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Deficits in Process-Specific Prefrontal and Hippocampal Activations Contribute to Adult Age Differences in Episodic Memory Interference

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The ability to distinguish currently relevant from familiar but irrelevant memories is important in everyday life. We used functional magnetic resonance imaging to examine the neural correlates of age differences in the ability to withstand interference from similar past events. Younger and older adults worked on a continuous recognition task consisting of 3 consecutive runs. Each run was composed of the same set of word pairs, and participants were instructed to recognize word pair repetitions *within* runs. The monitoring demands associated with rejecting familiar, but currently irrelevant information were assumed to increase over consecutive runs. Over runs, older, but not younger adults showed decline in memory performance, whereas younger, but not older adults showed increasing engagement of anterior prefrontal cortex. Individual differences in cortical thickness and task-related activation of anterior prefrontal areas predicted performance differences within and across age groups. Compared with younger adults, older adults also showed a reduced hippocampal response to novel associations of familiar stimuli. We conclude that monitoring deficits due to impaired involvement of prefrontal regions and reduced hippocampal responses to associative novelty contribute to aging-related deficits in disambiguating the contextual information of familiar events.

Keywords: aging, anterior frontal, associative novelty, FMRI, hippocampus, memory

Introduction

Episodic memory, the ability to remember past events bound in particular time and place (Tulving 1972), deteriorates with increasing age (Spencer and Raz 1995; Park et al. 2002; Rönnlund et al. 2005; Old and Naveh-Benjamin 2008). Old age is also accompanied by increased susceptibility to false memory, that is, the tendency to remember events that actually did not happen (Kliegl and Lindenberger 1993; Schacter et al. 1997; Jacoby and Rhodes 2006), particularly when event features are highly familiar (Bender et al. 2010; Shing et al. 2008). However, little is known about older adults' ability to distinguish memories for a current event from memories of highly similar past events, as needed in many everyday situations. One such example is remembering where you parked your car today or whether a medication that needs to be taken daily has already been taken today (Schnider et al. 2000; Schnider 2003). Age-related declines in this ability might result in increased propensity to commit memory errors. In this study, we used a modified version of the repeated continuous recognition task (rCRT; Schnider 2003) to examine adult age differences in the neural mechanisms that underlie the ability to distinguish among memories for highly familiar events, which is critical for maintaining independence in old age (Park and Liu 2007; Lindenberger et al. 2008).

Existing evidence from patient and neuroimaging studies suggests that regions in the medial-temporal lobes (MTL) and the prefrontal cortex (PFC) are involved when committing memory errors (Schacter et al. 1996, 1998). For instance, Cabeza et al. (2001) reported similar activation for true and false memories in anterior MTL, whereas blood-oxygen-level–dependent (BOLD) responses in bilateral PFC were stronger for true than for false memories. These findings are consistent with the idea that MTL regions are involved in the generation of false memories, whereas PFC regions contribute to reducing false memories by exerting monitoring control over interference in episodic memory (Schacter and Slotnick 2004).

In healthy adults, MTL regions, especially the hippocampus, but also PFC show age-related decline in gray and white matter volumes (Raz et al. 2005; Raz and Rodrigue 2006). So far, only a handful of studies have investigated how functional changes in MTL and PFC regions contribute to age-related increase in illusory memory (Dennis et al. 2007, 2008; Giovanello et al. 2009; Duarte et al. 2010). These studies consistently found that, compared with younger adults, older adults showed decreased activation in the hippocampus for true memories (Dennis et al. 2007, 2008; Giovanello et al. 2009; see also Stevens et al. 2008). In contrast, older adults showed increased activation in other temporal lobe regions when committing false memories. Specifically, using a modified version of the Deese–Roediger–McDermott (DRM) paradigm (Roediger and McDermott 1995), Dennis et al. (2007) demonstrated that false recognition in older adults was associated with higher activation in the middle temporal region, presumably reflecting higher reliance on semantic gist processing in old age. Another study with the conjunction error paradigm (Giovanello et al. 2009) found that falsely endorsing conjunction lures was associated with higher activation in the right parahippocampal gyrus in older adults compared with younger adults, presumably reflecting increased reliance on familiarity-based processing with aging (Daselaar et al. 2006).

Compared with medial-temporal regions, the contributions of PFC to adult age differences in memory errors are less clear. Using a source memory task with object drawings, Duarte et al. (2010) showed that areas in the dorsomedial PFC were more strongly activated for familiarity-based true compared with false recognition in younger adults, whereas neural activation in this area did not distinguish true and false recognition in older adults, mainly due to diminished activation for true recognition in this age group. In contrast, Giovanello et al. (2009) found the opposite pattern of age differences, namely, higher activity modulation for older adults in inferior and middle PFC during correct recognition of previously studied compound words compared with false recognition of novel conjunctions (see also Dennis et al. 2007,

2008). Taken together, the results of these studies show mixed patterns of age differences in PFC activation modulation, and the exact contribution of PFC to adult age differences in memory errors remains to be elucidated.

PFC might be related to false recognition in old age due to older adults' deficit in engaging monitoring processes that are needed to overcome interference from strong feelings of familiarity brought by previous experience with a stimulus (Schacter 1996). Monitoring processes are engaged to evaluate representations retrieved from episodic memory in the context of current task goals and agendas, in particular whenever the similarity and familiarity of retrieved representations is high (Burgess and Shallice 1996; Rugg and Wilding 2000; Fletcher and Henson 2001; Moscovitch and Winocur 2002; Badre and Wagner 2005; Mitchell and Johnson 2009). On the neural level, monitoring processes have been associated with increased activity modulation in lateral PFC regions, especially in the anterior PFC (APFC; Koechlin et al. 1999; Ranganath et al. 2000; Dobbins et al. 2002; but see Henson et al. 1999). Accordingly, APFC is consistently engaged during retrieval of source information (Nolde et al. 1998; Rugg et al. 1999; Ranganath et al. 2000; Dobbins et al. 2002; Nyberg et al. 2003), as well as in episodic memory tasks, in which the same context was associated with multiple events (Burgess et al. 2001; King et al. 2005), and during resolution of proactive interference in working memory (Braver et al. 2001; Nyberg et al. 2003; Badre and Wagner 2005; Nee et al. 2007).

Thus far, adult age differences in the neural mechanisms supporting the ability to monitor memory representations and withstand interference have been limited to working memory (Jonides et al. 2000; Hasher et al. 2002; Gazzaley et al. 2005; Clapp and Gazzaley 2012). For instance, Campbell et al. (2012) examined memory performance and neuronal activation in younger and older adults during a 1-back working memory task that also required control of relevant and irrelevant information. They demonstrated lower engagement of a frontal-parietal control network, also involving bilateral APFC, in older adults compared with younger adults. At the behavioral level, the ability to resolve interference decreases in old age (Zacks et al. 2000). Compared with younger adults, older adults are more susceptible to proactive interference in episodic memory because of difficulties to avoid memory errors for events that are highly familiar due to prior experience (Kliegl and Lindenberger 1993; Jacoby and Rhodes 2006). So far, no study has examined the extent to which age differences in prefrontal mechanisms supporting the ability to withstand interference contribute to increased false memory in aging. Hence, we aimed to investigate age differences in the neural mechanisms of monitoring processes crucial for resolving interference from previous presentation of the same stimuli. In particular, we examined whether age differences in functional activation under conditions of high proactive interference are related to older adults' increased susceptibility to commit memory errors.

