Regional specificity of age effects on the neural correlates of episodic retrieval

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Abstract

We investigated age-related differences in episodic retrieval using a source memory procedure. Age-related differences in retrieval-related activity were analyzed in conditions where source recollection performance was statistically equivalent in young and older subjects. Analyses of BOLD activity revealed a network of regions where recollection effects were equivalent in magnitude in the two age groups. There were no regions where these effects were of greater magnitude in young than in older subjects. In some regions, however, there was a crossover interaction, such that retrieval-related effects reversed in direction between the two age groups. Further analyses of these interactions revealed a dissociation between a posterior hippocampal region where recollection-related activity was confined to the older group, and right fusiform and occipital regions where, in the young group only, activity elicited by studied items was of lower magnitude than activity to new items. We interpret the first of these age-related effects as an example of 'over-recruitment' in response to decline in neural efficiency, and discuss whether the second effect indexes an age-related decline in repetition priming.
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1. Introduction

Healthy cognitive aging is characterized by a decline in performance in a range of cognitive domains. One prominent example is within the domain of episodic memory—memory for unique events and their contexts. Episodic memory declines markedly with increasing age, in contrast to other memory functions such as those supporting short-term, semantic, or implicit memory, which show more modest age-related effects (Craik, 1977; Craik and Jennings, 1992; Light, 1991; Nilsson, 2003). There have been numerous efforts to explain the relatively rapid decline in episodic memory with

age. These range from accounts that propose the decline is merely just one expression of a more general decline in processing efficiency (e.g., Birren, 1965; Cerella, 1985; Craik and Byrd, 1982; Salthouse, 1985, 1996), to those that argue that the decline reflects age-related changes in cognitive operations supporting specific mnemonic processes (e.g., Howard et al., 2006; Jennings and Jacoby, 1993; Naveh-Benjamin, 2000; Prull et al., 2006). Proponents of these latter accounts have highlighted the seemingly uneven decline that is observed with age in the volume of different brain regions (e.g., Raz, 1996; Raz et al., 2005, 2004). For example, Daselaar et al. (2006) (see also Scheibel, 1979) note that regions held to be particularly critical for episodic memory, such as the hippocampal formation, show especially marked age-related effects.

Numerous studies employing functional neuroimaging methods have addressed the question whether there are age-related differences in the neural correlates of episodic memory that might account for the differences in memory

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performance described above. These studies have investigated age-related effects both at the time of encoding (e.g., Daselaar et al., 2003a; Grady et al., 2003, 1995; Logan et al., 2002; Morcom et al., 2003) and retrieval (e.g., Cabeza et al., 2000; Daselaar et al., 2003b; Schacter et al., 1996; Schiavetto et al., 2002; see Park and Gutchess (2005) for review of both encoding and retrieval studies), generally reporting reliable age-related differences in both cases. Detailed findings differ across studies, but arguably the most consistent finding has been that, relative to younger subjects, older adults tend to demonstrate a pattern of 'over-recruitment', exemplified in several studies by a more bilateral pattern of memory-related activity than that evident in the young (e.g., Cabeza et al., 2002, 2004, 1997; Fernandes et al., 2006; Grady et al., 2005; Gutchess et al., 2005; Madden et al., 1999b; Maguire and Frith, 2003; Morcom et al., 2003; Rosen et al., 2002; van der Veen et al., 2006). In some studies, this pattern is accompanied by reduced memory-related activity in other regions activated in the young, prompting some authors to argue that over-recruitment reflects a compensatory response to an age-related decline in the functional integrity of these regions (e.g., Cabeza et al., 2002, 2004, 1997; Grady et al., 2005; Gutchess et al., 2005; Morcom et al., 2003; Rosen et al., 2002; see reviews by Cabeza, 2002; Dolcos et al., 2002; Rajah and D'Esposito, 2005; Reuter-Lorenz, 2002; Reuter-Lorenz and Lustig, 2005).

The focus of the present study is on age-related differences in the neural correlates of recollection. The specific goal of the study was to address the question whether, when the probability of successful recollection is equated between young and older subjects, age-related differences in the associated neural activity are none the less evident. As has been discussed previously (Morcom et al., 2003; Rugg and Morcom, 2005), for a variety of reasons age-related differences in the neural correlates of memory are difficult to interpret in the face of parallel differences in memory performance. In short, the question arises whether the neural differences should be interpreted as reflecting age-related differences in the neural correlates of memory or, more prosaically, as a reflection of differential memory performance. To address this question, it is necessary to compare the neural correlates of memory across age groups while controlling for differences in performance supported by the cognitive processes of interest. It is important to note that this does not necessarily amount to controlling for performance differences *per se*; if performance on a memory test is supported by multiple processes, then equating overall performance will not necessarily equate the influence of any one process, and hence confounds between age and the probability or level of engagement of the different processes may still exist (Rugg and Morcom, 2005). This is especially important in the case of recognition memory, when performance is generally held to be supported by the independent processes of 'recollection' and 'familiarity' (Yonelinas, 2002). Thus, when overall recognition performance is equated between young and older subjects, this leaves open the possibility that recognition was differentially supported by recollection and familiarity in the two groups. This possibility receives support from a study by Daselaar et al. (2006), who demonstrated that equivalent recognition performance between an older and a young group was accompanied by significantly lower estimates of recollection in the older subjects. Perhaps unsurprisingly, given that recognition was less likely to be supported by recollection in the older group, these authors reported that a putative neural correlate of recollection was of greater magnitude in their young group. Several other prior reports of age-related differences in retrieval-related activity are also arguably difficult to interpret unambiguously due to the confounding of age with performance (e.g. Anderson et al., 2000; Cabeza et al., 2002; Daselaar et al., 2006; Daselaar et al., 2003b; Grady et al., 2005; Schiavetto et al., 2002; however see Cabeza et al., 1997).

To our knowledge, only a single prior study has explicitly addressed this question (Morcom et al., 2007; see also Li et al. (2004) for a companion ERP study). In that study, successful recollection was operationalized in terms of accurate memory for both study items (pictures of everyday objects), and their encoding context (the study task employed to encode an object). The neural correlates of recollection were defined as the difference in the activity elicited by recollected relative to correctly rejected (new) test items. Recollection performance was equated between age groups by differential repetition of a subset of study items; whereas older subjects saw some items a total of three times, young subjects received only one repetition. In both groups, recollection-related effects were observed in many of the regions identified as recollection-sensitive in prior studies employing only young subjects (e.g., medial and lateral parietal cortex, left prefrontal cortex, and the medial temporal lobe (see, Dobbins and Davachi, 2006; Rugg et al., 2002; Rugg and Yonelinas, 2003 for reviews). In several regions however, mostly adjacent to or abutting regions where effects common to the two groups were observed, recollection-related activity was of greater magnitude in the older subjects, that is, there was a pattern of 'over-recruitment'. More strikingly, no region could be identified where recollection effects (defined as greater activity for recollected versus new items) were smaller in the older subjects; rather, in several regions where young subjects demonstrated greater activity for new items than recollected items, effects in the older group were either non-significant or showed enhanced activity for recollected items. Morcom et al. (2007) argued that, in order to sustain the same level of performance as young subjects, older individuals do indeed appear to 'over-recruit' cortical regions. The authors equivocated on whether this pattern reflected a primary, age-related change in how brain regions are engaged to support recollection, or was instead a secondary, compensatory response to a decline in cognitive efficiency.

As was acknowledged by Morcom et al. (2007), interpretation of their findings is clouded by the possibility that their young and older groups differed with respect to the information they retrieved to support source judgments. As noted

above, the source attribute that was varied across study trials was the nature of the study task (animacy judgment versus size judgment). The study task varied on a trial-by-trial basis, and was signaled ahead of each study presentation by one of two visually distinctive cues. Thus, the subsequent source memory judgments could, in principle, have been based either on memory for the study task itself (that is, retrieval of conceptual information) or on memory for the cue associated with the study item (retrieval of perceptual information). On the basis of their findings from a parallel ERP study, in which the neural correlates of source recollection were found to differ qualitatively according to age, Li et al. (2004) argued that the young subjects tended to rely on conceptual information, whereas older subjects were more reliant on perceptual details about the study episode. To the extent this was true in the study of Morcom et al. (2007), the findings may reflect, at least partially, a confound between age and retrieval strategy.

The present study builds on that of Morcom et al. (2007) by employing a similar logic, but with a source memory procedure that controls more tightly for retrieval strategy. Using a single study task, subjects encoded a series of pictures that were presented in one of two physically distinct display contexts. The subsequent retrieval task required subjects to identify study items, and allocate them to the correct context. Hence, accurate performance depended on retrieval of perceptual information about the study episode, removing the possibility of differential reliance on conceptual versus perceptual information in the two groups. As in the study of Morcom et al. (2007), probability of successful recollection was manipulated by repetition of a sub-set of study items, permitting the neural correlates of recollection to be compared between age groups when source performance was equated. In a further refinement of the procedures adopted by Morcom et al. (2007), the source memory task included a response option that permitted subjects to indicate when they recognized the item but could not retrieve its source, minimizing the 'diluting' effects of lucky guesses on recollection-related activity (Rugg and Morcom, 2005). At issue is whether, when the informational basis of source judgments is controlled in this manner, the pattern of age-related over-recruitment described by Morcom et al. (2007) is still evident.

