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RAPID COMMUNICATION

Functional Phenotyping of Successful Aging in Long-Term Memory: Preserved Performance in the Absence of Neural Compensation

Emrah Düzel,[1,2,3*] Hartmut Schütze,[1] Andrew P. Yonelinas,[4] and Hans-Jochen Heinze[3,5]

ABSTRACT: We investigated whether preservation of encoding-related brain activity patterns in older age reflects successful aging in long-term memory. Using a statistical matching technique, we identified groups of healthy older adults with different degrees of Functional Activity Deviation during Encoding (FADE) from young adults in a memory network comprising hippocampal, temporal, occipital, and retrosplenial regions. High FADE scores were associated with impairment in recollection, abnormal activity in the default mode network, and lower gray matter density in bilateral ventral prefrontal cortex and left rhinal cortex; a constellation previously associated with increased risk for dementia. Low FADE scores functionally phenotyped successful aging because recollection was well preserved and there was no evidence for compensatory prefrontal activation. Thus, for some individuals successful aging in long-term memory reflects the preservation of a functionally specific memory network, and can occur in the absence of compensatory brain activity. © **2010 Wiley-Liss, Inc.**

KEY WORDS: aging; encoding; recollection; functional imaging; default network

INTRODUCTION

Aging is usually associated with a decline in the ability to recollect the details of recent episodes, but some individuals manage to maintain remarkably preserved memory abilities despite advances in age (Rowe and Kahn, 1987; Morrison and Hof, 1997). The functional and anatomical factors that preserve this ability in the aging brain are still largely unknown. In functional imaging studies of memory encoding, compared to younger subjects older adults show decreases in activation in regions known to be critical for forming episodic memories, such as the hippocampus and adjacent structures in the medial temporal lobe (MTL; Grady, 2007, 2008; Pihlajamaki et al., 2009), but they also show increases in activation in frontal and parietal regions [e.g., (Cabeza et al., 1997; Morcom et al., 2003; Duverne et al., 2009); for reviews see Grady (2008) and Pihlajamaki et al. (2009). These increases in activation have been interpreted as reflecting a compensatory neural or cognitive response that arises as a consequence of neural changes that accompany aging (e.g., Cabeza et al., 2002; Persson and Nyberg, 2006). Although compensatory neural responses may underlie the preserved memory abilities of some individuals, here we explore an alternative possibility, which is that truly successful aging of memory may occur in the absence of compensatory neural responses [see Grady (2007) and Raz (2007) for a discussion].

While it is generally accepted that age reductions in memory function can be tied, at least in part, to encoding-related activity reductions in the MTL (Grady et al., 1995; Cabeza et al., 1997; Grady, 2008), it is still unclear whether preserved functional activity is predictive of preserved memory ability in aging [see Grady (2007) and Raz (2007) for a discussion]. Although some recent findings are supportive of this possibility (Rosen et al., 2002; Persson et al., 2006; Duverne et al., 2009) the question whether preserved functional activity patterns are indicative of preserved memory function has not yet been addressed directly. For instance, Duverne et al. (2009) have compared encoding-related brain activity patterns in older individuals with high and low recognition memory performance (using a median split of their sample of older adults) and observed that whose with high recognition memory performance showed activity patterns that were functionally more similar to those of young adults. Although this finding suggests that maintaining functional similarity to the young is beneficial it remains indirect. A priori classifications on the basis behavior do not predict the memory profile of older adults if classifications were defined purely in terms of functional similarity. Furthermore, an a priori behavioral subdivision of older individuals into high and low performers precludes the distinction of high

[1] **Institute of Cognitive Neurology and Dementia Research, Otto-von Guericke Universität Magdeburg, Germany;** [2] **Institute of Cognitive Neuroscience, University College London, London, WC1N 3AR, United Kingdom;** [3] **German Centre for Neurodegenerative Disorders Magdeburg, Otto-von Guericke Universität Magdeburg, Germany;** [4] **Department of Psychology, Center for Mind and Brain, University of California, Davis, California;** [5] **Department of Neurology and Centre for Advanced Imaging, Otto von Guericke Universität, 39120 Magdeburg, Germany**

Additional Supporting Information may be found in the online version of this article.

*Correspondence to: Emrah Düzel, Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London, WC1N 3AR, United Kingdom. E-mail: e.duzel@ucl.ac.uk

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performing older adults into whose who are functionally similar to young adults and those who have low functional similarity but show functional recruitment of additional brain regions. In our opinion, only this latter approach (which we have taken here) will identify older adults who successfully use additional brain regions to maintain high level of memory performance and hence unravel truly compensatory brain activity patterns.

Closely related to these questions is the issue of functional specificity of age-related activity changes. That is, do encoding-related activity changes in aging specifically predict long-term memory function, or do they also relate to abilities in other cognitive domains such as attention, processing speed, and memory span [for discussions see (Grady, 2007; Greenwood, 2007; Raz, 2007)]. Furthermore, it is also unknown to what extent the preservation of encoding-related activity patterns from early to late adulthood is related to structural integrity within MTL as opposed to frontal or parietal regions [e.g., (Grady, 2007; Greenwood, 2007; Raz, 2007)].

We used a statistical matching procedure with fMRI to quantify similarities in encoding-related functional activity patterns between young and old adults. In 24 young adults, successful encoding of images of natural scenes activated the hippocampus, temporal, occipital, and retrosplenial regions. We used this encoding network in the young to functionally phenotype a sample of 56 healthy older adults, who performed the same fMRI task, into those who activated similar networks from those who did not. The results indicated that deviation from functional similarity or "functional activity deviation during encoding" (FADE) provided a useful marker for successful aging, such that individuals with high FADE scores exhibited greater deficits in recollection, and exhibited evidence for loss of gray matter density in bilateral ventral prefrontal cortex and left rhinal cortex. Furthermore, high FADE was associated with a failure to deactivate a set of regions, including medial and lateral parietal cortices, often referred to as components of the "default mode network" (Raichle et al., 2001; Andrews-Hanna et al., 2007; Persson et al., 2008; Grady et al., 2010).

MATERIALS AND METHODS

Subjects

Fifty six older subjects (mean age 65 ± 5.6 yrs, 28 males) and 24 young subjects (mean age 23 ± 2.2 yrs, 8 males) participated in the study. All elderly subjects were recruited for paid participation via newspaper or adult education centers, evening classes and elderly people societies. Young subjects were students or employees of the University of Magdeburg. Inclusion criteria for the old subjects were an age above 55 yr. Exclusion criteria were metallic implants, tinnitus, metabolic disorders, a history of neurological or psychiatric disorders, any other current medical problems, obesity (mean Body Mass Index = 26.0, SD = 3.7), Mini-Mental State Examination [MMSE (Folstein et al., 1983)] score $\leq$27 (mean MMSE = 29.2, SD = 0.8; MMSE), a Geriatric Depression Scale [GDS (Yesavage et al., 1982)] score $\geq$5 (mean GDS = 1.1; SD = 1.2), drug addiction and severe untreated hypertonia. Mild hypertonia (according to the WHO classification) treated with only one antihypertensive drug was not an exclusion criterion. The older participants reported an average of 15 ± 4 yr of education. All subjects had normal or corrected to normal vision, 32% were acute or former smokers. This study was approved by the local ethics committee. All subjects gave written informed consent prior to participation; 100 older adults were invited for neuropsychological assessment and of these 56 were willing to participate in the functional MR imaging experiment.