Only a few studies have investigated the relationship between functional and structural changes with aging, and their unique and combined contributions to adult age differences in memory performance. While some of them did not find an association between structure and function in healthy older adults (Johnson et al. 2000; Madden et al. 2010), other studies reported less activity with less structural integrity in aging (Shafto et al. 2010; Kalpouzos et al. 2012; Davis et al. 2012). Still other studies found that greater functional activation in older adults was accounted for by lower structural integrity (Nyberg et al. 2010). In one study, age-related volume loss in the right middle frontal gyrus was associated with a disruption of retrieval-related activations in the episodic memory network activated by younger adults, presumably contributing to retrieval deficits in older adults (Rajah et al. 2011). Informed by these conflicting findings, we explored associations among structural integrity, functional activation, and the ability to reject familiar, but irrelevant information within and across age groups.

Correct rejection of information that seems familiar might also depend on the ability to detect novel configurations in the input as not seen before. Recent behavioral evidence suggests that the age-related decline in associative recognition is primarily driven by increased propensity to make conjunction errors by endorsing recombined pairs that consist of previously studied elements (Castel and Craik 2003; Old and Naveh-Benjamin 2008; Shing et al. 2008). The hippocampal formation plays a prominent role not only in forming and retrieving associations (Cohen and Eichenbaum 1993; Davachi and Wagner 2002; Aggleton and Brown 2006; Ranganath 2010), but also in detecting novel conjunctions of familiar stimuli (Kumaran and Maguire 2007, 2009). Accordingly, several studies (Düzel et al. 2003, 2004; Köhler et al. 2005; Dudukovic and Wagner, 2007) demonstrated that regions in the anterior hippocampus mediate associative novelty detection (see also Chen et al. 2011; Duncan et al. 2012). For both structural (Shing et al. 2011) and functional (Yassa et al. 2011) reasons, these mechanisms may decrease in efficiency with advancing adult age. However, the association between adult age differences in the hippocampal response to novel associations and differences in the susceptibility to memory conjunction errors has not yet been studied. Thus, the second major objective of this study was to determine whether the neural mechanisms of correctly rejecting novel conjunctions of familiar stimuli differ between younger and older adults. Furthermore, we examined the role of associative novelty detection in false memory for novel conjunctions.

We used event-related functional magnetic resonance imaging (fMRI) to test 28 younger adults and 30 older adults with the rCRT task, originally developed to characterize monitoring deficits in confabulating patients (Schnider 2003). Immediately before fMRI scanning, participants were familiarized with a set of word pairs. During scanning, they performed 3 consecutive runs of the task (Fig. 1; for detailed task description see Experimental Procedure section). In each run, participants viewed the same set of word pairs. Some of these pairs were repeated within the run (*target pairs*), the remaining ones were not (*lure pairs*). A subset of the lure pairs were recombined within a given run, such that the 2 words of the pair were familiar, but the conjunction between them was novel (*rearranged pairs*). Finally, novel word pairs that were never seen before during the experimental session were included in each run (*new pairs*). On each run, participants were instructed to indicate reoccurrences of the exact same word pair repeats within the same run, disregarding whether a pair had appeared in any of the previous runs. The present task setting is structurally similar to many reoccurring daily situations of trying to remember, for example, whether a medication that needs to be taken daily has already been taken, or where a car has been parked today rather than

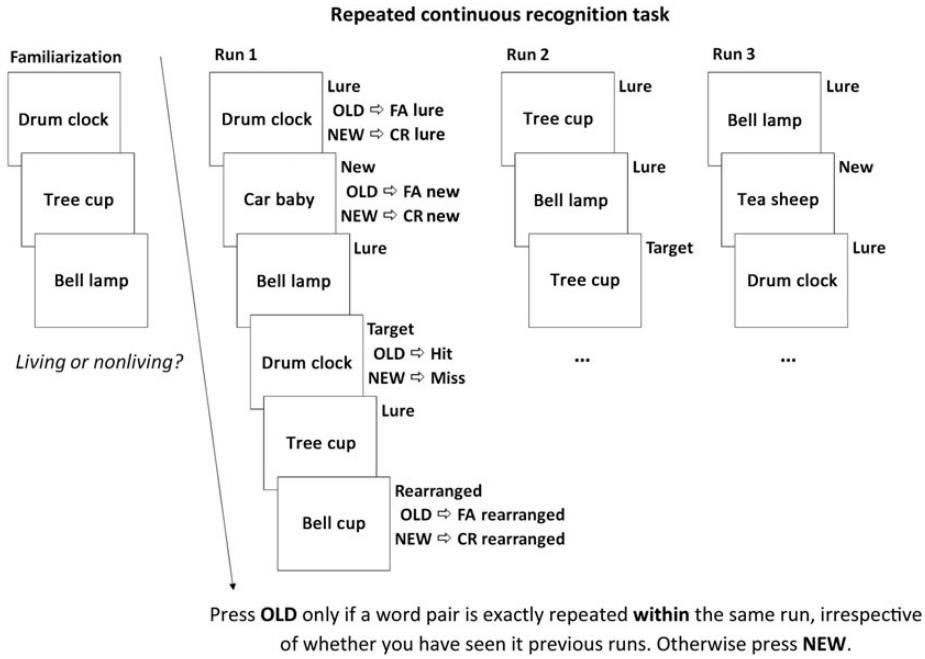

Figure 1. Experimental task design. FA, false alarm, CR, correct rejection.

yesterday, thus making the task ecologically relevant for the study of aging cognition.

Using this paradigm, we tested 2 main hypotheses. First, we expected that familiarity of the lure pairs would increase through multiple repetitions across runs, leading to higher demands on monitoring processes (Gilboa et al. 2006). For example, we expected that correctly rejecting "Drum-Clock" in run 3 (see Fig. 1) would be more difficult compared with run 1, because in run 1, this word pair has been encountered only once before in the familiarization phase, whereas in run 3, participants had seen it multiple times in the preceding runs, resulting in higher interference due to multiple previous presentations. We predicted that increased need to overcome interference from previous occurrences of the lure pairs would be reflected in an increased task-induced BOLD response in PFC across runs (Schnider et al. 2000). We hypothesized that PFC activity modulation would be less pronounced in older adults relative to younger adults, in line with older adults' deficits in withstanding proactive interference in memory (Kliegl and Lindenberger 1993; Jonides et al. 2000). Second, as memory for lure pairs is strengthened by across-run repetitions, we expected that the detection of novel word conjunctions—and hence the rejection of rearranged pairs—would become easier from run to run. This hypothesis is based on findings that repeated presentation leads to decreased false recognition of rearranged pairs (Light et al. 2004; Kilb and Naveh-Benjamin 2011; but see Kelley and Wixted 2001). Importantly, each rearranged pair was seen only once in the task. Hence, although the single words were familiar to the participants, the recombination of words was never repeated within and across runs. Hence, we expected that the rearranged pair "Bell-Cup" in run 1 would be more difficult to reject, as the participants encountered the corresponding lure pairs "Bell-Lamp" and "Tree-Cup" only twice before (in the familiarization phase and run 1), compared with rearranged pairs in later runs when the participants have already repeatedly seen the corresponding lure pairs in the preceding runs. Given that detecting novel parts in the input is facilitated by strengthening memory representations (cf. Johnson et al. 1993; Kumaran and Maguire 2007), we tested the extent to which task-induced MTL BOLD response, in particular in the hippocampus, would increase across runs of the task, reflecting this facilitation effect. Based on earlier findings that, compared with younger adults, older adults show less benefit from repeated encounters of the same stimuli to reduce false recognitions (Jacoby 1999; Light et al. 2004; Kilb and Naveh-Benjamin 2011), we expected that older adults in the present study would exhibit lower performance on novel word conjunctions. We tested whether hippocampal modulation to novel word conjunctions differs between younger and older adults.

Materials and Methods

Participants

Participants in this study were 28 younger adults (mean age 24.92 ± 1.84 years, 15 females) and 30 older adults (mean age 72.28 ± 2.01 years, 13 females). All participants were right-handed native German speakers, had normal or corrected-to-normal vision, had no history of psychiatric or neurological disease, and did not take psychiatric medication. Older adults were screened for cognitive impairment with the Mini-Mental State Exam (Folstein et al. 1975), $M = 29.6$, SD = 0.73. Both age groups were equated on levels of formal education ($P > 0.10$).