2. Method

2.1. Participants

Sixteen young healthy adults (9 female) aged between 18 and 26 years (mean age: 21), and 16 older healthy adults (12 female) aged between 65 and 78 years (mean age: 71), participated to the experiment. Data collected from five additional older adults were excluded from analyses because their source recollection was at chance in the experimental task. One additional older subject was also excluded because of scanner failure and a further older subject was excluded because her brain could not be successfully normalized to the

MNI template (see below). Young adults were recruited from the undergraduate and graduate student population of University of California, Irvine, and older adults were recruited from the surrounding community.

All subjects were right-handed, English native speakers, with a minimum of 12 years education and normal or corrected-to-normal vision. The subjects were free from neurological, cardiovascular, and psychiatric disease and none was taking CNS-active medication. Five of the older subjects included in the final analyses were taking antihypertensive medication. The study was approved by the Institutional Review Board of the University of California Irvine. Informed consent was obtained prior to participation in the first experimental session.

2.2. Neuropsychological testing

A battery of standardized neuropsychological tests was administered to all subjects in a separate session from the fMRI procedure. The battery was intended to assess a range of cognitive functions known to either decline or to be maintained with age. The Mini Mental State Examination (Folstein et al., 1975) was employed as a dementia screening measure. We adopted a nominal cut-off score of 26/30, although no potential subject was rejected on the basis of this criterion. Long-term memory was assessed with the California Verbal Learning Test-II (Norman et al., 2000), and the Immediate and Delayed NYU paragraph (Kluger et al., 1999). Short-term memory was assessed with the Digit Span Forward and Backward test of the WAIS-R (Wechsler, 1981). General cognitive functions were further assessed with the Digit/Symbol Coding test of the WAIS-R (Wechsler, 1981), the Trail Making Test A and B (Gordon, 1972; Soukup et al., 1998), and letter fluency and category fluency tests (Gladsjo et al., 1999). An estimate of full-scale IQ was obtained from the Wechsler Test of Adult Reading [WAIS®-III (Wechsler, 2001)]. The Beck Depression Inventory (Beck et al., 1961) was also administered. Paragraph recall and digit span data were unavailable for one older subject because of an error in how the tests were administered, and category fluency data were not obtained from one young subject.

2.3. Stimulus materials

The experimental stimuli comprised 120 color pictures of different common objects. For each yoked pair of older and young subjects (see below), pictures were randomly allocated to one of three conditions: 40 pictures were employed as 'easy' study items, 40 as 'hard' study items, and the remaining 40 items were presented in the test phase only, serving as new (unstudied) items. Sixteen stimulus lists were generated and allocated to yoked pairs of young and older subjects. The final sample of subjects, however, contained three pairs of subjects who were inadvertently administered different study lists, although they should have been yoked. At study, pictures were presented in one of two contexts: half

were presented to the left side of fixation against green rectangular background whereas the remainder were presented on the right against a red background. In addition, half of the study items were presented once only (hard condition), whereas the other half were presented twice (with the constraint that the context was maintained between presentations, and the presentations were separated by three or more other items).

At test the 80 studied pictures were re-presented, randomly intermixed with the 40 new items and 40 null (fixation only) events. The critical test items were preceded by two unstudied filler items. Test sequences were pseudo-randomly ordered such that no more than three items belonging to the same condition occurred sequentially.

An additional pool of 15 pictures served as the practice items, permitting the creation of a 10 items study list and 15 items test list.

2.4. Experimental tasks and procedure

The experiment comprised a non-scanned study phase and a scanned test phase. Study and test practice lists were administered prior to entering the scanner, and were repeated as necessary until the subject had mastered the task instructions and response button assignments. Inside the scanner, the pictures of each object were displayed using VisuaStim XGA MRI-compatible head-mounted goggles (Resonance Technology Inc., Northridge, CA) with a field of view of 30° horizontal and 23° vertical. Each object subtended a visual angle of approximately $5° \times 5°$, and was presented against a $7° \times 12°$ white background. At study, a central fixation cross and the two colored backgrounds were displayed continuously. Each background subtended a visual angle of $9° \times 14°$, with a separation of 1° between their inner edges. Five hundred ms prior to picture onset, the fixation cross changed color from gray to white. Each picture was presented for 1 s (centered 5° lateral from fixation), with a stimulus onset asynchrony (SOA) of 4 s. Instructions emphasized the need to respond before the onset of the subsequent trial. The study task required a judgment whether the presented object would fit inside a shoebox. The judgment was signaled by a button press with one of the two index fingers (the assignment of the judgments and button presses was counterbalanced across subjects). Speed and accuracy in responding were given equal emphasis. Subjects were asked to focus on the study judgments were informed that half of the objects would reappear against the same background. A short break was provided halfway through.

The test phase began about 5 min after the presentation of the last study item. Pictures were presented at fixation on a white background. The sizes of the objects and their backgrounds was the same as at study. Instructions were to judge if each item has been studied against the left/green background, the right/red background, or if it was new. A final response category was reserved for items recognized as old but for which the study context could not be recollected. At the beginning of each trial, a continuously presented fixation cross changed color from white to red. This was followed 500 ms later by the presentation of a test item for 1 s. The stimulus onset asynchrony (SOA) was 4 s (excluding null trials) and subjects were instructed to respond before the onset of the subsequent trial. Null events consisted of the continued presentation of the white fixation cross for an additional 4 s. Subjects responded with their left and right middle and index fingers. The four response categories (old:left/green, old:right/red, old:no source recollection, and new) were, respectively, assigned to the button presses left middle, left index, right index, right middle or right index, right middle, left index, left middle (the order being counterbalanced across subjects). Speed and accuracy were equally emphasized. Subjects were given a 30 s rest break at the middle of the test phase.

2.5. MR data acquisition

A Philips Eclipse 1.5 T MR scanner was used to acquire both T1-weighted anatomical images (256×256 matrix, 1 mm^3 voxels, spoiled gradient-recalled acquisition in a steady state sequence) and T2*-weighted echoplanar images (EPI; 64×94 matrix, 2.6×3.9 mm pixels, TE 40 ms) with blood-oxygenation level-dependent contrast. Each EPI volume comprised 27 axial slices (3 mm thickness, 1.5 mm gap), positioned to give full coverage of the cerebral cortex. Functional data were obtained in a descending sequential order in a single session of 320 EPI volumes with a repetition time (TR) of 2.5 s. The first five volumes were discarded to allow tissue magnetization to achieve a steady state.

2.6. Data analysis

Data preprocessing and statistical analyses were performed with Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, London, UK (Friston et al., 1995)) implemented in Matlab 6 (MathWorks, Natick, MS). EPI volumes were spatially realigned to the first volume. Time series of voxels within each slice were aligned to the middle slice by synch interpolation. The images were spatially normalized with reference to a sample-specific template. The template was created by normalizing (Ashburner and Friston, 1999) the first EPI image of the functional time-series of each of the 32 subjects (16 young and 16 older) with reference to a standard EPI template based on the Montreal Neurological Institute (MNI) reference brain (Cocosco et al., 1997), and then averaging the resulting images. Images were re-sampled into 3 mm isotropic voxels prior to normalization. Normalized images were smoothed with an isotropic 10 mm full-width half-maximum Gaussian Kernel to accommodate residual anatomical variation between subjects. T1 images were normalized using a procedure analogous to that applied to the EPI images. However, as only 15 images were available for the older subjects, individual images were first averaged within each age group, and then averaged across age groups,

so as to equally weight the contribution of the two groups to the sample-specific template.

Statistical analyses were performed in two stages. In the first stage, individuals' BOLD responses for each event type were modeled by a δ function (impulse response) at stimulus onset. The corresponding BOLD response was modeled by convolving each of these functions with two hemodynamic response functions (HRFs). One function (the 'early' function) was the canonical HRF as implemented in SPM2 (Friston et al., 1998). A second ('late') function was generated by shifting the canonical HRF one TR (2.5 s) later in time, and was included to capture possible delayed responses. The late function was orthogonalized with respect to the early function so as to attribute any shared variance to the early covariate (Andrade et al., 1999). Convolutions were performed in high-resolution time space, and downsampled at the midpoint of each scan to form covariates in a General Linear Model (GLM).

The design matrix of the GLM included five early and five late covariates that modeled events of interest according to subjects' responses at the test phase. These events comprised studied items accorded correct source judgments ('easy source hits' and 'hard source hits'), studied items accorded an incorrect source judgment or for which the source could not be recollected ('easy source misses' and 'hard source misses'), and correctly judged new items ('correct rejections'). Additional covariates modeled the rest break at the middle of the test phase and events of no interest (items that failed to elicit a response or elicited multiple responses, new items incorrectly judged old (false alarms), old items incorrectly judged new (misses) and fillers). The design matrix also included six covariates modeling movement-related variance (three rigid-body translations and three rotations determined from the realignment stage) and a constant that modeled the mean over scans.

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 both voxels and scans. Parameter estimates for events of interest were estimated using the aforementioned general linear model. Nonsphericity of the error covariance was accommodated by an AR(1) model, in which the temporal autocorrelation was estimated by pooling over suprathreshold voxels (Friston et al., 2002). The parameters for each covariate and the hyperparameters governing the error covariance were estimated using restricted maximum likelihood. In the second stage of the statistical analyses, the individual contrasts of interest were carried forward to a random-effects analysis. For the principal analyses we report results only for clusters that survived an uncorrected two-sided significance threshold of $P < .001$, and a cluster extent threshold of 5. The peak voxel of clusters showing reliable effects are reported in MNI coordinates.