Neuropsychological Testing

Each subject was tested with a neuropsychological test battery consisting of the German versions of the "California verbal learning test" (CVLT, verbal learning and memory), the "controlled oral word association" (COWA, verbal fluency, 1 min, no verbs, no person names), the "Diagnosticum für cerebrale Schädigung" ("Diagnostic for cerebral damage", DCS, nonverbal learning and memory), the D2 test (processing speed, attention and concentration), the "trail making test"; TMT (motor speed and visual attention), the "digit span test" (verbal working memory, two trials per sequence length) and a German vocabulary knowledge test (a component index of verbal IQ, MWT-B). MMSE and GDS were only administered to the older adults. The whole test battery usually took 60–90 min to complete.

Magnetic Resonance Imaging (MRI)

MRI data were acquired using a GE Signa LX 1.5T MR tomograph (General Electric, Milwaukee, WI) with actively shielded magnetic field gradients (maximum amplitude 40 mT m^{-1}) and a standard quadrature birdcage head coil.

Prior to the functional MRI session a T1-weighted sagittal 3D scan (contrast-optimized spoiled gradient-echo sequence, 124 slices, 256 × 256 pixel matrix, field of view (FOV) = 250 × 250 mm^2, slice thickness = 1.5 mm, TE = 8 ms, TR = 24 ms; flip angle = 30°, leading to a voxel size of 0.98 mm × 0.98 mm × 1.5 mm) an inversion recovery (IR)-EPI and a "Spin Echo T1-weighted" (SE-T1) image were acquired. This was followed by fMRI of the encoding session of our experiment. Then, additional structural scans (T2-weighted imaging, proton density imaging, magnetization transfer imaging, diffusion-tensor series) were acquired (data from these additional structural scans will be considered else where). After leaving the MRI scanner, memory for the stimuli presented during encoding was probed using a recognition memory test.

Stimuli

The stimuli consisted of 120 digital photographic images, half indoor and half scenes, with a size of 500 × 300 pixels and 8-bit gray scales (mean gray value 127, SD 75). Scrambled "noise" pictures were generated by using an 8-bit 50 × 30

pixel random gray value image (same mean and std. dev.) and upsampling this to a resolution of 500 × 300 pixels (without antialiasing or smoothing). The fixation target was a black image of the same size with a white fixation star in the middle. The stimuli were projected onto the center of a screen and the participants watched them through a mirror mounted on the head coil, subtending a visual angle of about ±9° by ±5°.

Task and Design

During the fMRI session the subjects performed an incidental encoding task. One hundred and twenty new images (60 indoor and 60 outdoor), 60 "noise" images and 60 repetitions of a familiar image were presented randomly. The familiar images (either indoor and outdoor images) and the "noise" images were familiarized using 20 repetitions directly before MR scanning. This also served to familiarize subjects with the task. The stimuli were shown for 2.5-s each, with an average interstimulus-interval (ISI) of 500 μs (jittered with a standard deviation of about 260 ms), during which the fixation target was shown. The order of stimulus presentation was optimized for efficiency of event-related fMRI time-series (Hinrichs et al., 2000). Subjects performed an indoor/outdoor judgment to each image by button presses (left index finger for inside scenes and right index finger for outside scenes, counterbalanced across participants).

After a delay interval of about 85 min after starting the fMRI session, subjects performed a recognition memory task on a mixture of the 120 pictures presented during the fMRI and 60 novel distracter pictures (30 indoor to 30 outdoor). The task was performed outside of the scanner. Subjects rated their confidence of recognition memory on a scale ranging from 1 to 5 ("1": sure new; "2": may be new; "3": unsure whether old or new; "4": old; "5": sure old). These confidence ratings were used as parametric modulators in the analysis of the fMRI data and for the calculation of receiver operating characteristics of recognition memory.

fMRI Data Acquisition

Each subject's functional MRI scan consisted of 370 volumes with 23 T2*-weighted echo planar slices per volume, with a resolution of 64 × 64 (FoV: 200 mm × 200 mm; spatial resolution: 3.13 mm × 3.13 mm × 6 mm; slice thickness = 5 mm; gap = 1 mm; TE = 35 μs; TR = 2,000 μs; flip angle = 80°) in a single session, summing to a session length of about 12 min. The slices were acquired in an odd-even interleaved fashion parallel to the anterior–posterior commissural plane. Prior to functional data collection, six EPI volumes were acquired to allow for magnetic field stabilization; these volumes were later discarded from the analysis. For normalization purposes, an IR-EPI with the same resolution and slice orientation as the functional volumes was acquired for each subject. Additionally, a "Spin Echo T1-weighted" (SE-T1) volume with the same dimensions, but higher in-plane resolution, was measured for later anatomical localization of activated regions.

fMRI data pre-processing and statistical modeling was done using "SPM" (Wellcome Department of Cognitive Neuroscience, University College, London, UK). The preprocessing included slice timing correction, coregistering to the first functional image, normalizing to the SPM5 standard EPI template, reslicing to 3-mm isometric voxels, and finally smoothing with an 8-mm full-width half-maximum Gaussian kernel.

fMRI Data Analysis

Encoding-related hemodynamic responses were analyzed as a function of subsequent recognition memory success in the recognition memory test by sorting the stimulus onsets according to the five confidence rates. The onsets of the familiar and noise stimuli constituted two additional conditions. Together with the movement parameters and one "trash" condition this results in 14 conditions.

Three types of analyses were conducted leading to five types of contrasts (Fig. 1A). First, encoding activity leading to successful recognition memory was measured by contrasting two positive weights for later recognized stimuli (confidence ratings 4 and 5) and two negative weights of equal value for the later forgotten items (confidence ratings 1 and 2). This successful encoding contrast, termed the "recognition-encoding contrast" was used to assess FADE ("functional activity deviation during encoding") scores (see below). Second, encoding activity leading to later "familiarity"-based recognition was modeled assuming a linear increase of activation as a function of later confidence (1 to 4) and not considering responses that fell into the highest confidence rating (5). To model encoding activity leading to later "recollection" a strong positive weight was given to the highest confidence rating (5) and weak negative weights for all other ratings. This was done under the assumption that recollection is associated with high confidence responses. Third, encoding-related "deactivations" were assessed using the negative weights of the familiarity and recollection regressors. All contrasts were balanced to a mean weight of zero.

Assessment of FADE (''Functional Activity Deviation During Encoding'') Using Goodness-of-Fit

The network of brain regions activated in the recognition-encoding contrast of the young (see Fig. 1) was used as a template to assess FADE. All activated clusters ($P < 0.001$, $N > 6$ voxels) were included to form a volume of interest (VOI). This VOI was used to calculate an individual "Goodness of Fit" value [for a similar procedure using structural data see (Seeley et al., 2009)] for older adults by subtracting the mean T value of all voxels inside from the mean T value of all voxels outside the VOI. A highly positive FADE score would signify a large deviation of an older adult's individual encoding effect from that seen in the young subjects. In contrast, a large negative value would indicate a high degree of similarity with young subjects. The FADE scores ranged from −1.3 to 1 (mean −0.028 ± 0.43). We subdivided the older adults into three groups with high (Group 1: > 0.3), intermediate (Group 2: −0.3 to 0.3) and low (Group 3: < −0.3) FADE scores.