Experimental Procedure

In the first session, participants were trained on getting comfortable with the MRI environment inside a scanner simulator. In the second session, participants performed the familiarization phase and 3 consecutive runs of the rCRT while lying in the MRI scanner.

During familiarization, each word pair was presented for 3 s, followed by a fixation cross (500 ms). Participants had to indicate via button press whether none, one, or both of the words depicted a

living object. Structural sequences were scanned during this phase of the experiment. Following this, participants performed 3 runs of the rCRT task during fMRI scanning (see Fig. 1). In each run, the complete task set of word pairs was presented once (termed *lure pairs*), resulting in 132 trials for younger adults and 102 trials for older adults. List length differed between groups to render the task manageable for both age groups. Owing to the preceding familiarization task, the lure pairs were already familiar to the participants in run 1. Additionally, one-third of the lure pairs (44 pairs for younger adults, 34 pairs for older adults) were selected to reappear once in each run (termed *target pairs*). Participants' task was to respond "OLD" only to target pairs (i.e., those pairs that are repeated *within* the same run) and "NEW" to all other pair types. For example, "Drum-Clock" (see Fig. 1) is a *lure pair* when presented the first time in run 1, but becomes a target pair when repeated in run 1. Target pairs were not repeated across runs, meaning that having been presented as a target pair in run 1, "Drum-Clock" would appear only as a *lure pair* in runs 2 and 3, respectively, but would not be repeated within runs 2 and 3. Another one-third of the lure pairs were selected to reappear as recombined pairs, with the left word of a given lure pair presented in conjunction with the right word from another lure pair (termed *rearranged pairs*). The rearranged pairs were unique, such that although the single words were familiar to the participants, the recombination of words was never repeated within and across runs. Finally, for both age groups, 25 novel word pairs were presented in each run (termed *new pairs*). For example, the word pair "Car-Baby" was presented only once in the whole experiment (see Fig. 1), and was also not included in the familiarization phase of the experiment. Within runs, lure, target, rearranged, and new pairs were presented in randomized order in an event-related design. Each word pair was displayed for 3000 ms, followed by a jittered fixation period, optimized with Optseq 2 (Dale 1999). Participants were instructed to indicate reoccurrences of exactly the same word pair within the ongoing run (i.e., target pairs) by using 4 different buttons—"sure new," "unsure new," "unsure old," and "sure old."

Data Acquisition

Whole-brain MRI data were collected with a Siemens 3T Trio Magnetom. Functional data were acquired using an echo-planar imaging sequence (TR, 2000 ms; TE, 30 ms; flip angle, 80°; FOV, 216 mm; matrix, 72 × 72; voxel size, 3 × 3 × 3 mm^3; 36 slices). Each run was preceded by 4 dummy volumes to achieve a steady state of tissue magnetization. For registration of the functional images, 2 structural sequences were collected; one T_2-weighted turbo-spin echo sequence (TR, 8170 ms; TE, 93 ms; matrix, 192 × 256; voxel size, 1 × 1 × 3 mm^3) in the same orientation as the functional sequences; one high-resolution T_1-weighted MPRAGE sequence (TR, 1550 ms; TE, 2.34 ms; TI, 900 ms; matrix, 350 × 263 × 350; voxel size, 1 × 1 × 1 mm^3).

Statistical Analysis: Behavioral Data

Repeated-measures ANOVAs were conducted with age as a between-subject factor and run as a within-subject factor. No outliers were found for any of the reported behavioral measures at $P < 0.001$ (2-tailed test). There were no age differences in the amount of "sure" and "unsure" correct responses across runs and stimuli types, and they were collapsed for the present analysis.

Statistical Analysis: fMRI Data

Data were preprocessed and analyzed using FEAT in FSL (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl, Smith et al. 2004). Preprocessing included nonbrain tissue removal, slice time and motion correction, and spatial smoothing using an 8-mm full-width half-maximum Gaussian filter. A prewhitening technique was used to account for the intrinsic temporal autocorrelation of BOLD imaging. Low-frequency artifacts were removed by applying a high-pass temporal filter (Gaussian-weighted straight-line fitting, sigma = 50 s). Registration to high-resolution and standard images was carried out using FLIRT (Jenkinson and Smith 2001).

Individual time series were modeled with separate regressors for correct responses to each of the 4 stimuli types (lure, rearranged, new, and target pairs). Error trials were modeled as regressors of no interest. The regressors were generated by convolving the impulse function related to the onsets of events of interest with a Gamma hemodynamic response function (HRF). Contrast images were computed for each run per subject, spatially normalized, transformed into MNI standard space and submitted to a within-subject fixed-effects analysis across runs. Higher-level analysis across subjects was carried out using a mixed-effects model in FSL (FLAME, Woolrich et al. 2004).

For exploratory whole brain analyses, Z (Gaussianized T/F) statistic images were thresholded using clusters determined by $Z > 3.1$ ($P < 0.001$) and a corrected cluster significance threshold of $P = 0.05$. In order to identify regions of interest (ROI) that, on the mean level, were activated in both age groups when correctly rejecting familiar, but currently irrelevant information, we compared correct rejections of lure and new pairs across all runs and all participants (CR lure > CR new). To identify regions involved in correct rejection of associative information, we compared correct rejections of rearranged and new pairs (CR rearranged > CR new). To identify common regions involved in monitoring of different trial types, we generated conjunction masks that included regions activated across both contrasts. Regions uniquely engaged in the correct rejection of lure or rearranged pairs were identified by exclusive masking of each of the contrasts with their common activation. The functional activation observed with these contrasts was used to define ROI for further analysis.

ROIs analyses were performed to examine age differences, and age × run interactions in the activation profiles of the regions constituting the task-specific brain network. These regions included left APFC (BA10), left inferior parietal lobe (IPL; BA39/40), and bilateral precuneus (BA7/31), left medial frontal gyrus (medial PFC; BA32/8), and left dorsal lateral PFC (lateral PFC; BA45/9/46). ROIs consisted of active voxels for contrasts performed across all runs and participants, after ensuring that they lay within the specific anatomical ROI of the Harvard-Oxford cortical atlas (http://www.cma.mgh.harvard.edu/fsl_atlas.html). Percent signal change from these ROIs was extracted per subject and run from the contrasts of CR lure versus CR new, and CR rearranged versus CR new. Outliers were identified at $P < 0.001$ (2-tailed test). The data of 2 younger adults and 1 older adult were consistently identified as outliers across ROIs and were excluded from reported behavioral and fMRI analysis.

To account for the interdependence of activity modulation across the ROIs, we used a multivariate analysis of variance (MANOVA) to test for effects of run and age. The MANOVA approach is well suited in situations with several correlated dependent variables, as it offers a single overall statistical test on the set of variables instead of performing multiple individual tests (Tabachnik and Fidell 2006). MANOVA was used in a first step to evaluate effects of run, age group and their interaction while accounting for the statistical dependence across ROIs. When statistically significant effects were present, the initial MANOVA was followed by univariate tests of the corresponding effect, separately for each ROI. To control for multiple comparisons on the number of univariate tests at this second step, we adjusted the corresponding *P*-values using a false discover rate (FDR) correction (Benjamini and Hochberg 1995). Finally, given significant univariate effects (after *P*-value adjustment), we proceeded to compare the age groups across runs. Here, a Bonferroni correction was used to control for multiple comparisons.

To identify regions that were uniquely activated only by younger or older adults, age interactions were examined in a whole-brain analysis performed on each of the 2 contrasts separately ($P < 0.001$). The resulting whole-brain masks were exclusively masked with the common activations across all participants to identify regions that were activated only in younger or older adults, after accounting for regions that were activated above threshold in both groups, but differed in magnitude of activation.