3. Results

3.1. Neuropsychological testing

The raw scores from the neuropsychological test battery are summarized in Table 1. As is evident from the table, young

Table 1
Participants' characteristics and raw scores (mean, standard deviation, and ranges) on the neuropsychological tests

	Young adults			Older adults		
	Mean	Standard deviation	Range	Mean	Standard deviation	Range
Age	21	1.9	18–26	71	3.6	65–78
Years of education	15	1.1	13–17	16	2.4	12–20
Mini Mental State Examination	29.4	0.8	28–30	29.2	1.0	30–26
CVLT[a] immediate free recall	11.9	2.3	9–16	10.7	2.3	7–16
CVLT[a] immediate cued recall	12.9	2.6	8–16	11.9	2.1	9–16
CVLT[a] delayed free recall[*]	12.8	2.0	10–15	10.8	2.8	7–15
CVLT[a] delayed cued recall[**]	13.6	2.1	10–16	11.5	2.2	7–15
NUY[b,c] paragraph immediate recall	8.3	2.3	6–13	8.4	2.1	6–12
NUY[b,c] paragraph delay recall[*]	11.8	2.8	7–13.5	9.6	1.8	7–13
Forward/backward Digit Span[c]	19.4	2.7	14–22	17.4	3.2	14–23
Digit/symbol substitution test[**]	67	8.9	56–86	49.6	9.9	28–65
Trail Making test A	23.6	6.7	12–33	26.9	5.9	18–39
Trail Making test B[**]	48.3	9.0	36–64	80.7	24.8	47–136
Letter Fluency	40.7	11.4	24–68	44.5	11.8	19–66
Category Fluency[d]	23.1	5.2	12–32	21.8	4.7	14–29
Wtar FSIQ[e]	114	4.9	104–120	114	3.0	108–117
Beck Depression inventory[*]	5.8	3.6	1–12	2.9	2.5	0–8

[a] California Verbal Learning Test.
[b] New York University.
[c] Scores for 15/16 older.
[d] Scores for 15/16 young.
[e] Wechsler Test of Adult Reading Full Scale Intellectual Quotient.
[*] Age-related difference significant at $P < .05$.
[**] Age-related difference significant at $P < .01$.

subjects out-performed the older group on tests of long-term memory and tests emphasizing speed of processing/executive functioning. The older subjects reported fewer depressive symptoms on the Beck depression inventory, although no subject in either group approached a score indicative of clinically significant depression. All but one older subject scored 28 or above on the MMSE. The remaining subject had a score of 26.

3.2. Behavioral performance

Percent accuracy on the study phase was analyzed with an age (young versus older adults) × difficulty (easy versus hard items) mixed design ANOVA. Performance in the easy condition was assessed by responses for the first presentation of each item only. Results revealed a main effect of age ($F(1,30) = 10.61$, $P = .003$), showing that young adults were more accurate than older adults in the easy condition (83% and 76% of accurate responses for young and older adults, respectively) and in the hard condition (84% and 80% for each age group, respectively). There was no difference in accuracy between the two conditions. ANOVA of the response time (RT) data revealed a significant effect of item difficulty ($F(1,30) = 13.63$, $P = .001$), reflecting a 63 ms advantage for items in the hard condition. There was neither an effect of age nor, importantly, and age by condition interaction (Fs < 1.5). This otherwise inexplicable difficulty effect in RT likely reflects a tendency across the study lists for the first presentations of items belonging to the easy condition to occur earlier rather than later in the list.

Behavioral performance in the test phase is summarized in Table 2. Proportion of correct rejections did not significantly differ between the two age groups ($F = 2.25$, $P > .1$). Item recognition performance was indexed by the discrimination index Pr, the proportion of studied items judged old, regardless of source accuracy, corrected by the false alarm rate (Pr = p(Hit) − p(False Alarm)) (Snodgrass and Corwin, 1988). A mixed age × difficulty ANOVA revealed a significant main effect of age ($F(1,30) = 7.76$, $P = .01$) and a significant age × difficulty interaction ($F(1.30) = 17.13$, $P < .001$). Follow-up pairwise contrasts showed that recognition performance was higher for young adults than for older adults in the hard condition ($t(30) = 3.31$, $P = .002$) but only marginally so in the easy condition ($t(30) = 2.02$, $P = .053$). Source recollection was measured using an index derived from a single high threshold model (Snodgrass and Corwin, 1988). This index ('Psr') estimates the proportion of correct source judgments that were associated with veridical source memory rather than lucky guesses, and was computed as: Psr = (p(Source Hit) − 0.5(1 − p(Source Unrecollected)))/(1 − (0.5(1 − p(Source Unrecollected)))), where Source Hit refers to studied items that were recognized and assigned to their correct encoding context and Source Unrecollected refers to recognized items for which the source could not be recollected (see Section 2). ANOVA revealed significant main effects of age ($F(1,30) = 9.23$, $P = .005$) and difficulty ($F(1,30) = 8.47$, $P = .007$), with no interaction between these two factors. Source recollection was greater in younger adults compared to older adults (.51 versus .33) and for easy items compared to hard items (.53 versus .31). Response bias was assessed with the index 'Br' (False Alarm rate/(1 − (Hit rate − False Alarm rate))), after adjusting hit and false alarm rates according to the formula ((number of hits or false alarms respectively + 0.5)/(number of old or new items respectively + 1)) (Snodgrass and Corwin, 1988). As there was only a single new item condition, the response bias index was computed using hit rates collapsed across the two difficulty conditions. The index did not differ across age groups ($t(30) = .26$, $P > .1$).

ANOVA of response latencies for source hits in the easy and hard conditions and for correct rejections revealed a main effect of age, with young adults responding more quickly than older adults (grand means of 1376 and 1636 ms, respectively; ($F(1,30) = 7.28$, $P = .01$). There were no reliable effects for

Table 2
Mean scores (and standard deviations in parentheses) on the test phase of the memory task

	Young adults		Older adults	
	Easy items	Hard items	Easy items	Hard items
Response rates				
Source hit	.78 (.15)	.59 (.13)	.66 (.14)	.47 (.21)
Source incorrect	.06 (.05)	.09 (.09)	.17 (.10)	.22 (.22)
Source unrecollected	.17 (.15)	.33 (.15)	.17 (.15)	.32 (.22)
Correct rejection	.94 (.10)		.88 (.13)	
Performance indices				
Item recognition (Pr)	.91 (.10)	.86 (.12)	.81 (.16)	.67 (.21)
Source recollection (Psr)	.64 (.20)	.39 (.16)	.43 (.20)	.22 (.22)
Response bias (Br)	.50 (.28)		.48 (.24)	
Latencies				
Source hit	1347 (291)	1484 (290)	1659 (287)	1803 (408)
Source incorrect	1478 (339)	1854 (584)	1671 (440)	1972 (518
Source unrecollected	1851 (481)	1794 (406)	2166 (500)	2281 (541)
Correct rejection	1295 (328)		1445 (217)	

response type or for the age × response type interaction ($P > .1$).

Overall, analyses of behavioral performance in the test phase revealed that young adults performed more accurately and more quickly than older adults. To determine whether, as anticipated (see Section 1), recognition performance and source recollection were equivalent for older subjects in the easy condition and young subjects in the hard condition, we directly contrasted Pr and Psr across these conditions. Results revealed no significant effects of age on either index (.86 and .81, respectively, for young and older adults on Pr, and .39 and .43, respectively, for each age group on Psr; $ts < 1$). ANOVA of the response latencies for source hits (from the easy and hard conditions for older and young subjects, respectively) and correct rejections revealed that correct rejections were associated with the faster responses ($F(1,30) = 22.44$, $P < .001$), but that the effects of age and its interaction with response type were not significant ($Ps > .08$).

Study judgments were associated with an error rate of around 19%. A substantial proportion of these errors likely reflect a degree of ambiguity with respect to the size of some of the presented objects relative to a 'shoe box'. When later memory performance was conditionalized on accuracy of the study judgment, no impact of accuracy at study could be detected in either age group on either recognition performance or source recollection ($Fs < 1.69$, $Ps > .10$). Accordingly, the fMRI subsequent memory analyses described below were based on all study items regardless of accuracy of the size judgment.

3.3. Functional data

Two main sets of analyses were conducted to identify the neural activity associated with successful source recollection in young and older adults. The first set of analyses identified the activity common to both age groups, and the second set of analyses sought for differences between the two groups. Activity associated with successful source rec-

ollection was identified by contrasting the BOLD response associated with successful source recollection with the activity elicited by correctly judged new items. In what follows, the term 'old > new' effect refers to greater activity for source hits compared to correct rejections, whereas the term 'new > old effect' refers to greater activity for correct rejections. As already noted, in the primary analyses described below, recollection-related activity was investigated independently of age-related differences in memory performance by restricting analyses to the source hit activity for hard items in the young group, and easy items in the older group.

Analyses were conducted separately on parameter estimates derived from the early and the late covariates. The results obtained from analyses of the late covariate either replicated, or did not alter, the interpretation of the results obtained with the early covariate. Therefore, we focus on the findings obtained for the early covariate, and we report results for the late covariate only when they provide additional information (the full set of results for the late covariate is available on request to the first author).

3.3.1. Old/new effects common to the two groups

Common effects were identified by exclusively masking the main effect of the old/new contrast with the two-sided (F) contrast of the age × old > new interaction, thresholded at $P < .05$. This procedure identifies voxels exhibiting statistically significant old/new effects that did not differ significantly between the two age groups. Results (see Table 3 and Fig. 1) revealed an extensive network of neural areas where activity was greater for source hits than for correct rejections. These areas included bilateral medial and lateral parietal cortex, left anterior and lateral prefrontal cortex.