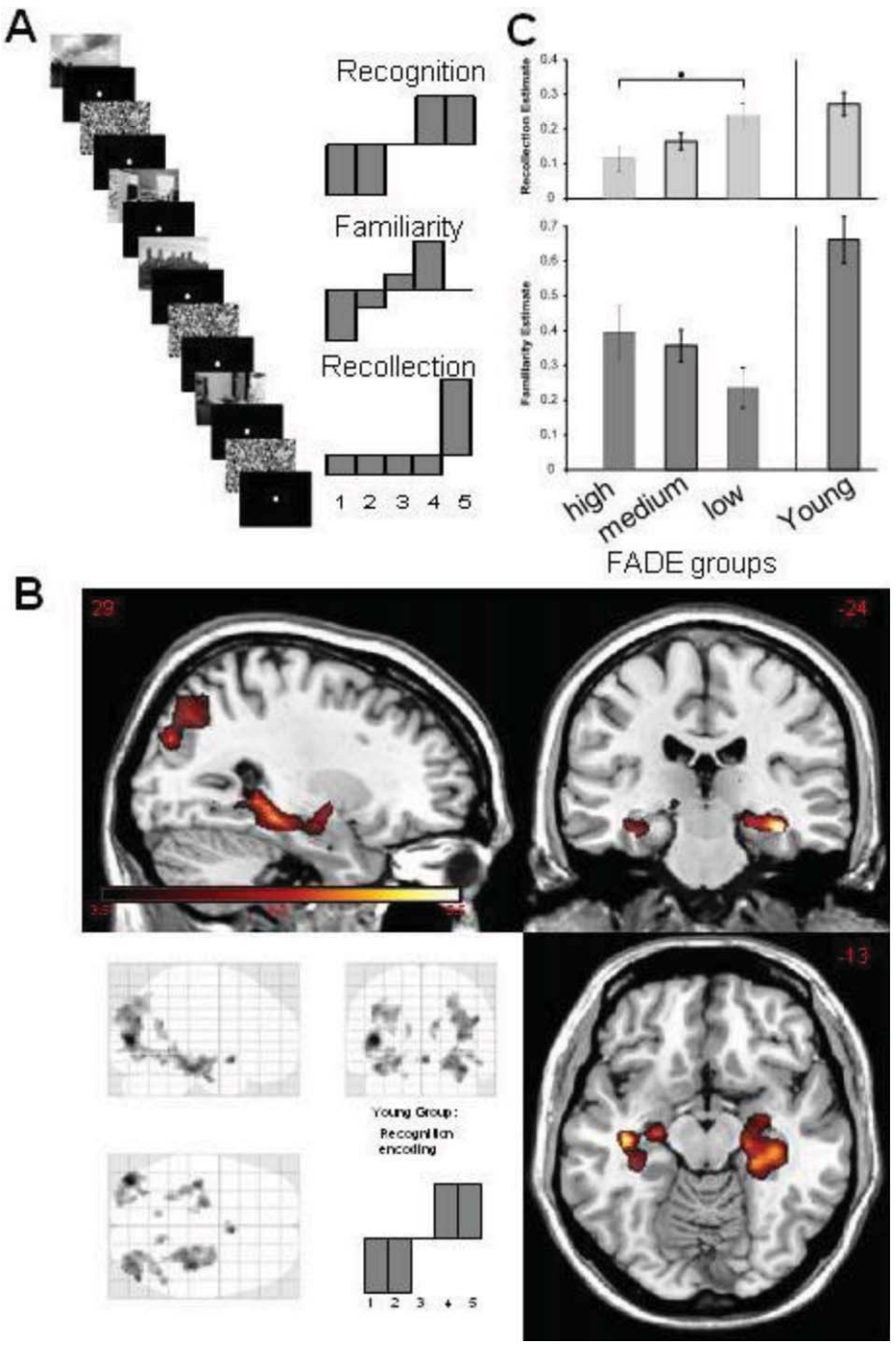

FIGURE 1. Analysis contrasts, behavioral and functional findings. (A) Contrast weights used to model hemodynamic responses at encoding as a function of later recognition memory confidence (1 to 5). There were three types of contrast: the recognition-encoding contrast (high confidence recognition items minus forgotten items), the familiarity-encoding contrast (linear increase in recognition confidence excluding the highest confidence level) and the recollection-encoding contrast (high weight for the highest recognition confidence and small negative weights for all other judgments). (B) Results of the recognition-encoding effect contrast in the young group ($P < 0.001$, $n > 6$ voxels) overlaid on a standard T1 image. C. Behavioral results obtained as a result of Functional Activity Deviance in Encoding (FADE) between young and older adults. Recollection and familiarity scores from receiver operating characteristics analyses in older adults increase from high (Group 1) to intermediate (Group 2) to low (Group 3) FADE scores. Error bars denote standard error of the mean. See also Supporting Information Table S1. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

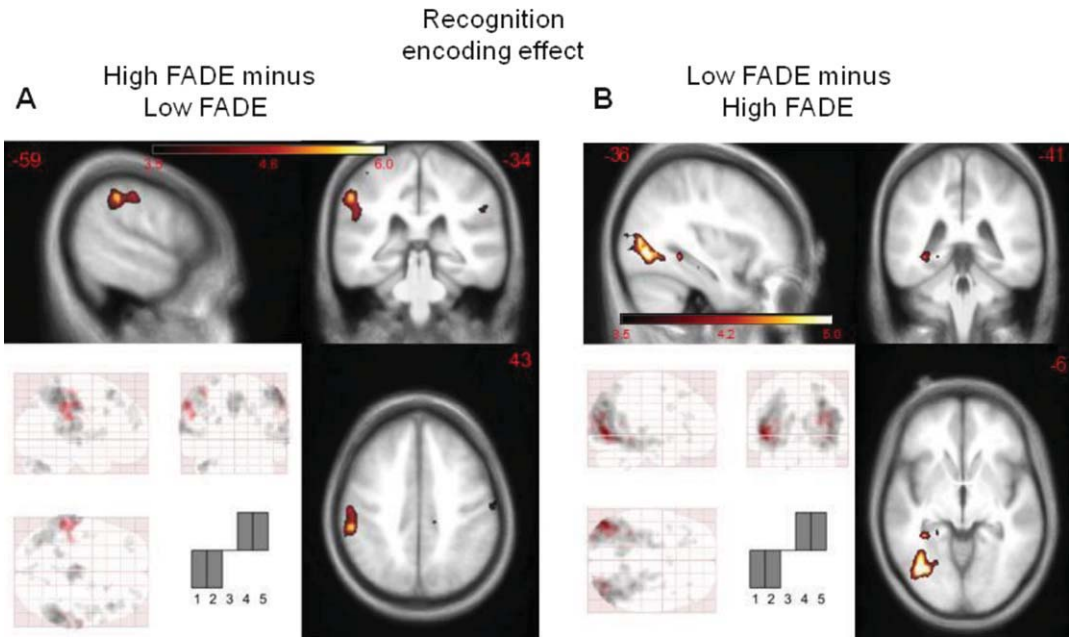

FIGURE 2. Functional results obtained with functional activity deviance in encoding (FADE) analysis within older adults. (A) Activity difference for recognition-encoding effects of old adults with high minus low FADE scores (Groups 1 minus 3). In the glass brains these activity differences are shown in red. Black clusters in the glass brains show the overlay of the FADE-related activity differences on the brain activity of young adults showing deactivations for recollection based encoding (inverse recollection contrast from Fig. 1A). (B) Activity difference for recognition-encoding effects of old adults with low minus high FADE scores (Groups 3 minus 1). In the glass brains these activity differences are shown in red. Black clusters in the glass brains show the overlay of the FADE-related activity differences on the brain activity of young adults showing activations for recollection based encoding (recollection contrast from Fig. 1A). See also Supporting Information Figure S2 and Table S2. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Familiarity and Recollection Estimates Using ROCs

ROCs were generated by plotting the proportion of hits against the proportion of false alarms as a function of confidence. The functions were fit to a dual process model to derive estimates of recollection and familiarity for each participant (Yonelinas et al., 2002).