To identify regions that are involved in the detection of novel configurations among familiar stimuli, brain regions were identified where correct rejections of rearranged pairs were associated with higher activation than correct recognitions of target pairs in younger and older adults separately (CR rearranged > hits; cf. Düzel et al.

2003). For both of these word pair types, the individual words were familiar to the participants, but only for rearranged pairs was there a novel association between them. To examine the effects of run and age group on a hippocampal cluster identified in this contrast, percent signal change from the hippocampal cluster was extracted separately for each subject and run, after checking that the cluster of activation lies within the corresponding anatomical ROI of the Harvard-Oxford cortical atlas. The goal of this analysis was to examine age differences in the neural correlates of associative novelty responses.

Given that the current paradigm represents a modified version of the original paradigm, we also examined the extent to which the brain network involved in the recognition of target pairs reported in previous studies with the original paradigm (cf. Schnider et al. 2000; Treyer et al. 2003) was also activated in the present study. This analysis revealed a network of several PFC and parietal regions that were activated in both younger and older adults (for peak activations see Supplementary Table 1).

Statistical Analysis: Cortical Thickness

We used FreeSurfer (version 4.4.0; http://surfer.nmr.mgh.harvard.edu/) to perform an automatic segmentation and reconstruction of the T_1-weighted images from each participant. The intensity and continuity information from the structural image was used to reconstruct a representation of the gray/white matter boundary (Dale et al. 1999; Fischl and Dale 2000). The reconstruction for each participant was evaluated manually, in line with FreeSurfer guidelines. We extracted cortical thickness for the APFC ROI mask used in the functional analysis in the following steps. First, the FSL standard brain was registered to the FreeSurfer template subject using an automatic method. Note that the APFC ROI mask is in the coordinate space of the FSL standard brain, as it is derived from the group analysis of the functional data. Second, the APFC ROI mask was mapped onto the FreeSurfer template subject. Next, the cortical thickness data of each participant were mapped onto the FreeSurfer template subject. Manual inspection of the registration results was performed at each step of the analysis. Finally, the cortical thickness values for the APFC ROI were extracted for each subject.

Results

Behavioral Data

The proportions of correct responses to target, new, lure, and rearranged pairs are presented in Figure 2. An ANOVA revealed no significant effects of age or run for correct responses to target pairs (Fig. 2*A*, $P > 0.10$). For new pairs, (Fig. 2*B*), only the main effect of run was reliable, $F_{(2,106)} = 4.65$, $P = 0.01$, $\eta_p^2 = 0.08$, reflecting increase in correct rejections across runs. The main effects of run were significant for correct responses to lure pairs (Fig. 2*C*), $F_{(2,106)} = 9.01$, $P = 0.001$, $\eta_p^2 = 0.15$, and rearranged pairs (Fig. 2*D*), $F_{(2,106)} = 38.80$, $P = 0.001$, $\eta_p^2 = 0.42$. These results indicate that, across runs, correct rejections decreased for lure pairs and increased for rearranged pairs. The age groups differed reliably with respect to the overall correct rejection of lure pairs, $F_{(1,53)} = 28.62$, $P = 0.001$, $\eta_p^2 = 0.35$, and rearranged pairs, $F_{(1,53)} = 34.18$, $P = 0.001$, $\eta_p^2 = 0.39$, with younger adults showing higher performance than older adults for both word pair types. Moreover, the age × run interactions were statistically reliable for both lure pairs, $F_{(2,106)} = 3.12$, $P = 0.048$, $\eta_p^2 = 0.06$, and rearranged pairs, $F_{(2,106)} = 3.53$, $P = 0.033$, $\eta_p^2 = 0.06$, suggesting that the effects of task manipulation differed between younger and older adults. Older adults showed

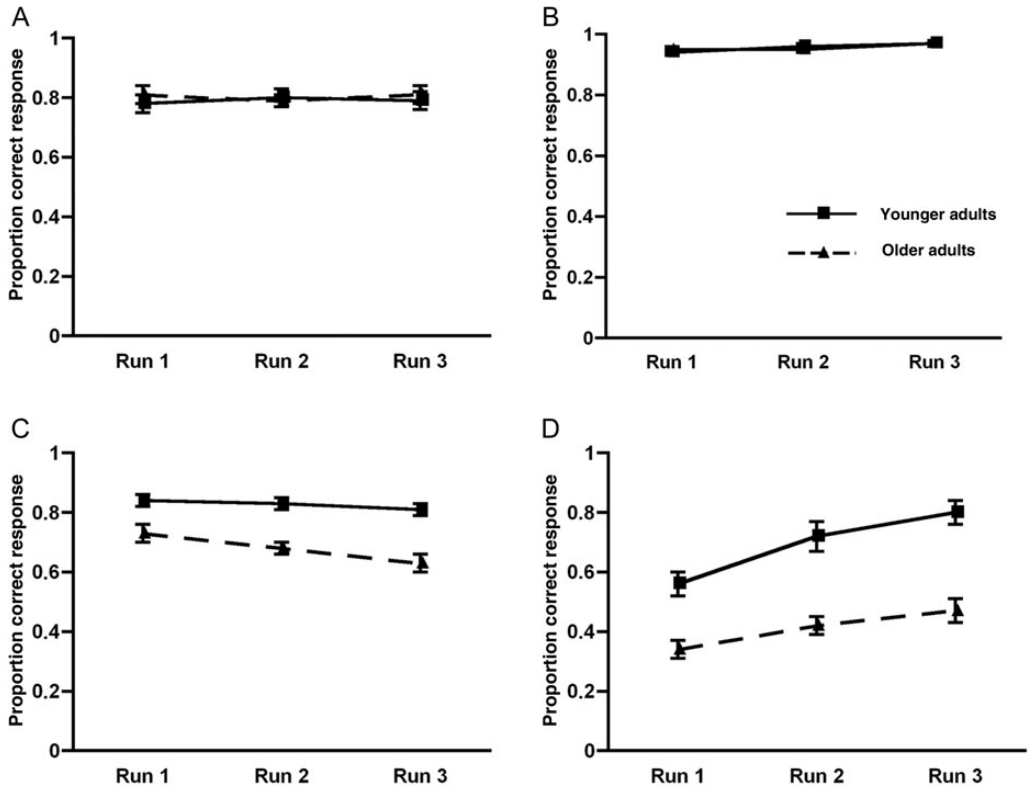

Figure 2. Behavioral performance across runs of the task. Proportion of correct responses to (*A*) target pairs, (*B*) new pairs, (*C*) lure pairs, (*D*) rearranged pairs. Error bars represent ± 1 SEM.

a steeper decrease in correct rejection of lure pairs as familiarity of these pairs increased across runs (see Fig. 2*C*). In contrast, the increase in correct rejections of rearranged pairs was more pronounced in younger adults (see Fig. 2*D*). Finally, an ANOVA on corrected recognition scores (hits – false alarms; Snodgrass and Corwin 1988) computed with lure pairs revealed significant effects of run, $F_{(2,106)} = 4.93$, $P = 0.01$, $\eta_p^2 = 0.09$, age, $F_{(1,53)} = 14.55$, $P = 0.001$, $\eta_p^2 = 0.22$, as well as a reliable age × run interaction, $F_{(2,106)} = 3.36$, $P = 0.038$, $\eta_p^2 = 0.06$. These results indicate that task performance decreased for both age groups across runs, and more so for older than for younger adults. Corrected recognition scores computed with rearranged pairs also revealed reliable effects of run, $F_{(2,106)} = 34.31$, $P = 0.001$, $\eta_p^2 = 0.39$, age, $F_{(1,53)} = 26.42$, $P = 0.001$, $\eta_p^2 = 0.33$, and an age × run interaction, $F_{(2,106)} = 4.70$, $P = 0.011$, $\eta_p^2 = 0.08$. While for recognition scores on rearranged pairs both groups improved their performance across runs of the task, the improvement was stronger in younger than in older adults.

fMRI Data

Age Differences in Memory Monitoring

Across all participants and runs of the task, the contrast of CR lure > CR new revealed activations in the left APFC, left IPL, and bilateral precuneus (for peak activations see Table 1). The contrast of CR rearranged > CR new revealed activations in left PFC, including APFC and lateral PFC, left medial PFC, right middle frontal gyrus, and bilateral parietal lobe, including precuneus and IPL (for peak activations see Table 1). Common activation across both contrasts were observed in left APFC, left IPL, and bilateral precuneus (see Table 1). Left lateral and medial PFC were selectively engaged in the rejection of rearranged pairs (see Table 1).