The reverse new > old contrast revealed no area where activity across the two groups was significantly greater for correct rejections than for source hits. However, analyses employing the late covariate revealed some regions, mainly located in the right hemisphere, which exhibited a reliable new > old effect (see Table 3).

Table 3
Peak voxel of regions showing common old > new effects across age groups exclusively masked with the bidirectional interaction between age and old > new effect

| Location (x, y, z)	Peak z	N	Region	Brodmann area
Old > new effect on the early covariate				
−42, 48, 0	4.75	60	Left middle frontal gyrus	BA10
−45, 15, 36	4.08	126	Left middle frontal gyrus	BA9
−36, 9, 21	3.60	14	Left insula	BA13
−36, 12, −3	3.44	5	Left insula	BA13
−15, −12, −6	3.97	50	Subthalamic nucleus	
−30, −18, 30	3.98	38	Left insula	BA13
−30, −84, 36	4.94	996	Left precuneus	BA19
9, 0, 6	4.83	313	Right thalamus	
39, −81, 36	4.45	101	Right precuneus	BA19
New > old effect on the late covariate				
48, −3, 30	3.55	5	Right precentral gyrus	BA6
6, −51, 33	3.97	72	Right precuneus	BA31
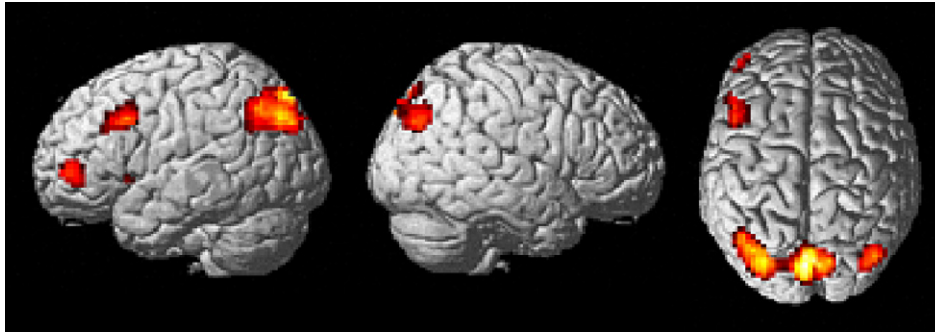
Fig. 1. Common effects of old vs. new items across age groups ($P < .0005$) exclusively masked with the bidirectional interaction between age and old vs. new effect ($P < .05$). The differential activity of old > new items is rendered onto the three-dimensional single-subject MNI reference brain.

3.3.2. Age-related differences in old/new effects

Age-related differences in recollection-related neural activity were identified by analysis of the age × old > new interaction effect. In the absence of a pre-experimental directional hypothesis, the two sides of the interaction were computed with directional *t*-test, each thresholded at $P < .0005$ to give a two-sided threshold of $P < .001$. The tests identified voxels where old > new differences were greater for older than for young subjects, and vice versa.

Six regions demonstrated old > new differences that were greater in magnitude in the older adults (see Table 4 and Fig. 2). To elucidate these interactions, the interaction contrast was inclusively masked with the old/new contrasts for each group separately (one-sided threshold of $P < .025$). This procedure revealed that in each of the aforementioned regions a substantial proportion of voxels (around 35% or more of the voxels in each region) demonstrated a reliable old > new effect in the older group. For the young subjects, reliable new > old effects were found in four of the regions, namely right fusiform and inferior occipital gyri, left anterior hippocampus and middle temporal gyrus (>40% of the voxels in each region). Thus, these four regions exhibited cross-over interactions. These interactions can be appreciated in the mean parameter estimates for voxels exhibiting the peak interaction effect in each region (see Fig. 2). In a fourth region (the left posterior hippocampus), fewer than 20% of the voxels in this cluster showed a reliable new > old effect across the young subjects. In the final region (the right middle temporal

gyrus), no voxels exhibited a reliable new > old effect. Thus, the age × old/new interactions in these two last regions were driven largely by the old > new effects in the older group.

For the early covariate, no voxels were detected where old > new effects were greater in magnitude in the young group. However, analyses of the late covariate revealed two regions – left inferior frontal and right medial frontal gyri – where old > new effects were larger in the young group (see Table 4). Inclusive masking between the interaction contrast and the old/new effects for each age group revealed reliable old > new effects in young adults for both areas. Older adults showed a reliable new > old effect in left inferior frontal gyrus, but no significant effects in right region.

3.3.3. Further analysis of age differences in old/new effects

The foregoing analyses employing data from the two conditions in which source memory performance was matched across the two age groups identified six regions where old > new effects (as characterized by the canonical HRF) were greater in magnitude in the older group. In four of these regions, the effects took the form of a cross-over interaction, such that younger subjects demonstrated reliable reversed effects. These findings raise two important questions: first, to what extent do they reflect the confounding effects of number of study presentations (whereas the hard condition required retrieval of items presented once only, the easy condition involved retrieval of items presented twice); and second, to

Table 4
Peak voxel of regions where old/new effects are greater in magnitude in one of the two age groups compared to the other group

| Location (x, y, z)	Peak z	N	Region	Brodmann area
Old > new effects of greater magnitude in older adults on the early covariate				
−57, 0, −21	3.88	23	Left middle temporal gyrus	BA21
−33, −18, −21	3.62	10	Left anterior hippocampus	
−33, −36, −3	4.73	37	Left posterior hippocampus	
60, −42, −6	3.43	5	Right middle temporal gyrus	BA21
48, −57, −21	4.60	56	Right fusiform gyrus	BA37
27, −93, −3	3.87	26	Right inferior/middle occipital gyrus	BA18
New > old effect of greater magnitude in young adults on the late covariate				
−39, 42, 3	3.67	23	Left inferior frontal gyrus	BA45
30, 60, 9	3.48	7	Right superior frontal gyrus	BA10
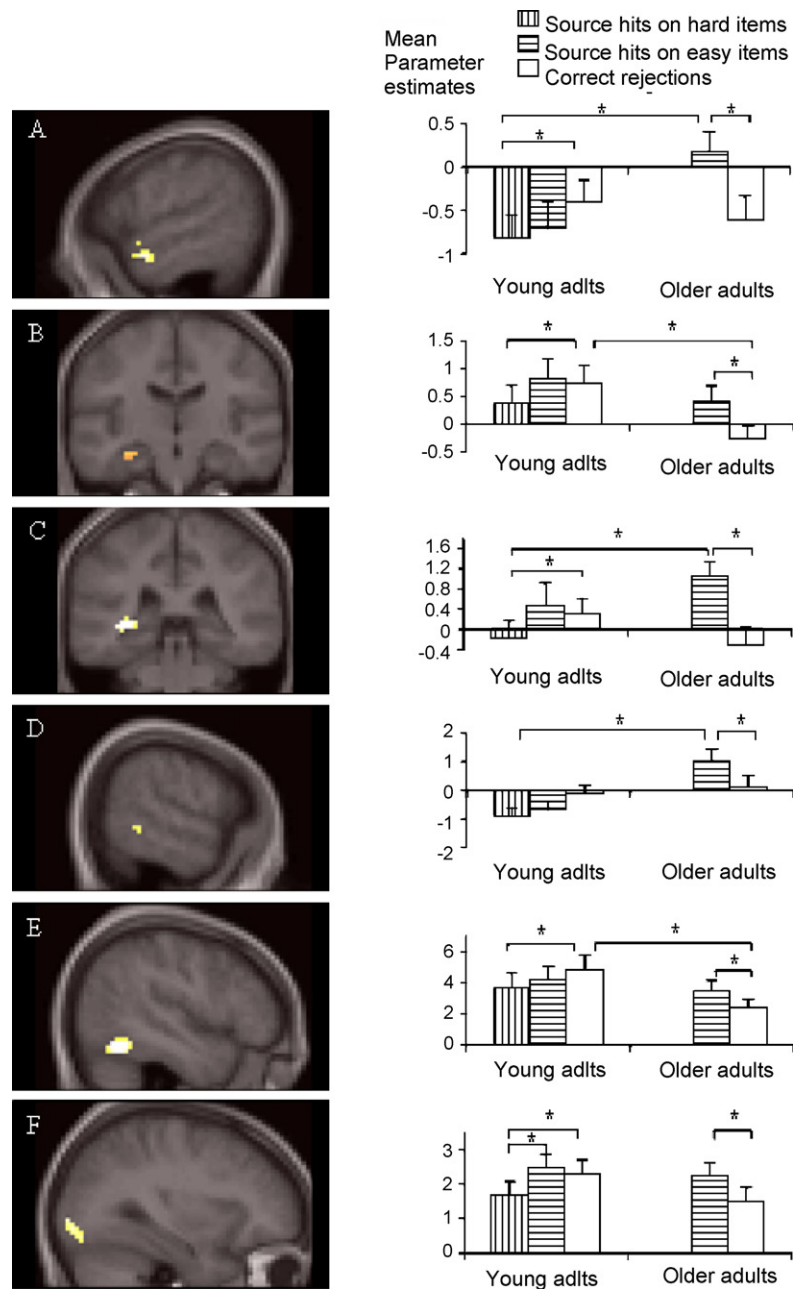
Fig. 2. Regions where old > new effects are greater in magnitude for older adults compared to young adults ($P < .0005$) are displayed on coronal and sagittal slices of the sample-specific template (i.e., average of subjects' normalized T1 images). Graphs represent the parameter estimates of the peak voxel for each region and class of test item. A: left middle temporal; B: left anterior hippocampus; C: left posterior hippocampus; D: right middle temporal; E: right fusiform gyrus; F: right inferior occipital gyrus (*$P < .05$).

what extent can these effects be linked specifically to recollective processing, rather than more generic effects of recognition memory or repetition of across the study and test phases?