RESULTS

Behavioral Measures in Young and Older Adults

Supporting Information Figure S1 shows performance of all older adults in neuropsychological tests. In agreement with previous studies, older adults performed significantly worse than young adults on standardized neuropsychological measures of verbal memory, digit span and attention (all tests $P < 0.05$), but performed better on the vocabulary knowledge test (MWT-B, $P < 0.05$). For the encoding phase of the recognition memory test, RTs for the indoor/outdoor-judgment were comparable in old and young adults (888 ms, SD = 126 ms and 829 ms, SD = 134 ms, respectively). Error rates were very low in both groups (1.8 and 1%, respectively). In the recognition test, old as well as young subjects recognized ~58% of the images as old (i.e., with confidence ratings 4 or 5). However, older adults had significantly higher false alarm rates (independent samples *T*-test, two-tailed, $P < 0.01$), leading to corrected hit rates of 21% ± 9% for the old, and 39% ± 11% for the young subjects. The recognition confidence responses were used to plot ROCs and showed that older subjects exhibited significantly lower estimates of recollection (0.17 ± 0.13 compared to 0.27 ± 0.16, $P < 0.05$), and familiarity (0.33 ± 0.24 compared to 0.66 ± 0.32, $P < 0.01$). Although aging is typically related to a larger drop in recollection than familiarity, the current results are consistent with several studies showing that both processes can be affected in aging (Duarte et al., 2006; Prull et al., 2006; Toth and Parks, 2006).

FMRI in the Young

In the young subjects, successful encoding (i.e., activity for recognized compared to forgotten items) was associated with increased activity in inferior and superior parietal and occipital areas, bilateral hippocampi and extrahippocampal medial temporal structures, parts of the amygdalae, retrosplenial areas (precuneus), and the nucl. Accumbens (Fig. 1B). This network was defined as the encoding network in the young and was used as a volume of interest to analyze FADE in older adults. Using the recollection contrast (Fig. 1A) we assessed which brain regions were more active as a function of subsequent recollection. These

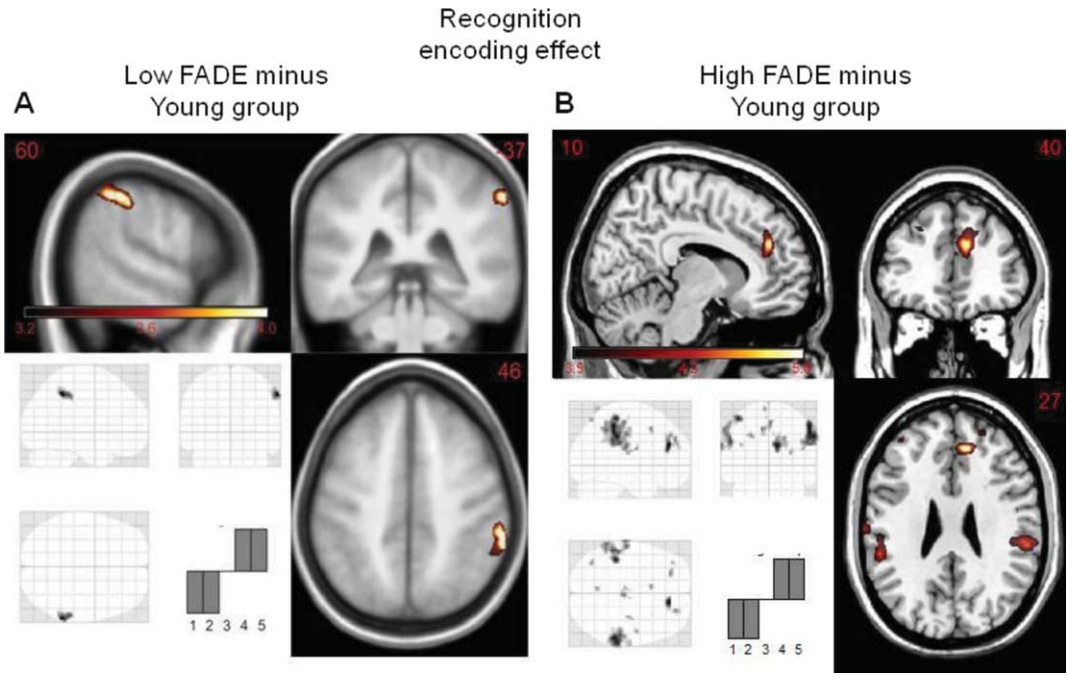

FIGURE 3. Functional results obtained as a result of functional activity deviance in encoding (FADE) between young and older adults. (A) Activity difference for recognition-encoding effects of old adults with low FADE scores minus young adults. In the glass brains these activity differences are shown in black. (B) Activity difference for recognition-encoding effects of old adults with high FADE scores minus young adults. In the glass brains these activity differences are shown in black. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

regions comprised the same areas that were apparent in the recognition contrast (Supporting Information Fig. S2 and Table S1). The inverse of the recollection contrast revealed regions that were deactivated as a function of subsequent recollection. These regions comprised components of the so-called "default network" including medial parietal cortex, and bilateral lateral parietal cortex (Supporting Information Fig. S2 and Table S1). Using a familiarity contrast of increasing or decreasing levels of activation across confidence levels of 1–4 produced very few regions of activity (Supporting Information Fig. S2 and Table S1). Activity patterns in the older adults is examined in the FADE analysis below, but the within-group results for recollection and familiarity are presented Supporting Information Table S2 and results are also displayed in Figures 2 and 3.

FADE Analysis in the Older Subjects

FADE groups 1–3

To assess the degree to which each older subject deviated from the pattern of activity observed in the young subjects, a FADE score was calculated for each of the older subjects (see methods). Based on this analysis, 16 individuals showed low, 27 intermediate and 13 high FADE scores compared to the encoding-related activity in the young. The proportions of males in the high, medium, and low FADE groups were 53, 44, and 44%, respectively. Analyses of variance (ANOVA) with FADE (three levels, low, intermediate, high) and memory (two levels, recollection and familiarity scores from the ROC analyses) revealed a significant interaction between FADE scores and memory ($F = 3.25$, $df = 2$, $P = 0.047$). Post hoc comparisons confirmed that increased FADE scores were associated with decreased recollection scores (Fig. 1C, Table 1). Concurrently, familiarity estimates appeared to increase but this difference was not significant. Across all older participants, FADE scores were negatively correlated with recollection (Pearson's correlation, two-tailed, $r = -0.279$, $P = 0.041$, see Supporting Information Fig. S3) but were not related to familiarity (Pearson's correlation, two-tailed, $r = 0.127$, $P = 0.36$) or chronological age (Pearson's correlation, two-tailed, $r = 0.073$, $P = 0.59$).

Activation patterns with high and low FADE scores

The recognition encoding effects for the older adults belonging to the high and low FADE groups were compared using a two-sample *T*-test. The high FADE group had significantly more activation in inferior parietal and supramarginal areas (BA 40, BA 2) than the low FADE group (areas in red in Fig. 2A). These areas largely overlapped with regions that showed recollection related deactivations in young adults (areas in black in Fig. 2A). This overlap suggests that regions of higher activity in older adults showing high FADE reflect a failure to show the normal encoding-related deactivation of components of the default network.