Table 1

Peak activations for correct rejection of lure (CR lure > CR new) and rearranged pairs (CR rearranged > CR new) across all runs and participants as well as in clusters showing age differences

Region	BA	*Z* max	MNI coordinates (mm)		
			X	*Y*	*Z*
CR lure > CR new					
Left and right precuneus	7/31	5.87	−10	−64	32
Left anterior PFC (APFC)	10	5.13	−40	64	2
Left inferior parietal lobe (IPL)	39/40	4.34	−36	−54	44
Younger adults > older adults					
Left occipital	18	3.56	−12	−88	24
CR rearranged > CR new					
Left and right precuneus/IPL	7/31/39/40	6.60	−30	−60	48
Left middle frontal gyrus	9/10/45/46	6.03	−30	8	54
Left medial frontal gyrus	8/32	6.15	−2	26	44
Right middle frontal gyrus	6	5.48	30	10	52
Younger adults > older adults					
Right intraclacarine cortex	17	3.61	14	−72	14
Posterior cingulate	23	4.22	0	−26	26
CR lure > CR new and CR rearranged > CR new					
Left and right precuneus	7/31	5.39	−12	−64	34
Left APFC	10	4.99	−30	54	6
Left IPL	39/40	4.34	−36	−54	44
CR rearranged > CR new only					
Left medial PFC	8/32	6.15	−2	26	44
Left lateral PFC	45/9/46	5.56	−50	26	28

Note. Age group difference contrasts ($P < 0.001$) are exclusively masked with activations across both age groups ($P < 0.01$). There were no regions where older adults > younger adults ($P < 0.001$).

To examine age differences in BOLD signal change across the 3 runs of the task, we extracted percent signal change (PSC) from ROIs in the left APFC (Fig. 3), left IPL, and bilateral precuneus, as well as for lateral and medial PFC (Fig. 4).

Lure Pairs (Figs 3A and 4A)

The multivariate ANOVA across all ROIs (APFC, precuneus, IPL) revealed a significant main effect of age group, Pillai's trace = 0.203, $F_{(3,51)} = 4.32$, $P = 0.009$, $\eta_p = 0.20$, as well as a reliable age group x run interaction, Pillai's trace = 0.257, $F_{(6,48)} = 2.77$, $P = 0.02$, $\eta_p = 0.26$. The main effect of run was not reliable, Pillai's trace = 0.104, $F_{(6,48)} = 0.93$, $P = 0.48$, $\eta_p = 0.10$. Next, we examined the effects of age group and age × run interaction for each ROI separately using an univariate repeated-measures ANOVA with an FDR correction for multiple comparisons.

The main effect of age group was significant in the precuneus, $F_{(1,53)} = 8.69$, $P = 0.005$, $P_{adj} = 0.03$, $\eta_p = 0.14$ with younger adults showing an overall higher activation than older adults. There were no age differences in activity modulation of the APFC, $F_{(1,53)} = 3.11$, $P = 0.08$, $P_{adj} = 0.096$, $\eta_p = 0.06$ and the IPL, $F_{(1,53)} = 1.18$, $P = 0.28$, $P_{adj} = 0.28$, $\eta_p = 0.02$.

The age group × run interaction was significant in the APFC, $F_{(2,106)} = 5.17$, $P = 0.007$, $P_{adj} = 0.021$, $\eta_p = 0.09$ and the precuneus, $F_{(2,106)} = 4.37$, $P = 0.015$, $P_{adj} = 0.03$, $\eta_p = 0.08$, but not in the IPL, $F_{(2,106)} = 2.73$, $P = 0.07$, $P_{adj} = 0.11$, $\eta_p = 0.05$. Post hoc pairwise comparisons in the APFC indicated that while activation did not differ between younger and older adults in run 1 ($P > 0.18$), APFC task-induced BOLD response was stronger in younger adults than older adults in run 2, $F_{(1,53)} = 6.94$, $P_{adj} = 0.011$, $\eta_p = 0.12$, and run 3, $F_{(1,53)} = 4.81$, $P_{adj} = 0.033$, $\eta_p = 0.08$. Similarly, in the precuneus, there was no difference between younger and older adults in run 1 ($P > 0.73$). However, activity modulation in the precuneus was higher for younger than for older adults in run 2, $F_{(1,53)} = 14.55$, $P_{adj} = 0.0001$, $\eta_p = 0.22$, and run 3, $F_{(1,53)} = 3.93$, $P_{adj} = 0.05$, $\eta_p = 0.07$.

There were no regions outside of the assessed ROIs that showed higher activation in older compared with younger adults. In younger adults, left lateral occipital cortex showed stronger activation compared with older adults (for peak activations see Table 1).

In sum, the correct rejection of lure pairs, which was expected to become more difficult across runs of the task due to increasing interference from previous presentations, was accompanied by stronger APFC and precunenus activations with increasing run for younger adults, presumably reflecting the concomitant increase in monitoring demands. For older adults, no such increase was observed.

Rearranged Pairs (Figs 3B and 4B)

The multivariate test across all ROIs (APFC, precuneus, IPL, lateral PFC, medial PFC) revealed only a significant main effect of age group, Pillai's trace = 0.290, $F_{(5,49)} = 4.01$, $P = 0.004$, $\eta_p = 0.29$. The main effect of run, Pillai's trace = 0.276, $F_{(10,44)} = 1.68$, $P = 0.12$, $\eta_p = 0.28$, as well as the run × age group interaction, Pillai's trace = 0.279, $F_{(10,44)} = 1.71$, $P = 0.11$, $\eta_p = 0.28$, were not reliable. The univariate tests of age group differences in each ROI indicated reliably stronger activations in younger adults in APFC,