To address the first question we repeated the original analysis, but employing data from the easy condition alone, when both groups were retrieving items that had received two study presentations. When the age × old > new interaction (thresholded at $P < .05$, two-sided) was inclusively masked by the original interaction contrast (thresholded as before at $P < .001$, two-sided), only one of the regions identified

in the original analysis – the left anterior hippocampus – failed to demonstrate an effect. These results suggest that the findings reported for the conditions where performance was matched do not in general reflect a confound with the number of study presentations. The outcome of analyses contrasting the parameter estimates illustrated in Fig. 2 adds further weight to this conclusion. For each region, the parameter estimates for the easy source hits and the correct rejections were subjected to a 2 (source hit versus correct rejection) by 2 (age group) ANOVA. In every region except for the right
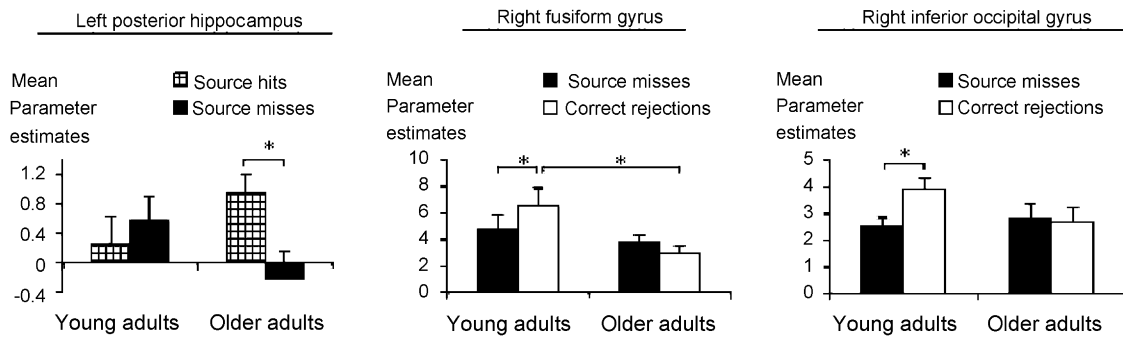
Fig. 3. Parameter estimates of peak voxel in left posterior hippocampus identified with the interaction between age and source hits vs. misses inclusively masked with the original interaction between age and old vs. new effect, and parameter estimates of peak voxel in right fusiform and inferior occipital gyri identified with the interaction between age and source misses vs. new items inclusively masked with the original interaction between age and old vs. new effect (*$P < .05$).

inferior occipital gyrus and left anterior hippocampus, there was a significant condition × age group interaction (minimum two-tailed $P < .005$). Moreover, pairwise contrasts of the parameter estimates for easy and hard source hits in the young subjects revealed only one region – right inferior occipital gyrus – where these estimates differed significantly ($P < .01$; all other $Ps > .1$) Together, these findings suggest that, in contrast to the remaining regions, caution is required in attributing the age × old > new interaction in the right inferior occipital gyrus or the left anterior hippocampus to the effects of age *per se*.

To address the question of the functional significance of the age × old > new interactions described above, two additional analyses were performed. Both analyses were based on an analysis model that collapsed the functional data across difficulty conditions. Three events of interest were defined: source hits, source misses, and correct rejections (additional covariates modeled the rest break, events of no interest, movement-related variance, and a constant). By comparing source hits with source misses, regions selectively associated with successful recollection can be identified. The contrast between source misses and correct rejections permits identification of regions exhibiting either generic recognition responses or mere repetition effects.

Inclusive masking of the age × source hit > miss interaction (thresholded at $P < .05$, two-sided) with the original bidirectional interaction between age and old > new items ($P < .001$, two-sided), revealed a single cluster in left posterior hippocampus ($x, y, z = -30, -36, 0$; $z = 2.89$). As is evident from the parameter estimates illustrated in Fig. 3, this effect reflected greater activity for source hits than for misses in the older group, coupled with no significant effects in the young subjects.

An analogous analysis was conducted in respect of the age × source miss > new item contrast. Two clusters were identified: in right fusiform gyrus ($x, y, z = 48, -60, -24$; $z = 3.90$) and right inferior occipital gyrus ($x, y, z = 33, -87, -12$; $z = 2.81$). The parameter estimates illustrated in Fig. 3 demonstrate that these effects are driven exclusively by new > old effects in the young group.

3.3.4. Age-related differences in the lateralization of old/new effects

In a final analysis we investigated whether, as predicted by the HAROLD model (Cabeza, 2002), laterality of retrieval-related cortical activity differed between young and older subjects. Parameter estimates were extracted from three pairs of voxels of interest. The regions were initially identified in the left hemisphere based on the main old > new effect common to both age groups: inferior frontal gyrus ($x, y, z = -42, 51, 0$), middle frontal gyrus ($x, y, z = -45, 15, 36$), and inferior parietal cortex ($x, y, z = -30, -84, 36$). Parameter estimates from these voxels were contrasted with those from homotopic loci in the right hemisphere. Analyses of variance with factors of age, old versus new, region (inferior frontal, middle frontal, parietal), and hemisphere, revealed a main old > new effect ($F(1,30) = 28.6$, $P < .001$), which interacted both with region ($F(2,29) = 4.90$, $P = .015$) and hemisphere ($F(1,30) = 12.40$, $P = .001$). The main effect of age was not significant and, crucially, age did not significantly interact with any other factor ($Fs < 2.2$, $Ps > .13$)).

4. Discussion

The purpose of the present study was to further elucidate age-related commonalities and differences in the neural correlates of episodic retrieval, in an experimental context where memory performance were closely matched between young and older adults. Overall, our results are consistent with the key findings of Morcom et al. (2007), and suggest that there is no major functional reorganization of the neural substrates of source recollection with increasing age. That said, robust age differences in retrieval-related activity were evident in medial temporal and posterior cortical regions. In a striking parallel with the findings of Morcom et al. (2007), these differences almost invariably took the form of larger old > new effects in the older than the young subjects. Also consistent with Morcom et al. (2007), there was no evidence for a more bilateral distribution of retrieval-related activity in the older than in the young

group, and thus no support for the HAROLD model (Cabeza, 2002).

At the behavioral level, memory performance of young and older subjects demonstrated the typical pattern of age-related differences with respect to item memory and source recollection. Crucially, through the manipulation of the number of study presentations, it was possible to compare retrieval-related activity between young and older subjects under conditions where item memory and source recollection were statistically equivalent, and differences in response latency were non-significant. Moreover, through the employment of a test procedure that allowed subjects to signal when they could not recollect the source of a recognized study item, the diluting effects of lucky guesses on recollection-related activity were minimized.

Before discussing the fMRI findings, one caveat should be noted. In our principal analyses, we operationalized recollection-related neural activity in the contrast between source hits and correct rejections, as was also the case in the study of Morcom et al. (2007). Whereas this contrast undoubtedly captures activity associated with successful recollection, it is not 'process pure'; to the extent that recollected items also elicited a familiarity signal, the outcome of the contrast would also include the neural correlates of familiarity. Thus, if these correlates differ according to age (see Duarte et al. (2006) for suggestive ERP evidence), the findings depicted in Fig. 2 may not be attributable solely to age-related differences in recollection-related activity. Whereas our subsidiary analyses go some way toward addressing this issue (see below), this caveat should nonetheless be borne in mind.

Turning to the fMRI data, we first discuss recollection-related effects common to the two age groups. As already noted, there was substantial overlap between the groups in the cortical regions demonstrating old > new effects. Among these regions were several that have been consistently identified in prior studies of episodic retrieval in young subjects, including medial and lateral parietal cortex bilaterally, as well as left dorsolateral and anterior prefrontal cortex (see Rugg et al., 2002; Rugg and Yonelinas, 2003; Wagner et al., 2005 for reviews). A very similar network of common effects was described by Morcom et al. (2007) (see also Cabeza et al. (2004) and Daselaar et al. (2003b)). In that study, however, several of these regions were adjacent to regions where recollection-related activity (in the form of old > new effects) was greater in the older group. These findings were interpreted by Morcom et al. (2007) as evidence that, in attaining the same level of performance as younger subjects, older subjects demonstrate a rather general pattern of cortical 'over-recruitment'. They suggested that this pattern might be a reflection of an age-related reduction in neural efficiency. In the present study, by contrast, regions exhibiting age-related interactions in retrieval-related activity were distinct from those showing common effects, and hence there was no indication of age-related over-recruitment in a common retrieval network. As was noted in Section 1 (see also Morcom et al., 2007), it is possible that the age-related effects

in the prior study reflected, in part, reliance on recollection of different types of information in the two groups (sensory/perceptual versus conceptual) rather than differential processing of a single kind of information. This possibility receives support from the present findings, in that the employment of a source memory task that enforced a more uniform retrieval strategy across the two groups (recollection of perceptual information) appears to have been sufficient to eliminate (or, at, least, to substantially attenuate) most of the cortical over-recruitment effects described by Morcom et al. (2007).