The low FADE group showed higher activation than the high FADE group in bilateral occipital cortex (BA 19), the precuneus and parts of the hippocampus and parahippocampus (areas in red in Fig. 2B). These areas largely overlapped with

TABLE 1.

Behavioral Parameters of Older Adults as a Function of FADE Scores and Young Adults

FADE	High	Medium	Low	
	1	2	3	Young
Group	$N = 13$	$N = 27$	$N = 16$	$N = 24$
Exp.: Recollection Est.	0.115 ± 0.133	0.165 ± 0.121	0.240 ± 0.128	0.272 ± 0.158
Exp.: Familiarity Est.	0.396 ± 0.254	0.357 ± 0.237	0.236 ± 0.228	0.661 ± 0.320
Exp.: FADE score	0.55 ± 0.21	−0.02 ± 0.15	−0.51 ± 0.23	1.09 ± 0.63
Exp.: Learning errors	2.23 ± 2.28	2.15 ± 1.70	2.19 ± 1.28	1.22 ± 0.90
Exp.: Corr. Hit rate	0.18 ± 0.10	0.22 ± 0.07	0.23 ± 0.11	0.39 ± 0.11
Exp.: FA	24.53 ± 9.57	22.07 ± 1.01	20.68 ± 9.00	11.17 ± 7.41
Exp.: A′	0.62 ± 0.07	0.64 ± 0.04	0.64 ± 0.06	0.75 ± 0.06
Exp.: Mean RT	0.88 ± 0.08	0.89 ± 0.15	0.88 ± 0.11	0.83 ± 0.13
BMI	27.44 ± 2.40	26.47 ± 4.28	25.36 ± 3.53	23.26 ± 3.65
Age	67.00 ± 5.39	65.00 ± 5.82	65.63 ± 5.23	23.25 ± 2.21
Years of education	15.46 ± 4.14	15.48 ± 4.61	13.75 ± 3.49	
Test: CVLT total	52.23 ± 9.18	53.67 ± 10.96	50.25 ± 8.58	64.22 ± 9.11
Test: DCS total	27.92 ± 10.58	27.41 ± 6.50	22.69 ± 7.46	41.54 ± 7.88
Test: D2 total	330.54 ± 58.27	364.74 ± 80.00	352.63 ± 58.15	493.50 ± 83.78
Test: MWTb	31.77 ± 3.19	32.67 ± 2.29	31.44 ± 3.33	30.48 ± 2.73
Test: Number Seq. +	6.31 ± 0.95	5.96 ± 1.09	5.69 ± 0.95	6.71 ± 1.08
Test: Number Seq. −	4.46 ± 0.78	4.56 ± 0.97	4.63 ± 1.09	5.63 ± 1.21
Test: trail making test A	41.54 ± 11.63	38.37 ± 9.41	39.63 ± 11.07	24.38 ± 9.78
Test: trail making test B	84.46 ± 19.90	81.37 ± 20.72	92.00 ± 28.99	49.63 ± 17.52
Test: COWA	39.31 ± 9.20	39.22 ± 10.52	36.19 ± 7.96	43.52 ± 10.45

Means and standard deviations are reported. Est.: estimate; Corr.: corrected; FA: false alarms; A′: A prime; BMI: body mass index; CVLT: California Verbal Learning Test; DCS: Diagnostikum für Cerebralschäden; Seq.+: forward sequence; Seq.-: backward sequence; COWA: controlled oral word association. MWTb: "Mehrfachwortschatztest" (a test of word knowledge). Exp.: data were obtained from the functional imaging experiment.

regions that showed recollection related activity in the young adults (areas in black in Fig. 2B). This overlap suggests that regions of higher activity in older adults showing low FADE reflect their ability to use recollection-based memory.

To determine whether there was evidence that the low FADE group differed from the young subjects we contrasted the recognition encoding effects for these two groups, and found higher activity in older adults in the right parietal cortex (Fig. 3A, Table 2); a region that was part of the default network which young adults deactivated during recollection based encoding.

We then contrasted the activity pattern of the high FADE group with that of the young adults and found higher activation in the older adults in a number of regions including bilateral parietal regions (Fig. 3B, Table 2), which were part of the default network in the young subjects, as well as in the anterior cingulate and the prefrontal cortex (Fig. 3B, Table 2). The increased activation in the latter regions may have reflected neural compensation in the low FADE group, but it was not sufficient to overcome the recollection deficit exhibited in this group.

It should be noted that all FADE groups performed equally fast and accurately on the indoor/outdoor discrimination of the visual images and this makes it unlikely that the groups differed in their ability to perceive visual detail or were not equally attentive during encoding (Table 1). This is supported by the observation that all FADE groups performed equally well on the Trail Making Test (Table 1) which also requires visual acuity.

Comparison of gray matter density in groups with high and low FADE scores

A two sample *T*-test of gray matter density showed that the low FADE group had significantly higher gray matter density in prefrontal regions (right ant. Insula, bilateral ventral prefrontal cortex), and the left rhinal (ento- and perirhinal) cortex compared with the high FADE group (Fig. 4).

Were there older individuals who showed preserved memory and evidence of neural compensation? To assess the possibility of successful compensatory brain activity in aging, we assessed brain activity and structure in older adults who had medium to high recollection scores (higher than 0.17). The 27 individuals that fulfilled this criterion were then separated using a median split into high ($N = 13$) and low FADE groups ($N = 14$). These two groups did not differ in their recollection scores or age (independent samples *t*-test; $P > 0.1$) but differed significantly in FADE (independent samples *t*-test; $P < 0.01$). Comparison of the encoding related activations in these two groups

TABLE 2.

Activation Differences Between Old and Young Adults

Cluster size	p (unc)	T	x,y,z (mm)	Anatomy
Two-sample t-test: DM-effect; low FADE vs. young group				
62	0.000	4.68	63, −42, 45	Supramarginal gyrus right
	0.000	4.19	60, −33, 45	Supramarginal gyrus right
Two-sample t-test: DM-effect; high FADE vs. young group				
298	0.000	5.27	57, −36, 51	Inferior parietal lobule right
	0.000	5.23	57, −36, 42	Supramarginal gyrus right
	0.000	4.93	63, −33, 36	Supramarginal gyrus right
89	0.000	5.09	12, 42, 27	Anterior cingulate right
	0.000	4.05	21, 51, 33	Superior frontal gyrus right
	0.000	3.74	24, 54, 24	Middle frontal gyrus right
44	0.000	5.02	−42, −33, 60	Postcentral gyrus left
199	0.000	4.64	−54, −36, 30	Supramarginal gyrus left
	0.000	4.38	−66, −18, 24	Postcentral gyrus left
	0.000	4.30	−63 −45, 45	Supramarginal gyrus left
17	0.000	4.33	−60, −18, 39	Supramarginal gyrus left
30	0.000	4.25	3, −21, 54	Supplementary motor area right
12	0.000	4.22	−9, 15, 48	Supplementary motor area left
14	0.000	4.11	−24, 42, 39	Superior frontal gyrus left
10	0.000	3.98	−6, −60, 72	Precuneus left
6	0.000	3.91	48, −3, 21	Rolandic area right
9	0.000	3.88	−39, −66, 60	Superior parietal gyrus
11	0.000	3.84	30, −15, 15	Insula right
6	0.000	3.75	−39, 45, 27	Middle frontal gyrus left
7	0.000	3.75	−6, −21, 39	Medial cingulate left

Group differences are assessed separately for low and high FADE groups.