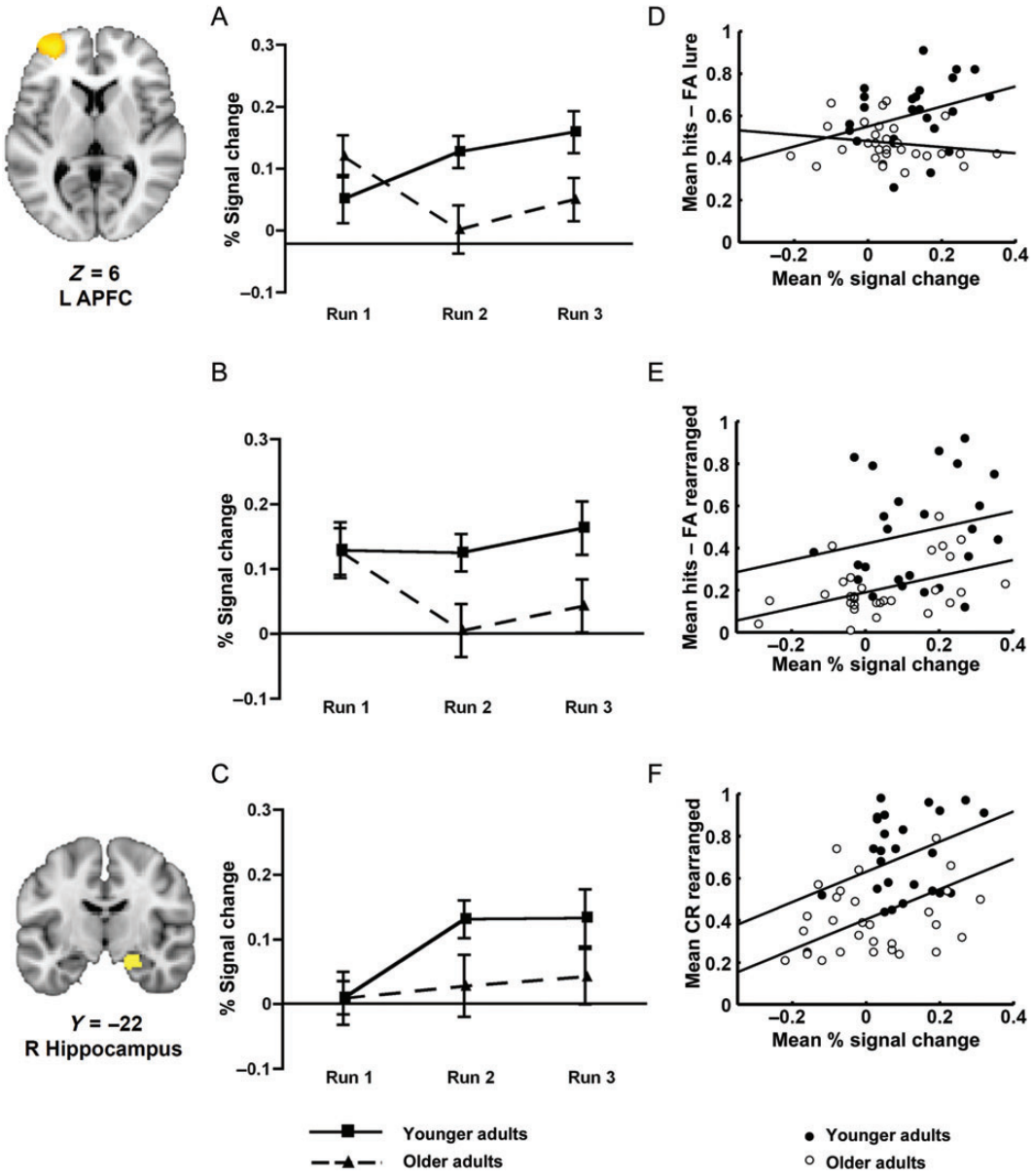

Figure 3. Regions-of-interest analysis for left APFC and right anterior hippocampus. The plots show age and run effects for the difference in % signal change extracted from the contrasts CR lure > CR new in left APFC (*A*), CR rearranged > CR new in left APFC (*B*), and CR rearranged > hits in right anterior hippocampus (*C*). The mean difference in % signal change in left APFC averaged across runs predicts mean recognition scores with lure pairs (*D*) and rearranged pairs (*E*), averaged across runs. The mean difference in % signal change in the right anterior hippocampus averaged across runs predicts mean rate of correct rejection of rearranged pairs averaged across runs (*F*).

$F_{(1,53)} = 5.16$, $P = 0.027$, $P_{adj} = 0.05$, $\eta_p = 0.09$, precuneus, $F_{(1,53)} = 6.76$, $P = 0.012$, $P_{adj} = 0.03$, $\eta_p = 0.11$, and IPL, $F_{(1,53)} = 7.10$, $P = 0.010$, $P_{adj} = 0.05$, $\eta_p = 0.12$. No age differences were observed in the lateral, $F_{(1,53)} = 0.85$, $P = 0.36$, $P_{adj} = 0.45$, $\eta_p = 0.02$, and medial PFC, $F_{(1,53)} = 0.03$, $P = 0.88$, $P_{adj} = 0.88$, $\eta_p = 0.00$.

No regions outside of the assessed ROIs showed higher activation in older adults than in younger adults. Task-induced BOLD signals were higher in younger adults than in older adults in the posterior cingulate and intracalcarine cortex (for peak activations see Table 1).

Taken together, in APFC, IPL, and the precuneus, task-induced BOLD responses to correct rejection of rearranged pairs were stronger in younger than in older adults. These age differences in activations did not change reliably across runs.

Age Differences in Associative Novelty Detection (Fig. 3C)

A whole-brain analysis across all runs of the task revealed that younger adults, but not older adults, showed higher BOLD responses for correctly rejected rearranged pairs than for correctly detected target pairs in the right anterior hippocampus. To directly test the age and run effects in this anterior hippocampal cluster, we performed a repeated-measures ANOVA on PSC from this cluster. This ANOVA revealed a significant effect of age, $F_{(1,53)} = 4.09$, $P = 0.05$, $\eta_p^2 = 0.07$ with younger adults showing an overall stronger activation in the right