Although age differences in retrieval-related activity were considerably less widespread than in the study of Morcom et al. (2007), those that were detected took the same general form as in the prior study. For the analyses conducted with the early covariate, on which we focus below, no region was found where old > new effects were smaller in magnitude in the older group. By contrast, in all but one region, age by old/new interactions took the form of a cross-over, such that old > new effects in the older group were accompanied by new > old effects in the young subjects. Together with the findings of Morcom et al. (2007), the present results suggest that, when recollection is equated, there is little evidence for attenuated activity in older subjects in regions considered to support recollection-related processes in the young. These findings contrast with those of Daselaar et al. (2006), who described an age-related reduction in recollection-related activity in both the medial temporal lobe and lateral parietal cortex. As was noted in Section 1, this finding likely reflects the fact that the probability of successful recollection was higher in the young than in the older group. A similar explanation may underlie the findings of reduced retrieval-related activity in older subjects that have been reported in some studies employing blocked rather than event-related designs (e.g., Anderson et al., 2000; Cabeza et al., 1997; Grady et al., 2005; Madden et al., 1999a; Schiavetto et al., 2002).

In the present study, we attempted to elucidate the functional significance of the age by old/new interaction effects discussed above by employing two further contrasts intended to identify which of these effects were associated specifically with source recollection, and which with item-specific memory. The outcomes of these contrasts should be treated with some caution, since they are based on data derived from collapsing the two difficulty conditions to yield categories of recognized study items associated with successful or unsuccessful source retrieval. The contrast between the two classes of study item revealed, in the left posterior hippocampus, a recollection effect (source correct > source incorrect) in older subjects, but no significant effects in the young. The finding of greater hippocampal activity in older subjects for successfully recollected relative to unrecollected items is reminiscent of recollection-selective hippocampal effects in studies of young subjects (e.g., Dobbins et al., 2003; Eldridge et al., 2000; Yonelinas et al., 2005).

The question arises however why, in the present case, the posterior hippocampus demonstrated recollection effects for

older subjects only. One possibility is that this finding is a consequence of differences in the processing accorded to new items. By this argument (Morcom et al., 2007), young subjects devoted processing resources to the encoding of new items, such that both old and new items activated the hippocampus (Stark and Okado, 2003). The more limited resources available to older subjects however were focused on recollective processing, giving rise to differential old and new item activity. A second possible explanation of differential hippocampal effects concerns an age-related degradation in hippocampal efficiency, perhaps related to the micro-structural and neurochemical changes that occur in this structure with increasing age (Driscoll et al., 2003; Schiltz et al., 2006). By this argument, the enhanced hippocampal effects observed here represent a form of compensatory over-recruitment, reflecting the need for greater neuronal activation to achieve the same level of recollection performance as in younger subjects. Similar proposals have been advanced to account for the finding of enhanced hippocampal activity in older subjects carrying the e4 allele of the apolipoprotein E (APOE) gene relative to carriers of the e3 allele (Bondi et al., 2005; Bookheimer et al., 2000; see however Lind et al., 2006, for a different account). Enhanced hippocampal activity was also observed in patients in the early stages of mild cognitive impairment compared to controls (Celone et al., 2006; Dickerson et al., 2004, 2005), prompting Dickerson et al. (2004, 2005) to argue that hippocampal over-recruitment may be pathognomic of MCI, reflecting the early pathological changes that eventually culminate in Alzheimer's disease. The present finding that a similar phenomenon can be observed in high functioning older adults relative to younger subjects casts doubt on this proposal, and suggests that hippocampal over-recruitment may be a more general response to a decline in neural efficiency regardless of whether or not the decline is pathological in origin.

As was noted previously, some prior studies of healthy aging have reported attenuated retrieval-related medial temporal lobe activity in older relative to young subjects (Cabeza et al., 2004; Daselaar et al., 2006; Grady et al., 2005; Schiavetto et al., 2002; see however Maguire and Frith (2003) for age-related enhancement of hippocampal activity in autobiographical event memory). We have already noted that findings of reduced retrieval-related activity may be a reflection of differences in performance between the two groups. In the present study, however, the finding of greater recollection-related hippocampal activity in older subjects was obtained from data that, because they were collapsed across the two difficulty conditions, were associated with substantially poorer source recollection in the older subjects. On the assumption that the 'source miss' responses in the present study would have been divided equally between correct and incorrect source judgments in a conventional forced choice test of source memory, had such a test been employed here approximately 76% of younger subjects' correct source judgments would have been associated with veridical source

memory, whereas only 55% of the older subjects' judgments would have been veridical (Rugg et al., 1998). Under these circumstances, therefore, recollection-related activity in the older group would have been diluted by lucky guesses to a markedly greater extent than in the young. To the extent that subjects in the present study employed the 'no source recollection' option as instructed, however, the proportion of source correct trials due to lucky guessing would be negligible. Thus, the impact of the aforementioned age-related difference in source recollection was substantially mitigated by the employment of this response option.

In a second analysis, we addressed the question whether any of the regions demonstrating an age × old/new interaction were associated with item-specific memory, rather than source recollection. This was accomplished by contrasting activity elicited by recognized items for which source recollection was inaccurate or unavailable, with activity elicited by correctly judged new items. The results revealed that the effects of age on retrieval-related activity in right fusiform cortex were driven by a new > old effect in young subjects, in the absence of a reliable effect in either direction in older subjects. The interpretation of these findings is uncertain. On the one hand, 'repetition suppression' effects in extrastriate visual cortex have consistently been associated with visual repetition priming, a form of implicit memory (see Henson, 2003 for review). From this perspective, the fact that the locus of the fusiform region demonstrating new > old effects in the current study overlaps right fusiform regions implicated in visual object repetition priming in prior studies (Buckner et al., 1998; Koutstaal et al., 2001) might be taken as evidence that present effects reflect an influence of age on such priming processes. On the other hand, the present effects were obtained in a direct test of recognition memory, wherein repeated items were overtly discriminated from the new items. Thus, it is not possible to definitively rule out an association between these effects and item-specific recognition memory. Whereas new > old effects in anterior medial temporal cortex have been linked to familiarity-driven recognition memory (Henson et al., 2003), however, we are unaware of prior evidence supporting such a link between recognition memory and new > old effects in other cortical regions. For the present, therefore, we assume that the fusiform effects obtained here in our young subjects are more likely to reflect processes linked to repetition priming than to overt recognition memory.

If the age by old/new interaction observed in right fusiform cortex does indeed reflect an age effect on the neural correlates of repetition priming, how should this be explained? Numerous studies have reported that behavioral measures of implicit memory, including repetition priming, differ little, if at all, as a function of age (see Fleischman and Gabrieli, 1998; Light et al., 2000 for reviews). It is noteworthy, however, that a few behavioral studies have reported age-related attenuation of perceptual priming effects (Cherry and St Pierre, 1998; Maki et al., 1999; Pilotti et al., 2003). Moreover, a recent fMRI study (Daselaar et al., 2005) reported age-related

attenuation of the neural correlates of word-stem completion priming in right occipital regions. Further, using an adaptation procedure, Chee et al. (2006) reported an age-related attenuation of repetition suppression effects in fusiform cortex for visual objects. Importantly, this finding was selective for a condition in which the background context associated with the objects varied across successive presentations. To the extent that the present study implemented a similar manipulation (objects were presented against laterally positioned colored backgrounds at study, and against a central black background at test), the present findings may also reflect an age-related sensitivity to the effects of context change on fusiform repetition suppression effects.

Alternatively, the findings might be a reflection of age-related changes in the functional organization of visually selective processing in extrastriate cortex (see also Chee et al., 2006). This account is motivated by the finding that, relative to young subjects, older subjects demonstrate a 'de-differentiation' in the functional response of this cortical region (Park et al., 2004). That is, regions that in young subjects demonstrate selectivity for specific classes of visual stimuli (e.g. faces, objects, or scenes) are more uniformly responsive (i.e. less selective) in older subjects. By this account, the present findings reflect a shift from a relatively focal locus for visual object processing in young subjects, to a more diffusely distributed network of neural populations in older individuals. This breakdown in functional specialization would lead to a repetition priming effect that is diffusely distributed over a relatively large cortical expanse, such that the effect is weaker (and, in the present case, undetectable) at the voxel level. In support of this account, it is noteworthy that, in the present study, the magnitude of the right fusiform response to new items was reliably smaller in the older group ($P < .02$, two-tailed). This is consistent with the possibility that compared to young subjects, the magnitude of right fusiform functional response in older subjects is spatially diluted. Adjudicating between these two hypotheses, that propose an age-related decline in processes supporting priming, and age-related changes in cortical functional organization, respectively, will require the combined study of behavioral and neural indices of object repetition priming in the setting of an indirect memory test.

5. Concluding comments

The present findings are consistent with prior results suggesting that successful recollection engages much of the same neural circuitry in young and older subjects (Cabeza et al., 2004; Daselaar et al., 2003b; Morcom et al., 2007). The findings further suggest that, when differences in retrieval strategy and memory performance between age groups are controlled, age-related differences in retrieval-related activity are confined to relatively few regions, and provide little evidence for a diminution in such activity with increasing age. Furthermore, these differences do not appear to

be easily subsumed under a single explanatory principle. Whereas the age-related differences in hippocampal activity that were observed here may reflect a compensatory response to a decline in neural efficiency (Dickerson et al., 2004, 2005), differential effects in extrastriate visual cortex may be better explained as a consequence of de-differentiation of cortical function (Park et al., 2004), or a decline in context-dependent repetition priming (Chee et al., 2006). A crucial issue for future research is to determine whether these age-related changes in the neural correlates of memory retrieval contribute to, or ameliorate, age-related decline in memory performance.

Disclosure statement

Acknowledgments

References

Anderson, N.D., Iidaka, T., Cabeza, R., Kapur, S., McIntosh, A.R., Craik, F.I., 2000. The effects of divided attention on encoding- and retrieval-related brain activity: a PET study of younger and older adults. J. Cogn. Neurosci. 12, 775–792.