(Fig. 4) showed that the high FADE group exhibited stronger activation in left prefrontal, bilateral occipital, and inferior temporal regions. It is possible that these activations reflect successful compensatory neural responses in this subgroup of aged subjects.

Importantly, when the activity difference between these two groups were overlaid over the results of the analysis of gray matter density differences between the original low vs. high FADE groups (Fig. 4; $P < 0.001$, $n > 10$ voxels) it became evident that increased activity in the high FADE group involved brain regions that did not show gray matter loss (the left prefrontal cluster of increased activity in the low FADE group is neighboring prefrontal regions that show gray matter loss in the high FADE group). This suggests that those individuals who are capable of maintaining high levels of recollection despite having high FADE scores may be achieving this by recruiting more strongly those prefrontal regions that do not undergo FADE-related gray matter loss.

DISCUSSION

In older adults, functional activity deviance in encoding (FADE) from the pattern of activation observed in young adults was associated with a specific impairment of recollection, such that increased FADE scores were related to a decrease in recollection, whereas other cognitive measures such as familiarity, verbal fluency, working memory, attention were not related to FADE scores. The only other task that was reduced as a function of FADE was a nonverbal learning and recall test (a nonverbal analogue of the California Verbal Learning Test, CVLT; see Schiltz et al., 2006).

Recollection is a hallmark of episodic memory (Tulving, 1985) and is very often reduced in healthy older adults when compared to young adults (Craik and McDowd, 1987; Balota et al., 2000). Here, the issue of specificity is of general importance as it is has been debated to what extent certain neurobiological changes in aging specifically influence recollection in comparison to other cognitive faculties that also show age-related decline and have been shown to be correlated with learning and memory performance in aging, in particular measures of executive functions (Kray and Lindenberger, 2000; Lindenberger et al., 2000), working memory (Baddeley et al., 1999; Gazzaley et al., 2005), and processing speed (Salthouse, 2000). Our results show that the behavioral consequences of high FADE scores are quite specific to the memory contrast that was used for the functional activity template.

Voxel-based morphometry (VBM) comparison of groups with high and low FADE showed that FADE was accompanied by loss of gray matter density in ventral PFC and rhinal cortex (Fig. 4). Evidence from lesion studies in humans and animals

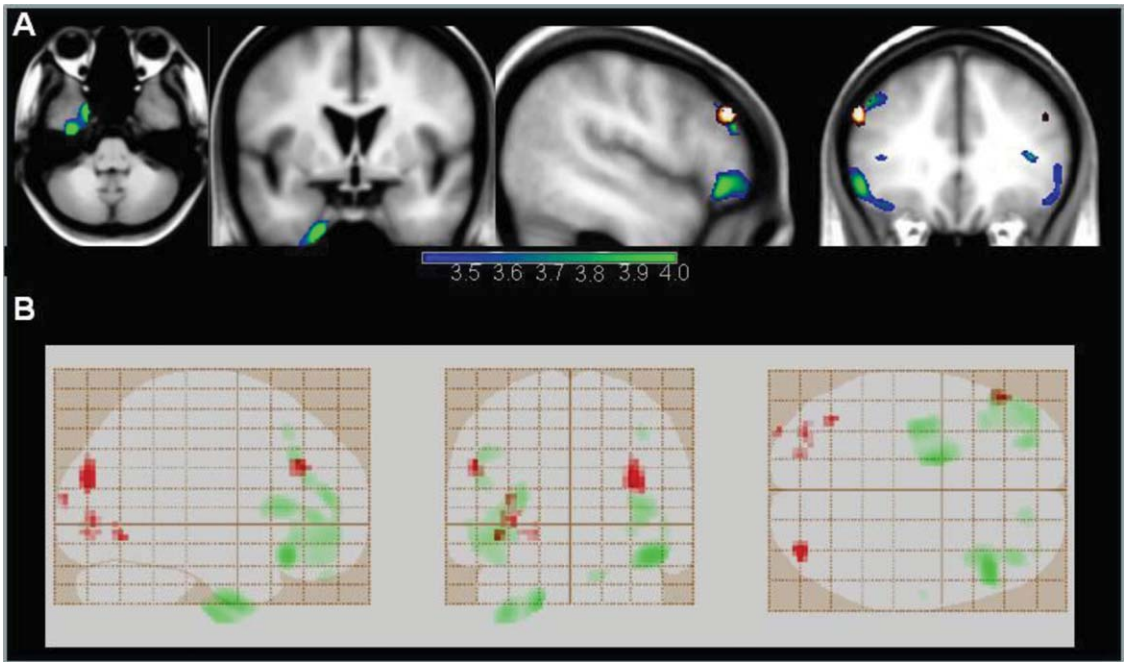

FIGURE 4. FADE-related changes in gray matter density and evidence for functional compensation. Voxel-based morphometry analysis of gray matter density differences between low vs. high FADE groups overlaid over the mean T1 image of all older adults (green clusters in the upper row) that participated in the study and displayed as a "glass brain" (green cluster in the lower row), ($P < 0.001$, $n > 10$ voxels). Red clusters show functional activity differences between two groups of older adults that were matched for recollection scores (from the ROC analysis) but differed in their FADE scores. This group was formed from the same sample of individuals. Comparison of activation patterns related to the recognition-encoding effect (images that were subsequently recognized with confidence Levels 4 and 5 vs. subsequently forgotten with confidence Levels 1 and 2; red clusters) between these performance matched low and high FADE groups ($P < 0.001$, $n > 6$ voxels) shows stronger activation in bilateral occipital and inferior temporal regions and left prefrontal cortex in the high FADE group. The figure shows that those individuals who are capable of maintaining high levels of recollection despite having high FADE scores may be achieving this by recruiting more strongly left prefrontal regions that do not undergo FADE-related gray matter loss. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

indicate that episodic memory is critically dependent on the integrity of the medial temporal lobes (MTL; Mishkin et al., 1997; Squire et al., 2004) and the prefrontal cortex (Stuss and Levine, 2002). Therefore, recent studies have sought to investigate the relationship between structural age-related degeneration of gray and white matter in these regions and learning and recall (Mungas et al., 2005; Raz et al., 2005; Craik, 2006; Schiltz et al., 2006; Dickerson et al., 2009; Seeley et al., 2009) as well as investigating functional alterations within these networks using functional imaging.

Our findings are compatible with the recent report that prefrontal regions show very pronounced age-related volume loss (Seeley et al., 2009). One prevailing hypothesis is that a major source of impairment of encoding in older adults is caused by deficient cognitive control processes mediated by prefrontal and parietal regions and include the failure to inhibit irrelevant information (Gazzaley and D'Esposito, 2007; Gazzaley et al., 2008; Stevens et al., 2008) or utilize contextual distinctiveness (Mantyla and Backman, 1990; Mantyla and Craik, 1993) and source information (Dennis et al., 2008; Old and Naveh-Benjamin, 2008). For instance, it has been suggested that the requirement to integrate item and source information at encoding, a prerequisite for successful episodic memory formation, may place greater demands on prefrontal executive or working memory processes in older adults than in younger adults and this may pose a limit for episodic memory performance (Glisky and Kong, 2008). According to this hypothesis, functional underrecruitment of MTL and visual brain regions during encoding, that is a high FADE score, could be caused by structural degeneration outside the MTL, most notably in prefrontal or parietal brain regions. In our study, the coexistence of a high FADE score together with bilateral ventral prefrontal atrophy provides support for this underrecruitment hypothesis. An interesting challenge for future studies will be to determine more directly which cognitive control functions these ventral prefrontal regions may have subserved during our encoding task. Also, the fact that FADE scores were not strongly related to measures of working memory span and attention suggests that these regions may make quite specific contributions to episodic memory rather than serving general executive and working memory processes.