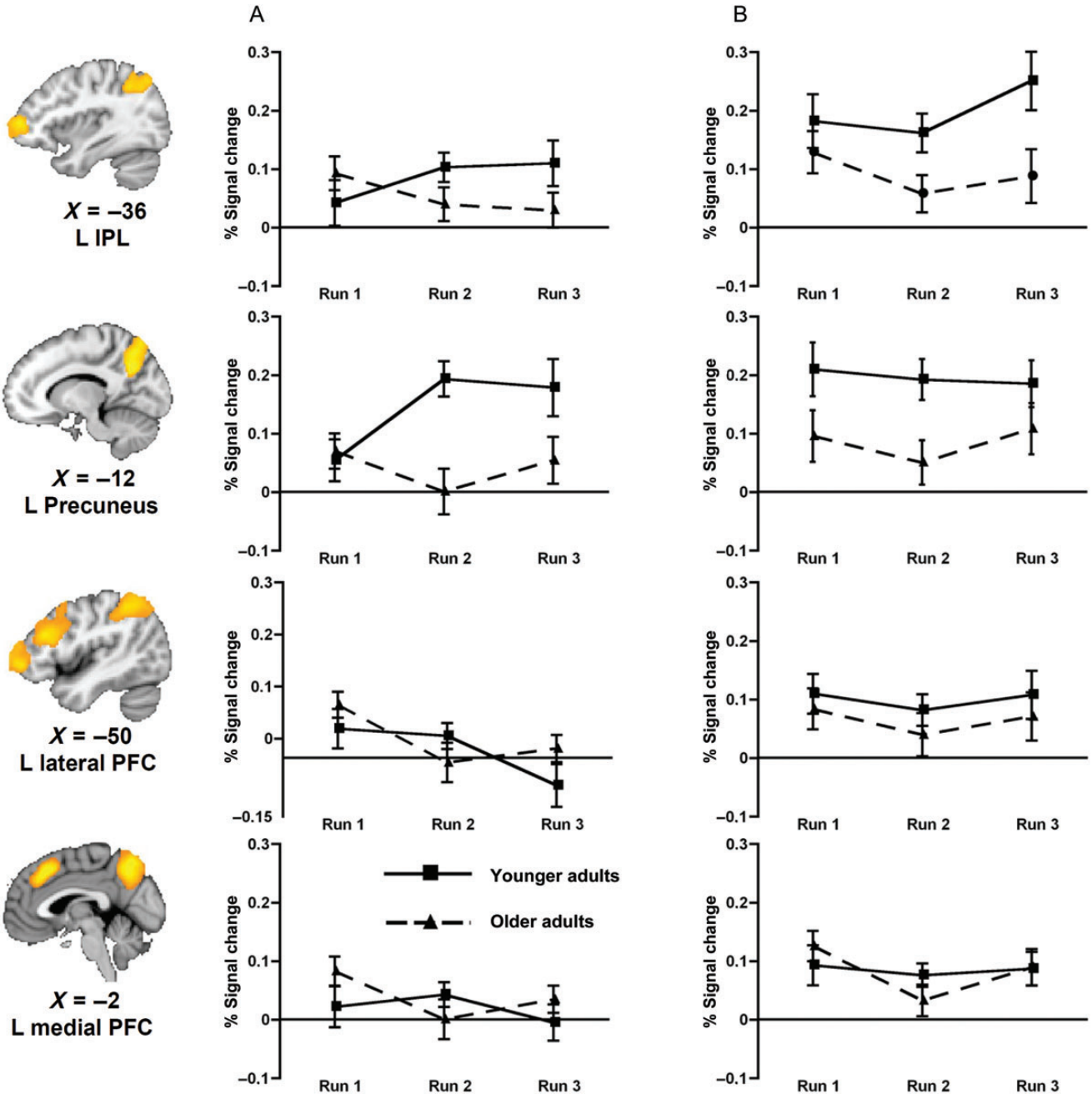

Figure 4. Regions-of-interest analysis for parietal and PFC regions during correct rejection of lure and rearranged pairs. The plots show age and run effects for the difference in % signal change extracted from the contrasts CR lure > CR new (*A*) and CR rearranged > CR new (*B*). Left IPL and the precuneus were involved in the correct rejection of both lure and rearranged pairs. Left lateral and medial PFC were uniquely associated with correct rejection of rearranged pairs.

anterior hippocampus for correct rejection of rearranged pairs than for correct recognition of target pairs. The effects of run as well as the run × age group interaction were not statistically significant ($P > 0.10$).

Associations Between BOLD Signal Change and Behavior

We used a series of hierarchical regression analyses to explore whether individual differences in task-related PFC and MTL activations would predict individual differences in memory performance after statistically controlling for age group differences, and whether these predictive relations would interact with age group (for a similar approach, see Nagel et al. 2011). The results of these analyses are summarized in Table 2.

For lure pairs, the observed association between PSC in APFC and recognition differed reliably between the age groups, with younger adults showing a stronger positive relationship of activation with memory performance than older adults (Fig. 3*D*).

For rearranged pairs, PSC in APFC accounted for variance in recognition scores beyond age (Fig. 3*E*), and this predictive relation did not differ reliably between the age groups.

Table 2
Results of hierarchical regression analyses in PFC and MTL regions

Predictor	
	Hits – false alarms lure pairs
Age group	$R^2_{change} = 0.22$, F_{change} (1/53) = 14.55, $P < 0.001$
APFC PSC (from CR lure > CR new)	$P > 0.10$
APFC PSC × age	$R^2_{change} = 0.06$, F_{change} (1/51) = 4.1, $P = 0.047$
APFC cortical thickness[a]	$R^2_{change} = 0.053$, F_{change} (1/52) = 3.75, $P = 0.058$
APFC cortical thickness × age[a]	$P > 0.10$
	Hits – false alarms rearranged pairs
Age group	$R^2_{change} = 0.33$, F_{change} (1/53) = 26.42, $P < 0.001$
APFC PSC (from CR rearranged > CR new)	$R^2_{change} = 0.06$, F_{change} (1/52) = 4.6, $P = 0.036$
APFC PSC × age	$P > 0.10$
APFC cortical thickness[a]	$P > 0.10$
APFC cortical thickness × age[a]	$R^2_{change} = 0.07$, F_{change} (1/51) = 5.71, $P = 0.02$
	Correct rejection rearranged pairs[b]
Age group	$R^2_{change} = 0.40$, F_{change} (1/53) = 34.18, $P < 0.001$
PSC hippocampus (from CR rearranged > hit)	$R^2_{change} = 0.044$, F_{change} (1/52) = 4.1, $P = 0.048$
PSC hippocampus × age	$P > 0.10$

Note. Mean recognition scores averaged across runs are used as the dependent variable. Age group is entered first, and mean PSC averaged across runs or cortical thickness is entered second in the prediction equation. The age group × PSC or thickness interaction was added last to test for age group differences in linear predictive relations.
[a]The relationships of memory performance and cortical thickness are examined in a separate hierarchical regression.
[b]In the hippocampal cluster, no reliable associations between neural activation and overall recognition performance were observed.

In contrast, mean PSC in lateral and medial PFC did not account for additional variance in mean performance on rearranged pairs beyond age group. In the hippocampal cluster, PSC was associated with correct rejection of novel configurations similarly across both age groups (Fig. 3*F*), suggesting that the contribution of associative novelty detection to false memory did not differ between younger and older adults.

Taken together, the observed task-specific activations in PFC and MTL were associated with higher performance in the task, revealing the functional significance of the observed activations.

Age Differences in APFC Cortical Thickness

The results above indicate that younger and older adults differed in task-specific APFC activity modulation. To examine to what extent the observed age differences in activation were accompanied by age differences in APFC structure, we extracted cortical thickness from the APFC ROI used in the analysis of the functional activation data.

As expected, cortical thickness in the APFC ROI was higher in younger adults ($M_{younger} = 2.51$) than in older adults ($M_{older} = 2.30$), $t(53) = 3.25$, $P = 0.002$, $d = 0.88$. Higher cortical thickness of the APFC ROI was associated with better memory on lure pairs, similarly across both age groups (see Table 2). For rearranged pairs, the positive association between structural integrity of the APFC ROI and recognition performance was more pronounced for younger adults than for older adults (see Table 2). Importantly, functional activation continued to account for substantial variance in recognition performance beyond age group (lure pairs: $R^2_{change} = 0.06$, $P = 0.057$, rearranged pairs: $R^2_{change} = 0.06$, $P = 0.036$) after statistically controlling for individual differences in APFC cortical thickness. Thus, while APFC cortical thickness was associated with better memory performance, statistical control of individual differences in cortical thickness did not eliminate the contribution of task-induced BOLD response to performance.

Discussion

We investigated age differences in memory monitoring mechanisms and their contribution to increased memory errors in old age. We found that age-related differences in the ability to distinguish currently relevant memories from memories pertaining to the past are associated with age-related deficits in the modulation of monitoring processes involving the APFC. Based on the present findings, we draw 2 major conclusions: 1) in younger adults, APFC activity is boosted in response to greater demands on monitoring processes; 2) in older adults, both structural integrity of the left lateral APFC as well as activity boosts in this region in response to greater monitoring demands are lower, resulting in impairments to reject highly familiar but currently irrelevant representations.

Age Differences in Monitoring Processes in APFC

By manipulating the current relevance of presented information, we demonstrated increased activation in APFC under conditions of high proactive interference due to multiple encounters of similar events. This finding is in line with previous studies showing that the APFC is critical for monitoring retrieved information in the service of currently relevant task goals (Koechlin et al. 1999; Ranganath et al. 2000; Rugg et al. 2002; Badre and Wagner 2005). Such control processes are especially important when memories are difficult to retrieve or associated with high degree of familiarity that needs to be overcome to achieve successful performance (Burgess and Shallice 1996; Moscovitch and Winocur 2002).

In contrast to younger adults, APFC activation did not increase over runs in older adults. At the same time, older adults showed an increase in memory errors over runs, whereas younger adults did not. Given that proneness to memory interference increased over runs, these findings in combination strongly suggest that reduced efficiency of memory monitoring processes contributes to greater false memory in old age. This conclusion is in line with the results of previous studies examining the effects of deficits in control processes on memory performance in old age. For instance, Jonides et al. (2000) found that older adults showed lower activation of left lateral PFC regions and greater proactive interference relative to younger adults in a working memory task (see also Clapp et al. 2011). Also, older adults were found to be impaired at inhibiting task-irrelevant auditory input, and showed more memory failures than younger adults (Stevens et al. 2008). What the present study adds to these previous findings is that the reduced ability to engage PFC-based monitoring mechanisms, in addition to impairing memory performance for to-be-remembered stimuli, also underlies older adults' elevated tendency to falsely remember events that did not happen in the past.

