Relationship between Hippocampal Structure and Memory Function in Elderly Humans

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Abstract

■ With progressing age, the ability to recollect personal events declines, whereas familiarity-based memory remains relatively intact. It has been hypothesized that age-related hippocampal atrophy may contribute to this pattern because of its critical role for recollection in younger humans and after acute injury. Here, we show that hippocampal volume loss in healthy older persons correlates with gray matter loss (estimated with voxel-based morphometry) of the entire limbic system and shows no correlation with an electrophysiological (event-related potential [ERP]) index of recollection. Instead, it covaries with more substantial and less specific electrophysiological changes of stimulus processing. Age-related changes in another complementary structural measure, hippocampal diffusion, on the other hand, seemed to be more regionally selective and showed the expected correlation with the ERP index of recollection. Thus, hippocampal atrophy in older persons accompanies limbic atrophy, and its functional impact on memory is more fundamental than merely affecting recollection. ■

INTRODUCTION

A hallmark of age-related declarative memory impairment in healthy older persons is that the ability to recollect personal episodes is more strongly affected than familiarity-based memory (Grady & Craik, 2000; Grady, 1998; Verhaeghen, Marcoen, & Goosens, 1993). Based on observations in animals and humans that the hippocampus is more critical for recollection-like memory than it is for familiarity (Fortin, Wright, & Eichenbaum, 2004; Yonelinas et al., 2002; Aggleton & Pearce, 2001; Brown & Aggleton, 2001; Duzel, Vargha-Khadem, Heinze, & Mishkin, 2001; Mishkin, Vargha-Khadem, & Gadian, 1998; Vargha-Khadem et al., 1997), several studies have investigated whether impaired recollection in aging is related to hippocampal atrophy. Although these studies have shown that smaller hippocampal volumes are associated with poorer declarative memory performance in older persons (Hackert et al., 2002; Petersen et al., 2000; Golomb et al., 1994), it still remains unclear whether there is a selective relationship between age-related hippocampal atrophy and impaired recollection.

Studies of the link between memory and hippocampal integrity in the elderly are complicated by a putative lack of regional selectivity of hippocampal atrophy and by the possibility of pathological heterogeneity of age-related changes in hippocampal structure. The notion of a lack of regional selectivity stems from the observation that age-related morphological changes of the hip-

pocampus might merely accompany correlated age-related changes in other medial temporal structures, in the prefrontal cortex and frontal white matter tracts (Buckner, 2004; Hedden & Gabrieli, 2004; Sowell et al., 2003). If atrophy of extrahippocampal brain regions were correlated with hippocampal volume changes, the relationship between hippocampal atrophy and memory impairment would also have to be interpreted in the light of dysfunction of these other brain regions. Correlations between age-related changes of memory and hippocampal volume would then reflect the alteration of a widespread network rather than selective hippocampal dysfunction.

Pathological heterogeneity refers to recent evidence that there are age-related changes of hippocampal structure other than loss of volume, such as an increase in the free diffusion of water in hippocampal tissue (Szentkuti et al., 2004; Cook et al., 2002; Kantarci et al., 2002). Atrophy and increased diffusion are likely to represent complementary, uncorrelated hippocampal changes (Duzel, Kaufmann, et al., 2004; Szentkuti et al., 2004; Kantarci et al., 2002), the former probably reflecting loss of dendritic branching (neuropil) and the latter, widening of extracellular space (Schaefer, Grant, & Gonzalez, 2000). Given their complementary nature, a comprehensive study of the relationship between memory and hippocampal integrity should take into account both measures.

We assessed the relationship between age-related hippocampal changes and memory by taking into account regional selectivity and pathologic heterogeneity. To account for pathologic heterogeneity we obtained two

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structural measures of the hippocampus: volumes and diffusion. To account for regional selectivity we correlated these measures with the local gray matter amount (estimated with voxel-based morphometry) throughout the brain. We then investigated the relationship between hippocampal measures and neuropsychological scores of declarative memory as well as functional measures of recollection-based and familiarity-based recognition memory in an event-related potential (ERP) paradigm of associative face recognition using multivariate analyses (Lobaugh, West, & McIntosh, 2001).