Our observation that the left rhinal cortex also showed gray matter loss in individuals with high FADE scores indicates that a decrease of encoding-related activation of medial temporal lobe structures and hippocampus cannot be reduced to functional underrecruitment of frontal and parietal regions, but is also a direct consequence of degenerative processes within the MTL itself. The rhinal cortex is a major input and output structure of the hippocampus (Lavenex et al., 2002;

Lavenex et al., 2004; Canto et al., 2008) and its atrophy may have fundamental consequences for the hippocampal encoding of episodic memories. Thus our structural findings are consistent with the "processing view of remembering" (Craik, 1994) according to which age-related memory decrements are associated with impaired prefrontal processing operations, but also show some evidence for disruption of components of medial temporal memory storage mechanisms themselves, as evidenced in the atrophy of the rhinal cortex.

A controversial area in aging research is to what extent older adults recruit additional frontal or parietal lobe structures to compensate for sensory perceptual deficits or medial temporal lobe dysfunction [e.g., (Cabeza et al., 2002), see Grady (2007) and Raz (2007) for a discussion]. That is, do older adults with well preserved memory, function well because they have less severe age-related changes in memory structures and therefore do not need to compensate much, or have they compensated and are functioning well as a result (Grady, 2007)? Our findings show that high functioning in terms of preserved recollection abilities was related to low FADE scores, that is, highly preserved activity patterns in medial temporal, inferior temporal and visual brain areas and precuneus. Individuals with low FADE scores did not show evidence of prefrontal overactivation compared to young adults (Supporting Information Fig. S6). The only region showing evidence of increased activity in the low FADE individuals was a right parietal area that was overactivated compared to young adults. However, this increased parietal activation pattern involved a region that young adults deactivated during recollection-based encoding (Fig. 3A, Table 2). Hence, this "overactivation" in the low FADE score group would seem to reflect a failure to successfully deactivate components of the so-called default network (Raichle et al., 2001; Andrews-Hanna et al., 2007; Grady et al., 2010), rather than a compensatory strategy per se (also see Duverne et al., 2009).

However, an analysis including only individuals that were able to maintain high levels of recollection provided evidence that there were individuals who did exhibit evidence of compensatory prefrontal activation (Fig. 4). That is, in the high performing group of aged subjects there were those who exhibited low FADE scores and those that exhibited high FADE scores. The individuals with higher FADE scores exhibited greater left prefrontal and right parietooccipital encoding related brain activity than lower FADE scores, suggesting that individuals with high FADE scores were able to compensate for their diminished activation of the normal encoding network by recruiting additional left prefrontal and right parietooccipital regions. These regions were outside of the brain regions that in showed FADE-related gray matter loss. Together the results of this analysis indicate that some older adults can maintain high levels of recollection by utilizing the same encoding network as the young subjects, whereas others may do so via a compensatory recruitment of intact prefrontal and parietooccipital regions.

The rhinal cortex is one of the earliest regions that are affected by Alzheimer pathology in the course of dementia (Van Hoesen et al., 2000) and is therefore a target region in longitudinal MR studies aimed at early identification of individuals at risk of incipient dementia (e.g., Arnold et al., 1991; Van Hoesen et al., 2000; Scheltens et al., 2002). Rhinal atrophy in old age (e.g., Dickerson et al., 2009) increases the risk of mild cognitive impairment (MCI) to progress to dementia within a few years (Risacher et al., 2009). Left rhinal cortical thinning is evident in individuals who carry the e4 allele of the gene encoding apolipoprotein E (Shaw et al., 2007), a major risk factor for early onset dementia [for a review see (Kim et al., 2009)].

FADE assessment can assign individuals a single score that captures function, behavior and structure to quantify a functional phenotype. The high specificity and reduced dimensionality of a FADE score make it an ideal tool for longitudinal studies in aging that aim to identify risk factors for rapid progression to dementia or therapeutic interventions to slow down cognitive decline. In fact, the older adults in our study would not have been classified to suffer from MCI yet. Therefore high FADE scores in healthy older adults may provide a means for detecting individuals at risk for earlier onset of MCI and dementia before MCI criteria develop. Thus from the vantage point of longitudinal studies, the approach outlined here may have general utility for the "functional phenotyping" of specific behavior–structure relationships in healthy older adults that pose individuals at risk for earlier onset of dementia. It should be noted that the high, medium, and low FADE scores used here were not meant to be real breakpoints for risk assessment. Rather they were driven by a need to subdivide our sample of older adults into age- and gender-matched groups that differed in FADE. Whether such breakpoints exist and which these may be remains to be determined in prospective studies.

Low FADE scores indicate minimal or no decline in recollection compared to young adults and can be viewed as an index of successful aging from a functional perspective; the functional integrity of recollection processes are sufficiently intact to allow maintaining high levels of recollection without the requirement to functionally compensate for age-related degeneration. That is, low FADE scores help identifying "functionally" successful aging. An extension of functionally successful aging is the ability to maintain high levels of performance over time (Habib et al., 2007). To what extent low FADE scores also predict such stability is an interesting issue for future studies. One important implication of our findings is that at an early time point of age-related memory decline in recollection, MTL regions are structurally sufficiently intact to provide room for plasticity by cognitive training. At the same time, our findings highlight the importance of developing very specific cognitive training paradigms that also target the prefrontal brain regions showing the most prominent structural atrophy. As a final point, we would like to emphasize that our findings regarding successful aging specifically relate to long-term memory performance and we cannot say to what extent similar principles of preserved of cognitive abilities also hold in other cognitive domains.

REFERENCES

Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, Buckner RL. 2007. Disruption of large-scale brain systems in advanced aging. Neuron 56:924–935.

Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW. 1991. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cereb Cortex 1:103–116.

Baddeley A, Cocchini G, Della Sala S, Logie RH, Spinnler H. 1999. Working memory and vigilance: Evidence from normal aging and Alzheimer's disease. Brain Cogn 41:87–108.

Balota AD, Dolan PO, Duchek JM. 2000. Memory changes in healthy older adults. In: Craik ETaFIM, editor. The Oxford Handbook of Memory. Oxford: Oxford University Press.

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

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

Canto CB, Wouterlood FG, Witter MP. 2008. What does the anatomical organization of the entorhinal cortex tell us? Neural Plast 2008:381243.

Craik FIM. 1994. Memory changes in normal aging. Curr Direct Psychol Sci 3:155–158.

Craik FIM. 2006. Brain-behavior relations across the lifespan: A commentary. Neurosci Biobehav Rev 30:885–892.

Craik FIM, McDowd JM. 1987. Age differences in recall and recognition. J Exp Psychol Learn Mem Cogn 13:474–479.

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

Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, Grodstein F, Wright CI, Blacker D, Rosas HD, Sperling RA, Atri A, Growdon JH, Hyman BT, Morris JC, Fischl B, Buckner RL. 2009. The cortical signature of Alzheimer's disease: Regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cereb Cortex 19:497–510.

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

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

Folstein MF, Robins LN, Helzer JE. 1983. The mini-mental state examination. Arch Gen Psychiatry 40:812.

Gazzaley A, D'Esposito M. 2007. Top-down modulation and normal aging. Ann N Y Acad Sci 1097:67–83.

Gazzaley A, Cooney JW, Rissman J, D'Esposito M. 2005. Top-down suppression deficit underlies working memory impairment in normal aging. Nat Neurosci 8:1298–1300.

