and Pfefferbaum 2006). Loss of anterior callosal integrity may also be associated with more general degradation of cortical function (Kochunov et al. 2007; Inoue et al. 2008). Notably, Inoue et al. (2008) reported that anterior callosal FA in a small group of older subjects (n = 15, aged 70–78 years) varied with both the integrity of the white matter underlying left and right frontal cortex and the bilateral frontal cortex metabolism as assessed with 18F-fluoro-2-deoxy-glucose positron emission tomography.

Unlike in the study of Persson et al. (2006), but in line with some other reports (Kennedy and Raz 2009; Voinieskos et al. forthcoming), we did not find a direct relationship between anterior callosal FA and memory performance. As we discuss below, however, anterior (but not posterior) callosal FA turned out to be an important explanatory variable with respect to older subjects’ subsequent memory effects. For both the right frontal effects and the subsequent memory effects in regions belonging to the “default network,” anterior callosal FA accounted for a significant proportion of the variance in the effects. Furthermore, a relationship between the “default” effects and memory performance was only evident after controlling for callosal FA. As is discussed below, it is presently unclear to what extent the influence of callosal FA on these fMRI effects is mediated specifically by ease or efficacy of interhemispheric communication, as opposed to neural integrity more generally. Regardless, the present findings suggest that the relationship in older individuals between fMRI memory effects and performance cannot be fully characterized without taking this (and, most likely, additional) structural brain measures into account.

Frontal Subsequent Memory Effects

Echoing the findings from studies of associative encoding in young subjects (Jackson and Schacter 2004; Park and Rugg 2008), robust age-invariant subsequent memory effects were evident along the extent of the left inferior frontal gyrus. Unlike in the 2 studies that preceded the present one, however

Table 7

Results of the regression model investigating variables that predict older subjects’ associative memory performance (pR)

<table>
<thead>
<tr>
<th>Model</th>
<th>b</th>
<th>SE b</th>
<th>β</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(constant)</td>
<td>−0.587</td>
<td>0.348</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left frontal effect</td>
<td>0.167</td>
<td>0.055</td>
<td>0.795</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Right frontal effect</td>
<td>−0.305</td>
<td>0.077</td>
<td>−1.129</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anterior callosal FA</td>
<td>1.562</td>
<td>0.650</td>
<td>0.404</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Note: b, unstandardized coefficient; SE b, standard error of the unstandardized coefficient; and β, standardized coefficient.
Aging, Over-recruitment, and Memory Performance

cortical over-recruitment is compensatory (e.g., Cabeza et al. 2002; Park and Reuter-Lorenz 2009)—is that right frontal subsequent memory effects reflect the engagement of processes that compensate for functional decline in left frontal cortex but only partially. One possibility is that the emergence of right frontal subsequent memory effects reflects the engagement of processes that compensate for the failure of left frontal cortex to meet the online demands of the study task. Crucially, though, right frontal recruitment contributes little or nothing to episodic memory encoding, which remains the province of the left hemisphere (for evidence that encoding remains dependent upon left frontal cortex with increasing age, see Rossi et al. 2004). According to this “partial compensation hypothesis,” therefore, the negative relationship between right frontal subsequent memory effects and memory performance arises because the effects are inversely correlated with the functional integrity of left frontal regions necessary for episodic encoding of verbal information. Testing this hypothesis will likely require the employment of methods—such as transcranial magnetic stimulation (cf., Rossi et al. 2004)—that permit assessment of the consequences of disrupting right frontal function during an encoding task in individuals with large versus small right frontal subsequent memory effects.

Neural Predictors of Memory Performance

When combined in a single multiple regression model, left and right frontal subsequent memory effects, along with anterior callosal FA, each independently explained variance in associative recognition performance and collectively accounted for around 36% of the total variance. This finding—strengthened by the fact that variation in frontal subsequent memory effects alone accounted for over 20% of the variance in later memory performance—strongly suggests that variation in the efficacy of encoding operations accounts for a significant fraction of the variance in verbal episodic memory function among healthy older individuals.

Whereas the negative correlation between associative recognition performance and right frontal effects was to be expected in light of the prior analyses, the finding of a relationship between performance and left frontal effects was unanticipated. This finding is significant for 2 reasons. First, it indicates that left and right frontal subsequent memory effects can be doubly dissociated with respect to later memory performance, providing compelling evidence for the specificity of the negative relationship between the processes reflected by right frontal effects and episodic encoding. Second, the finding suggests that preservation of efficient verbal encoding in the face of advancing age is associated with recruitment of the same left frontally mediated encoding operations engaged in the young and not by the engagement (over-recruitment) of homotopic cortex.

The ability of the frontal subsequent memory effects to predict memory performance was not limited to performance on the experimental subsequent memory task but extended to CVLT recall. This finding is of particular significance because the CVLT was administered up to several weeks before the MRI session. Thus, left and right frontal subsequent memory effects reflect temporally stable cognitive processes that are not idiosyncratic to the specific experimental circumstances in which they are elicited.

Negative Subsequent Memory Effects

As in a previous study of associative encoding in young subjects (Park and Rugg 2008), robust negative subsequent memory
effects were evident in the young group in a widely distributed set of cortical regions. These regions largely overlap with the “default-mode network,” a set of regions that collectively exhibit task-induced deactivation (greater activity during rest than during task engagement) and whose resting state activity is strongly intercorrelated (Buckner et al. 2008). It is widely thought that the regions belonging to this network support one or more “internally directed” processes that must be disengaged in order to permit optimal allocation of processing resources to an external stimuli event such as a study item. From this perspective, therefore, negative subsequent memory effects reflect the benefit to episodic encoding that ensues when resources are optimally redirected from internal to external events (Daselaar et al. 2004; Park and Rugg 2008).

The finding that negative subsequent memory effects were absent (and, indeed, reversed) in the older group is broadly consistent with several previous reports (Morcom et al. 2003; Kukolja et al. 2007; Miller et al. 2008; Duverne et al. 2009). In the present case, negative effects were absent in the older group in every region where the effects were reliable in the young (Figs. 3 and 4). Thus, age appears to have affected the functioning of an entire cortical network, rather than just 1 or 2 especially vulnerable regions.

As in previous studies (Miller et al. 2008; Duverne et al. 2009), there was a trend in the older subjects for memory performance to be inversely correlated with the degree to which negative subsequent memory effects in putative default regions were attenuated or reversed. As discussed by Duverne et al. (2009), a possible explanation for this finding is that it reflects the deleterious consequences of failing to disengage the default-mode network and reallocate processing resources to the study items. It is not obvious from this account, however, why the young subjects’ negative effects should have been replaced in older subjects by significant positive, rather than by null, effects. The account is further challenged by the finding that anterior callosal FA correlated positively with the size of null, effects. The account is further challenged by the finding that anterior callosal FA correlated positively with the size of null, effects. The account is further challenged by the finding that anterior callosal FA correlated positively with the size of null, effects. The account is further challenged by the finding that anterior callosal FA correlated positively with the size of null, effects.

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**Notes**
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**References**