METHODS

Subjects

Thirteen healthy young subjects (mean age 25 years, range 22–27 years, SD 1.4, four women) and 20 healthy nondemented (clinical dementia rating = 0) (Morris, 1993) elderly subjects (mean age 66 years, range 60–75 years, SD 4.5, 10 women) were included in the magnetic resonance (MR) study. None of the elderly subjects took any medication. Inclusion criterion for the elderly group was age between 60 and 75 years. Exclusion criteria were history of neurologic or psychiatric disease, hypertension, diabetes mellitus, cardiac pacemaker, chronic pulmonary disease, endocrinologic disease, and previously experienced hypoxemia. Visual acuity was normal or corrected to normal in all subjects. All were right-handed (self-report). The project was approved by the local ethics committee and subjects gave written informed consent preceding the experimental procedures. ERPs were obtained in a recognition memory paradigm from all 20 older adults and from 9 of the young adults. Four of the younger subjects had moved out of town and did not contribute ERPs.

EEG Recording

EEG was recorded from 29 scalp electrodes mounted in an elastic cap, positions including those of the international 10/20 system. Eye movements and blinks were monitored by two electrodes near the right eye. Electrodes were referenced to the right mastoid electrode during recording and re-referenced off-line to the average of the left and right mastoids. The EEG was amplified (band pass 0.01 to 64 Hz), digitized online at a sampling rate of 250 Hz, and a continuous record of the raw EEG was stored on hard disk. Trials with a voltage change greater than 200 μV were considered artifacts and excluded.

ERP Stimuli

A set of 450 photographs of human faces (in the manner of passport photographs, 164 women) was used in the ERP recognition memory paradigm. A subset of 225 faces (82 women) was used for the study phase and the remainder (82 women) was used to provide unstudied stimuli for the test phase. During study, the faces were presented in front of one out of three different line drawings (the skyline of a city, a church, a tree).

ERP Study Procedure

During the study phase of each of 15 blocks, subjects were presented with a series of 15 faces each of which was paired pseudorandomly with one of the background drawings. The face–background pairs were displayed for 2500 msec, then the background disappeared and the face was displayed alone for another 2500 msec followed by a fixation cross for 1000 msec. Subjects were instructed to describe each stimulus (e.g., woman in front of church) when the background had disappeared. Responses were monitored online to exclude incorrect trials.

The distractor task immediately followed the study task and required determining the gaze direction (right, left, up, down, straight) of a face (different from the studied faces). The distractor task comprised 10 subsequent presentations of 1000-msec duration that had to be responded to as fast as possible. Stimuli were separated by the intermittent presentation of a fixation cross for 500 msec.

In the test phase of each block the 15 studied and 15 new faces were presented in a random order without background drawings. Each face was displayed for 300 msec, followed by a fixation cross for 2700 msec. Subjects had first to make a speeded old/new decision and were instructed that reaction time and accuracy were equally important. For all faces considered old, subjects were then prompted to recall the background scene that had been presented during study. Old/new and source judgments were indicated by button press (sides counterbalanced across subjects). The next trial was preceded by a fixation cross that appeared for 1000 msec.

ERP Data Analysis

ERPs were averaged off-line for the following response classes in the test phase:

- R+: correct old response to a studied face followed by correct associative recall of the background.
- R−: correct old response to a studied face followed by wrong associative recall of the background.
- M: misses; incorrect new response to a studied face.
- CR: correct rejections; correct new response to an unstudied face.
- FA: false alarms; incorrect old response to a new face.

ERPs were quantified by mean amplitude measures in the time windows given in the Results section followed by ANOVA statistics. Measurements were performed on frontocentral (FC1/FC2) and parietal (P3/P4) electrodes.

To assess the functional effects of hippocampal volume and hippocampal diffusion changes on recognition memory, correlations with the parietal (electrodes P3 and P4) and frontal (electrodes FC1 and FC2) magnitudes of the early (400–500 msec) and late (500–700 msec) ERP old/new effects were calculated. To improve the signal-to-noise ratio of the ERPs contributing to the correlation, both R+ and R− responses were collapsed for the old/new effect.