Gazzaley A, Clapp W, Kelley J, McEvoy K, Knight RT, D'Esposito M. 2008. Age-related top-down suppression deficit in the early stages of cortical visual memory processing. Proc Natl Acad Sci USA 105:13122–13126.

Glisky EL, Kong LL. 2008. Do young and older adults rely on different processes in source memory tasks? A neuropsychological study. J Exp Psychol Learn Mem Cogn 34:809–822.

Grady CL. 2007. Solving the puzzle of structure/function relations in the aging brain? (Comment on Greenwood). Neuropsychology 21:674–675; discussion 680–683.

Grady CL. 2008. Cognitive neuroscience of aging. Ann N Y Acad Sci 1124:127–144.

Grady CL, McIntosh AR, Horwitz B, Maisog JM, Ungerleider LG, Mentis MJ, Pietrini P, Schapiro MB, Haxby JV. 1995. Age-related reductions in human recognition memory due to impaired encoding. Science 269:218–221.

Grady CL, Protzner AB, Kovacevic N, Strother SC, Afshin-Pour B, Wojtowicz M, Anderson JA, Churchill N, McIntosh AR. 2010. A Multivariate analysis of age-related differences in default mode and task-positive networks across multiple cognitive domains. Cereb Cortex 20:1432–1447.

Greenwood PM. 2007. Functional plasticity in cognitive aging: Review and hypothesis. Neuropsychology 21:657–673.

Habib R, Nyberg L, Nilsson LG. 2007. Cognitive and non-cognitive factors contributing to the longitudinal identification of successful older adults in the betula study. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 14:257–273.

Hinrichs H, Scholz M, Tempelmann C, Woldorff MG, Dale AM, Heinze HJ. 2000. Deconvolution of event-related fMRI responses in fast-rate experimental designs: Tracking amplitude variations. J Cogn Neurosci 12 (Suppl 2):76–89.

Kim J, Basak JM, Holtzman DM. 2009. The role of apolipoprotein E in Alzheimer's disease. Neuron 63:287–303.

Kray J, Lindenberger U. 2000. Adult age differences in task switching. Psychol Aging 15:126–147.

Lavenex P, Suzuki WA, Amaral DG. 2002. Perirhinal and parahippocampal cortices of the macaque monkey: Projections to the neocortex. J Comp Neurol 447:394–420.

Lavenex P, Suzuki WA, Amaral DG. 2004. Perirhinal and parahippocampal cortices of the macaque monkey: Intrinsic projections and interconnections. J Comp Neurol 472:371–394.

Lindenberger U, Marsiske M, Baltes PB. 2000. Memorizing while walking: Increase in dual-task costs from young adulthood to old age. Psychol Aging 15:417–436.

Mantyla T, Backman L. 1990. Encoding variability and age-related retrieval failures. Psychol Aging 5:545–550.

Mantyla T, Craik FI. 1993. Context sensitivity and adult age differences in encoding variability. Eur J Cogn Psychol 5:319–336.

Mishkin M, Suzuki WA, Gadian DG, Vargha-Khadem F. 1997. Hierarchical organization of cognitive memory. Philos Trans R Soc Lond B Biol Sci 352:1461–1467.

Morcom AM, Good CD, Frackowiak RS, Rugg MD. 2003. Age effects on the neural correlates of successful memory encoding. Brain 126 (Part 1):213–229.

Morrison JH, Hof PR. 1997. Life and death of neurons in the aging brain. Science 278:412–419.

Mungas D, Harvey D, Reed BR, Jagust WJ, DeCarli C, Beckett L, Mack WJ, Kramer JH, Weiner MW, Schuff N, et al. 2005. Longitudinal volumetric MRI change and rate of cognitive decline. Neurology 65:565–571.

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

Persson J, Nyberg L. 2006. Altered brain activity in healthy seniors: What does it mean? Prog Brain Res 157:45–56.

Persson J, Nyberg L, Lind J, Larsson A, Nilsson LG, Ingvar M, Buckner RL. 2006. Structure-function correlates of cognitive decline in aging. Cereb Cortex 16:907–915.

Persson J, Lind J, Larsson A, Ingvar M, Sleegers K, Van Broeckhoven C, Adolfsson R, Nilsson LG, Nyberg L. 2008. Altered deactivation in individuals with genetic risk for Alzheimer's disease. Neuropsychologia 46:1679–1687.

Pihlajamaki M, Jauhiainen AM, Soininen H. 2009. Structural and functional MRI in mild cognitive impairment. Curr Alzheimer Res 6:179–185.

Prull MW, Dawes LL, Martin AM III, Rosenberg HF, Light LL. 2006. Recollection and familiarity in recognition memory: Adult age differences and neuropsychological test correlates. Psychol Aging 21:107–118.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. 2001. A default mode of brain function. Proc Natl Acad Sci USA 98:676–682.

Raz N. 2007: Which side of plasticity? Comment on Greenwood. Neuropsychology 21:676–677, 2007; discussion 680–683.

Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, Gerstorf D, Acker JD. 2005. Regional

brain changes in aging healthy adults: General trends, individual differences and modifiers. Cereb Cortex 15:1676–1689.

Risacher SL, Saykin AJ, West JD, Shen L, Firpi HA, McDonald BC. 2009. Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. Curr Alzheimer Res 6:347–361.

Rosen AC, Prull MW, O'Hara R, Race EA, Desmond JE, Glover GH, Yesavage JA, Gabrieli JD. 2002. Variable effects of aging on frontal lobe contributions to memory. Neuroreport 13:2425–2428.

Rowe JW, Kahn RL. 1987. Human aging: Usual and successful. Science 237:143–149.

Salthouse TA. 2000. Aging and measures of processing speed. Biol Psychol 54:35–54.

Scheltens P, Fox N, Barkhof F, De Carli C. 2002. Structural magnetic resonance imaging in the practical assessment of dementia: Beyond exclusion. Lancet Neurol 1:13–21.

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

Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. 2009. Neurodegenerative diseases target large-scale human brain networks. Neuron 62:42–52.

Shaw P, Lerch JP, Pruessner JC, Taylor KN, Rose AB, Greenstein D, Clasen L, Evans A, Rapoport JL, Giedd JN. 2007. Cortical morphology in children and adolescents with different apolipoprotein E gene polymorphisms: An observational study. Lancet Neurol 6:494–500.

Squire LR, Stark CE, Clark RE. 2004. The medial temporal lobe. Annu Rev Neurosci 27:279–306.

Stevens WD, Hasher L, Chiew KS, Grady CL. 2008. A neural mechanism underlying memory failure in older adults. J Neurosci 28:12820–12824.

Stuss DT, Levine B. 2002. Adult clinical neuropsychology: Lessons from studies of the frontal lobes. Annu Rev Psychol 53:401–433.

Toth JP, Parks CM. 2006. Effects of age on estimated familiarity in the process dissociation procedure: The role of noncriterial recollection. Mem Cognit 34:527–537.

Tulving E. 1985. Memory and consciousness. Can Psychol 26:1–12.

Van Hoesen GW, Augustinack JC, Dierking J, Redman SJ, Thangavel R. 2000. The parahippocampal gyrus in Alzheimer's disease. Clinical and preclinical neuroanatomical correlates. Ann N Y Acad Sci 911:254–274.

Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. 1982. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res 17:37–49.

Yonelinas AP, Kroll NE, Quamme JR, Lazzara MM, Sauve MJ, Widaman KF, Knight RT. 2002. Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. Nat Neurosci 5:1236–1241.