Andrade, A., Paradis, A.-L., Rouquette, S., Poline, J.-B., 1999. Ambiguous results in functional neuroimaging data analysis due to covariate correlation. Neuroimage 10, 483–486.

Ashburner, J., Friston, K.J., 1999. Nonlinear spatial normalization using basis functions. Hum. Brain Mapp. 7, 254–266.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.

Birren, J.E., 1965. Age changes in speed of behavior: its central nature and physiological correlates. In: Welford, A.T., Birren, J.E. (Eds.), Behavior, Aging, and the Nervous System. Thomas, Springfield, IL, pp. 191–216.

Bondi, M.W., Houston, W.S., Eyler, L.T., 2005. Brown GG. fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. Neurology 64, 501–508.

Bookheimer, S.Y., Strojwas, M.H., Cohen, M.S., Saunders, A.M., Pericak-Vance, M.A., Mazziotta, J.C., Small, G.W., 2000. Patterns of brain activation in people at risk for Alzheimer's disease. N. Engl. J. Med. 343, 450–456.

Buckner, R.L., Goodman, J., Burock, M., Rotte, M., Koutstaal, W., Schacter, D., Rosen, B., Dale, A.M., 1998. Functional-anatomic correlates of object priming in humans revealed by rapid presentation event-related fMRI. Neuron 20, 285–296.

Cabeza, R., 2002. Hemispheric asymmetry reduction in old adults: the HAROLD Model. Psychol. Aging 17, 85–100.

Cabeza, R., Anderson, N.D., Houle, S., Mangels, J.A., Nyberg, L., 2000. Age-related differences in neural activity during item and temporal-order memory retrieval: a positron emission tomography study. J. Cogn. Neurosci. 12, 197–206.

Cabeza, R., Anderson, N.D., Locantore, J.K., McIntosh, A.R., 2002. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage 17, 1394–1402.

Cabeza, R., Daselaar, S.M., Dolcos, F., Prince, S.E., Budde, M., Nyberg, L., 2004. Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. Cereb. Cortex 14, 364–375.

Cabeza, R., Grady, C.L., Nyberg, L., McIntosh, A.R., Tulving, E., Kapur, S., Jennings, J.M., Houle, S., Craik, F.I., 1997. Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. J. Cogn. Neurosci. 17, 391–400.

Celone, K.A., Calhoun, V.D., Dickerson, B.C., Atri, A., Chua, E.F., Miller, S.L., DePeau, K., Rentz, D.M., Selkoe, D.J., Blacker, D., Albert, M.S., Sperling, R.A., 2006. Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. J. Neurosci. 26, 10222–10231.

Cerella, J., 1985. Information processing rates in the elderly. Psychol. Bull. 98 (1), 67–83.

Chee, M.W., Goh, J.O., Venkatraman, V., Tan, J.C., Gutchess, A., Sutton, B., Hebrank, A., Leshikar, E., Park, D., 2006. Age-related changes in object processing and contextual binding revealed using fMR adaptation. J. Cogn. Neurosci. 18, 495–507.

Cherry, K.E., St Pierre, C., 1998. Age-related differences in pictorial implicit memory: role of perceptual and conceptual processes. Exp. Aging Res. 24, 53–62.

Cocosco, C.A., Kollokian, V., Kwan, R.K.S., Evans, A.C., 1997. Brainweb: online interface to a 3D MRI simulated brain database. Neuroimage 5, 425.

Craik, F.I.M., 1977. Age differences in human memory. In: Birren, J.E., Schaie, K.W. (Eds.), Handbook of the Psychology. Van Nostrand Reinhold, New York.

Craik, F.I.M., Byrd, M., 1982. Aging and cognitive deficits: the role of attentional resources. In: Craik, F.I.M., Trehub, S. (Eds.), Aging and Cognitive Processes. Plenum Press, New York, pp. 191–211.

Craik, F.I.M., Jennings, J.M., 1992. Human memory. In: Craik, F.I.M., Salthouse, T.A. (Eds.), The Handbook of Aging and Cognition. Erlbaum, Hillsdale, NJ, pp. 51–110.

Daselaar, S.M., Fleck, M.S., Dobbins, I.G., Madden, D.J., Cabeza, R., 2006. Effects of healthy aging on hippocampal and rhinal memory functions: an event-related fMRI study. Cereb. Cortex.

Daselaar, S.M., Veltman, D.J., Rombouts, S.A., Raaijmakers, J.G., Jonker, C., 2003a. Deep processing activates the medial temporal lobe in young but not in old adults. Neurobiol. Aging 24, 1005–1011.

Daselaar, S.M., Veltman, D.J., Rombouts, S.A., Raaijmakers, J.G., Jonker, C., 2003b. Neuroanatomical correlates of episodic encoding and retrieval in young and elderly subjects. Brain 126, 43–56.

Daselaar, S.M., Veltman, D.J., Rombouts, S.A., Raaijmakers, J.G., Jonker, C., 2005. Aging affects both perceptual and lexical/semantic components of word stem priming: an event-related fMRI study. Neurobiol. Learn. Mem. 83, 251–262.

Dickerson, B.C., Salat, D.H., Bates, J.F., Atiya, M., Killiany, R.J., Greve, D.N., Dale, A.M., Stern, C.E., Blacker, D., Albert, M.S., Sperling, R.A., 2004. Medial temporal lobe function and structure in mild cognitive impairment. Ann. Neurol. 56, 27–35.

Dickerson, B.C., Salat, D.H., Greve, D.N., Chua, E.F., Rand-Giovannetti, E., Rentz, D.M., Bertram, L., Mullin, K., Tanzi, R.E., Blacker, D., Albert, M.S., Sperling, R.A., 2005. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. Neurology 65, 404–411.

Dobbins, I.G., Davachi, L., 2006. Functional neuroimaging of episodic memory. In: Cabeza, R., Kingstone, A. (Eds.), Handbook of Functional Neuroimaging of Cognition, 2nd ed. MIT Press, Cambridge, MA, pp. 229–268.

Dobbins, I.G., Rice, H.J., Wagner, A.D., Schacter, D.L., 2003. Memory orientation and success: separable neurocognitive components underlying episodic recognition. Neuropsychologia 41, 318–333.

Dolcos, F., Rice, H.J., Cabeza, R., 2002. Hemispheric asymmetry and aging: right hemisphere decline or asymmetry reduction. Neurosci. Biobehav. Rev. 26, 819–825.

Driscoll, I., Hamilton, D.A., Petropoulos, H., Yeo, R.A., Brooks, W.M., Baumgartner, R.N., Sutherland, R.J., 2003. The aging hippocampus: cognitive, biochemical and structural findings. Cereb. Cortex 13, 1344–1351.

Duarte, A., Ranganath, C., Trujillo, C., Knight, R.T., 2006. Intact recollection memory in high-performing older adults: ERP and behavioral evidence. J. Cogn. Neurosci. 18, 33–47.

Eldridge, L.L., Knowlton, B.J., Furmanski, C.S., Bookheimer, S.Y., Engel, S.A., 2000. Remembering episodes: a selective role for the hippocampus during retrieval. Nat. Neurosci. 3, 1149–1152.

Fernandes, M.A., Pacurar, A., Moscovitch, M., Grady, C., 2006. Neural correlates of auditory recognition under full and divided attention in younger and older adults. Neuropsychologia 44, 2452–2464.

Fleischman, D.A., Gabrieli, J.D., 1998. Repetition priming in normal aging and Alzheimer's disease: a review of findings and theories. Psychol. Aging 13, 88–119.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini mental state: a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12 (3), 189–198.

Friston, K.J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M.D., Turner, R., 1998. Event-related fMRI: characterizing differential responses. Neuroimage 7, 30–40.

Friston, K.J., Glaser, D.E., Henson, R.N., Kiebel, S., Phillips, C., Ashburner, J., 2002. Classical and Bayesian inference in neuroimaging: applications. Neuroimage 16, 484–512.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.-B., Frith, C.D., Frackowiak, R.S.J., 1995. Statistical parametric maps in functional imaging; a general linear approach. Hum. Brain Mapp. 2, 189–210.

Gladsjo, J.A., Schuman, C.C., Evans, J.D., Peavy, G.M., Miller, S.W.H.R., 1999. Norms for letter and category fluency: demographic corrections for age, education, and ethnicity. Assessment 6, 147–178.

Gordon, N.G., 1972. The Trail Making Test in neuropsychological diagnosis. J. Clin. Psychiatry 28, 167–169.

Grady, C., McIntosh, A.R., Craik, F.I., 2005. Task-related activity in prefrontal cortex and its relation to recognition memory performance in young and old adults. Neuropsychologia 43, 1466–1481.

Grady, C.L., McIntosh, A.R., Craik, F.I., 2003. Age-related differences in the functional connectivity of the hippocampus during memory encoding. Hippocampus 13, 572–586.

Grady, C.L., McIntosh, A.R., Horwitz, B., Maisog, J.M., Ungerleider, L.G., Mentis, M.J., Pietrini, P., Shapiro, M.B., Haxby, J.V., 1995. Age-related reduction in human recognition memory due to impaired encoding. Science 269, 218–221.

Gutchess, A.H., Welsh, R.C., Hedden, T., Bangert, A., Minear, M., Liu, L.L., Park, D.C., 2005. Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. J. Cogn. Neurosci. 17, 84–96.

Henson, R.N., 2003. Neuroimaging studies of priming. Prog. Neurobiol. 70, 53–81.

Henson, R.N.A., Cansino, S., Herron, J.E., Robb, W.G.K., Rugg, M.D., 2003. A familiarity signal in human anterior medial temporal cortex? Hippocampus 13, 259–262.