We observed different patterns of activation across PFC subregions in relation to rearranged pairs. Whereas APFC

activation was reduced in older adults, the magnitude of lateral PFC activity modulation did not differ between younger and older adults. Lateral PFC has been repeatedly associated with recall-to-reject processes during associative recognition (Lepage et al. 2003; Gallo et al. 2010), but the relationship between recall-to-reject and monitoring processes has not yet been fully understood (but see Achim and Lepage 2005). Here, 2 unexpected findings emerged in the present study. First, we observed that detection of novel configurations improved across runs, while APFC engagement in this condition was and remained high throughout. This apparent discrepancy between the behavioral and BOLD signal trends may be due to the relatively high demands on control processes in the current paradigm. Even during the last run of the task, younger adults did not attain perfect performance; rather, their performance fell within the range of previous studies on associative recognition (Lepage et al. 2003; Achim and Lepage 2005) that reliably detected lateral PFC activations.

Second, the absence of reliable age group differences in task-related activation within the lateral PFC is at odds with several studies reporting age-related reductions in activity modulation in lateral PFC during episodic memory tasks (e.g., Cabeza et al. 2002; Duarte et al. 2008). However, the pattern of adult age differences in different PFC subregions is not homogeneous across studies (Cabeza et al. 2002; Morcom et al. 2007; Duverne et al. 2009; Duarte et al. 2010). While most aging studies examined memory recognition, a study on memory recall reported a pattern of age differences in PFC subregions that is similar to those in the present study (Schacter et al. 1996). Similar to the present paradigm, memory recall is typically associated with high monitoring demands (Moscovitch and Winocur 2002; Mitchell and Johnson 2009). Thus, the observed differences in results across studies may reflect differences in the nature and amount of control processes required during memory encoding and retrieval. Various theoretical accounts of PFC involvement in cognitive control have proposed that different PFC subregions contribute distinct mechanisms, which may map onto a rostro-caudal axis of increasing control demands (Dobbins et al. 2002; Fuster 2003; Badre and D'Esposito 2007). Our results are in line with these accounts by suggesting that multiple PFC subregions contribute to overcoming interference in episodic memory, including mechanisms in lateral PFC that may facilitate selection between competing memories through recall-to-reject processes (Ranganath and Knight 2003), as well as supervisory processes in APFC that monitor recovered information in accordance to current task goals and decision criteria (Fletcher and Henson 2001).

Finally, our study also addressed, to some extent, the relation between adult age differences in structural and functional aspects of the brain. Age differences in structural integrity (Raz et al. 2005) and functional activation (Park and Reuter-Lorenz 2009) have been extensively documented, but the association between them remains largely unexplored (cf. Shafto et al. 2010; Persson et al. 2012). The finding of reduced APFC cortical thickness corroborates previous research demonstrating age-related cortical thinning across a wide network of brain regions (Fjell et al. 2009; Burzynska et al. 2012). Furthermore, it has been found that older adults with thinner cortex in PFC areas tend to commit more perseveration errors (Gunning-Dixon and Raz 2003; Burzynska et al. 2012). Clearly, longitudinal work is needed to better understand the association between structural and functional changes in areas that contribute to age-related changes in monitoring processes and their effect on preservation and memory errors.

MTL-mediated Associative Novelty Deficits in Old Age

The present study replicates and extends previous findings that the anterior hippocampus is involved in the recognition of novel conjunctions of familiar stimuli (Düzel et al. 2003, 2004; Kohler et al. 2005; Lisman et al. 2011). First, the age difference in hippocampal activation suggests that the ability to recognize novel associations may be reduced in old age, both at behavioral and neural levels. This effect is small and needs to be interpreted with caution. However, such age-related deficits might be related to deficits in pattern separation mechanisms (Yassa et al. 2011), or comparator mechanisms within the hippocampus (Kumaran and Maguire 2007, 2009). Second, a stronger associative novelty response in the hippocampus was directly related to committing less memory errors, both in younger and older adults. Detecting the mismatch between the novel conjunction and the details previously associated with this event may lead to further elaborative processing that preferentially benefits later recollection and better discriminability of representations (via recall-to-reject), thus preventing false memory (Kumaran and Maguire 2007; Shohamy and Wagner 2008). As shown in Figure 3*C*, strengthening memory for lure pairs through across-run repetitions may facilitate associative novelty responses in the hippocampus in younger adults. Future research needs to examine more closely the extent to which variation in the quality of memory representations is associated with change in novelty signals, and age differences therein.

It is important to note that individuals who engaged APFC and the hippocampus in the context of the task achieved better memory performance regardless of age group, but that older adults as a group were less likely to activate these regions in a task-relevant manner. In line with analogous findings for verbal (Nagel et al. 2011) and visuo-spatial (Nagel et al. 2009) working memory, these results suggest that major aspects of the functional circuitry required for successful memory monitoring remain largely invariant throughout adulthood, but function less efficiently in old age (Nyberg et al. 2012).

Age Differences in Parietal Contributions

In this study, we also found pronounced age differences in the involvement of the bilateral precuneus and left IPL during the correct rejection of lure and rearranged pairs. Parietal activations have been repeatedly observed during memory encoding and retrieval, but the functional role of these activations is a matter of debate (Wagner et al. 2005; Cabeza 2008; Villberg and Rugg 2008; Nelson et al. 2010). Findings with respect to age-related changes and differences in the parietal lobes are mixed, with some evidence of volume reductions in the IPL (Raz et al. 2005) and lower BOLD response during false recognition (Duarte et al. 2010). Given that parietal regions are structurally connected to both PFC and MTL, activations of these regions may help to coordinate PFC-MTL interactions during episodic retrieval. Previous studies indicate that such functional connectivity may differ between younger and older age (Daselaar et al. 2006; Clapp et al. 2011; Nagel et al. 2011). For example, in the

working memory study by Campbell et al. (2012), older adults did not only show lower activation in bilateral APFC but also exhibited lower resting state functional connectivity between APFC and the parietal lobes, the main regions involved in the present task. Taken together, these findings call for longitudinal studies to better understand the functional value of these shifts in connectivity with advancing adult age.

A few caveats in this study must be taken into consideration. First, the rCRT task as used in this study does not allow for a clear separation between encoding and retrieval processes. Hence, we cannot rule out that age differences in the ability to shift between encoding and retrieval mode, in addition to differences in monitoring processes, have contributed to the pattern of age group differences in behavior and brain activation observed in this study (Huijbers et al. 2009). Another potential concern with the current task design is that the observed age effects are confounded by time in the scanner. However, such confound is unlikely to explain the reported results. At the behavioral level, the observed run effects in memory performance were driven by specific changes in performance on lure and rearranged pairs, whereas there were no run or age effects for target pairs, suggesting that an overall drop of attention is unlikely to underlie the results. At the neural level, our results are based on the use of an active baseline condition, that is, the reported APFC effects reflect relative differences in task-induced BOLD response for lure and rearranged pairs relative to new pairs. Therefore, the specificity of APFC effects is actually enhanced by referencing them to another task condition.

In conclusion, the results of this study provide insights into the manner in which normal aging affects the neural networks supporting the ability to avoid illusory memories for highly familiar events. Task-related engagement of the APFC and the anterior hippocampus contributed to successful memory performance in both age groups, but older adults were less likely to activate these regions in a task-relevant manner. The current findings shed light on the individual contributions of MTL and PFC in service of memory functioning, providing important evidence for the mechanisms through which older adults experience elevated false memory (Shing et al. 2010), and may help to identify suitable targets for intervention (Lövdén et al. 2010).

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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