Howard, M.W., Bessette-Symons, B., Zhang, Y., Hoyer, W.J., 2006. Aging selectively impairs recollection in recognition memory for pictures: evidence from modeling and receiver operating characteristic curves. Psychol. Aging 21, 96–106.

Jennings, J.M., Jacoby, L.L., 1993. Automotic versus intentional uses of memory: aging, attention, and control. Psychol. Aging 8, 283–293.

Kluger, A., Ferris, S.H., Golomb, J., Mittleman, M.S., Reisberg, B., 1999. Neuropsychological prediction of decline to dementia in nondemented elderly. J. Geriatr. Psychiatry Neurol. 12, 168–179.

Koutstaal, W., Wagner, A.D., Rotte, M., Maril, A., Buckner, R.L., Schacter, D.L., 2001. Perceptual specificity in visual object priming: functional magnetic resonance imaging evidence for a laterality difference in fusiform cortex. Neuropsychologia 39, 184–199.

Li, J., Morcom, A.M., Rugg, M.D., 2004. The effects of age on the neural correlates of successful episodic retrieval: an ERP study. Cogn. Affect Behav. Neurosci. 4, 279–293.

Light, L.L., 1991. Memory and aging: four hypotheses in search of data. Annu. Rev. Psychol. 42, 333–376.

Light, L.L., Prull, M.W., La Voie, D., Healy, M.R., 2000. Dual-process theories of memory in old age. In: Perfect, T.J., Maylor, E.A. (Eds.), Models of Cognitive Aging. Oxford University Press, New York.

Lind, J., Persson, J., Ingvar, M., Larsson, A., Cruts, M., Van Broeckhoven, C., Adolfsson, R., Backman, L., Nilsson, L.G., Petersson, K.M., Nyberg, L., 2006. Reduced functional brain activity response in cognitively intact apolipoprotein E epsilon4 carriers. Brain 129, 1240–1248.

Logan, J.M., Sanders, A.L., Snyder, A.Z., Morris, J.C., Buckner, R.L., 2002. Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. Neuron 33, 827–840.

Madden, D.J., Gottlob, L.R., Denny, L.L., Turkington, T.G., Provenzale, J.M., Hawk, T.C., Coleman, R.E., 1999a. Aging and recognition memory: changes in regional cerebral blood flow associated with components of reaction time distributions. J. Cogn. Neurosci. 11, 511–520.

Madden, D.J., Turkington, T.G., Provenzale, J., Denny, L.L., Hawk, T.C., Gottlob, L.R., Coleman, R.E., 1999b. Adult age differences in functional neuroanatomy of verbal recognitinon memory. Hum. Brain Mapp. 7, 115–135.

Maguire, E.A., Frith, C.D., 2003. Aging affects the engagement of the hippocampus during autobiographical memory retrieval. Brain 126, 1511–1523.

Maki, P.M., Zonderman, A.B., Weingartner, H., 1999. Age differences in implicit memory: fragmented object identification and category exemplar generation. Psychol. Aging 14, 284–294.

Morcom, A.M., Good, C.D., Frackowiak, R.S., Rugg, M.D., 2003. Age effects on the neural correlates of successful memory encoding. Brain 126, 213–229.

Morcom, A.M., Li, J., Rugg, M.D., 2007. Age effects on the neural correlates of episodic retrieval: increased cortical recruitment with matched performance. Cereb. Cortex 17, 2491–2506.

Naveh-Benjamin, M., 2000. Adult age differences in memory performance: tests of an associative deficit hypothesis. J. Exp. Psychol. Learn Mem. Cogn. 26, 1170–1187.

Nilsson, L.G., 2003. Memory function in normal aging. Acta Neurol. Scand. Suppl. 179, 7–13.

Norman, M.A., Evans, J.D., Miller, W.S., Heaton, R.K., 2000. Demographically corrected norms for the California Verbal Learning Test. J. Clin. Exp. Neuropsychol. 22, 90–94.

Park, D.C., Gutchess, A.H., 2005. Long-term memory and aging: a cognitive neuroscience perspective. In: Cabeza, R., Nyberg, L., Park, D.C. (Eds.), Cognitive Neuroscience of Aging. Oxford University Press, New York, NY, pp. 218–245.

Park, D.C., Polk, T.A., Park, R., Minear, M., Savage, A., Smith, M.R., 2004. Aging reduces neural specialization in ventral visual cortex. Proc. Natl. Acad. Sci. U.S.A. 101, 13091–13095.

Pilotti, M., Meade, M.L., Gallo, D.A., 2003. Implicit and explicit measures of memory for perceptual information in young adults, healthy older adults, and patients with Alzheimer's disease. Exp. Aging Res. 29, 15–32.

Prull, M.W., Dawes, L.L., Martin AMr, Rosenberg, H.F., Light, L.L., 2006. Recollection and familiarity in recognition memory: adult age differences and neuropsychological test correlates. Psychol. Aging 21, 107–118.

Rajah, M.N., D'Esposito, M., 2005. Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. Brain 128, 1964–1983.

Raz, N., 1996. Neuroanatomy of aging brain: evidence from structural fMRI. In: Bigler, E.D. (Ed.), Neuroimaging. II. Clinical Implications. Academic Press, New York.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb. Cortex 15, 1676–1689.

Raz, N., Rodrigue, K.M., Head, D., Kennedy, K.M., Acker, J.D., 2004. Differential aging of the medial temporal lobe: a study of a five-year change. Neurology 62, 433–438.

Reuter-Lorenz, P., 2002. New visions of the aging mind and brain. Trends Cogn. Sci. 6, 394–400.

Reuter-Lorenz, P.A., Lustig, C., 2005. Brain aging: reorganizing discoveris about the aging mind. Curr. Opin. Neurobiol. 15, 245–251.

Rosen, A.C., Prull, M.W., O'Hara, R., Race, E.A., Desmond, J.E., Glover, G.H., Yesavage, J.A., Gabrieli, J.D.E., 2002. Variable effects of again on frontal lobe contributions to memory. Neuroreport 13, 2425–2428.

Rugg, M.D., Morcom, A.M., 2005. The relationship between brain activity, cognitive performance, and aging: the case of memory. In: Cabeza, R., Nyberg, L., Parlk, D. (Eds.), Cogntive Neuroscience of Aging. Oxford University Press, New York, NY, pp. 132–154.

Rugg, M.D., Otten, L.J., Henson, R.N., 2002. The neural basis of episodic memory: evidence from functional neuroimaging. Philos. Trans. R. Soc. Lond. B: Biol. Sci. 357, 1097–1110.

Rugg, M.D., Schloerscheidt, A.M., Mark, R.E., 1998. An electrophysiological comparison of two indices of recollection. J. Mem. Lang. 39, 47–69.

Rugg, M.D., Yonelinas, A.P., 2003. Human recognition memory: a cognitive neuroscience perspective. Trends Cogn. Sci. 7, 313–319.

Salthouse, T.A., 1985. A Theory of Cognitive Aging. Elsevier Science, Amsterdam.

Salthouse, T.A., 1996. The processing-speed theory of adult age differences in cognition. Psychol. Rev. 103, 403–428.

Schacter, D.L., Savage, C.R., Alpert, N.M., Rauch, S.L., Albert, M.S., 1996. The role of hippocampus and frontal cortex in age-related memory changes: a PET study. Neuroreport 7, 1165–1169.

Scheibel, A.B., 1979. The hippocampus: organizational patterns in health and senescence. Mech. Ageing Dev. 9, 89–102.

Schiavetto, A., Kohler, S., Grady, C.L., Winocur, G., Moscovitch, M., 2002. Neural correlates of memory for object identity and object location: effects of aging. Neuropsychologia 40, 1428–1442.

Schiltz, K., Szentkuti, A., Guderian, S., Kaufmann, J., Munte, T.F., Heinze, H.J., Duzel, E., 2006. Relationship between hippocampal structure and memory function in elderly humans. J. Cogn. Neurosci. 18, 990–1003.

Snodgrass, J.G., Corwin, J., 1988. Pragmatics of measuring recognition memory: applications to dementia and amnesia. J. Exp. Psychol. Gen. 117, 34–50.

Soukup, V.M., Ingram, F., Grady, J.J., Schiess, M.C., 1998. Trail Making Test: issues in normative data selection. Appl. Neuropsychol. 5, 65–73.

Stark, C.E., Okado, Y., 2003. Making memories without trying: medial temporal lobe activity associated with incidental memory formation during recognition. J. Neurosci. 23, 6748–6753.

van der Veen, F.M., Nijhuis, F.A., Tisserand, D.J., Backes, W.H., Jolles, J., 2006. Effects of aging on recognition of intentionally and incidentally stored words: an fMRI study. Neuropsychologia 44, 2477–2486.

Wagner, A.D., Shannon, B.J., Kahn, I., Buckner, R.L., 2005. Parietal lobe contributions to episodic memory retrieval. Trends Cogn. Sci. 9, 445–453.

Wechsler, D., 1981. Wechsler Adult Intelligence Scale-Revised. Psychological Corporation, New York.

Wechsler, D., 2001. Wechsler Test of Adult Reading. The Psychological Corporation, San Antonio, TX.

Yonelinas, A.P., 2002. The nature of recollection and familiarity: a review of 30 years of research. J. Mem. Lang. 46, 441–517.

Yonelinas, A.P., Otten, L.J., Shaw, R.J., Rugg, M.D., 2005. Separating the brain regions involved in recollection and familiarity in recognition memory. J. Neurosci. 25, 3002–3008.