Neuropsychological Assessment

All 20 elderly adults underwent neuropsychological assessment including a German version of the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987), the ''Diagnosticum für Cerebralschädigung'' (DCS, meaning ''diagnostic tool for cerebral damage'') that requires subjects to repeatedly study and reproduce spatial arrangements of five wooden sticks (each 12 cm in length) (example arrangements are given in Figure 1F) and is known to assess nonverbal figural memory (Weidlich & Lamberti, 1993), the Non Verbal Learning Test (NVLT) (Sturm & Willmes, 1999), an adapted German version of the Controlled Oral Word Association Test (COWAT) (Sturm, Willmes, & Horn, 1993), the Trail Making Test Part A and B (Reitan, 1992), and the d2 test of attention (Oswald, Hagen, & Brickenkamp, 1997).

MR Volumetry

A 3-D data set of T1-weighted images was obtained (contrast-optimized spoiled gradient-echo sequence, 124 slices, slice thickness 1.5 mm, TE = 8 msec, TR = 24 msec, flip angle 30°, field of view = 250 × 182.5 mm, resolution 256 × 256, voxel size 0.976 × 0.976 mm, bandwidth 10.42 kHz) that was used to obtain hippocampal volumes and to conduct voxel-based morphometry (VBM).

Hippocampal volume was assessed on a voxel-by-voxel basis using the DISPLAY software package developed at the Brain Imaging Centre of the Montreal Neurological Institute. Hippocampal borders were defined according to the procedure of Pruessner et al. (2000). Special care was taken not to include cerebrospinal fluid into hippocampal volume. This resulted in a conservative estimate of hippocampal volumes. To assess reliability of these measurements a subset of five subjects were measured by three different raters resulting in a kappa of .91. All other subjects were rated by

one investigator who was blinded with respect to identity and age of the subjects. Statistical group comparisons were achieved by ANOVAs, and heterogeneity of variances was assessed with Levene's test of the equality of variances.

Voxel-based Morphometry

Voxel-based morphometry was performed using the SPM99 package (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College, London, UK) according to the optimized VBM protocol described in detail elsewhere (Good et al., 2001). T1 raw images from all subjects were spatially normalized into stereotactic Montreal Neurological Institute (MNI) space using the SPM99 standard template and averaged yielding a customized template image. T1 raw images were then normalized to this customized template (resliced to a voxel size of 1 × 1 × 1 mm) and thereafter segmented. The normalized segmented images were then cleaned from nonbrain tissue involving a series of fully automated morphological operations for removing unconnected nonbrain voxels from the segmented images. The cleaned segmented gray matter images were smoothed using a 8-mm full width at half maximum (FWHM) isotropic Gaussian kernel and an average of all smoothed images was obtained to serve as a normalization template. Original raw T1 images were then segmented and cleaned in native space and normalization parameters were obtained for the resulting gray matter partitions. These parameters were reapplied to the raw T1 images, the resulting normalized whole-head images were segmented and the derived gray matter partitions were cleaned. Voxel values were rescaled by multiplying them with their relative volumes reflected in the Jacobian determinants derived from the applied deformation field (normalization parameters) in order to be able to test for the amount of gray matter in a region (local gray matter [LGM] amount) (Ashburner & Friston, 2000). Finally, images were smoothed using an isotropic Gaussian kernel of 4 mm FWHM (4-mm data set) and a second set was produced using a kernel of 2 mm FWHM (2-mm data set). Smoothing conditions the data to conform more closely to the Gaussian field model underlying the statistical procedures used for making inferences about regionally specific effects (Salmond et al., 2002). An in-depth discussion of the influence of data smoothing on conformity to distributional assumptions by the statistical tests used with VBM is available in Salmond et al. (2002). The kernel widths of 4 and of 2 mm that were applied here are smaller than the usually applied kernel width of 8 mm. We chose such a small kernel width to achieve an optimal trade-off between violating the distributional normality assumptions (i.e., no smoothing) and losing volume information for the small limbic structures of
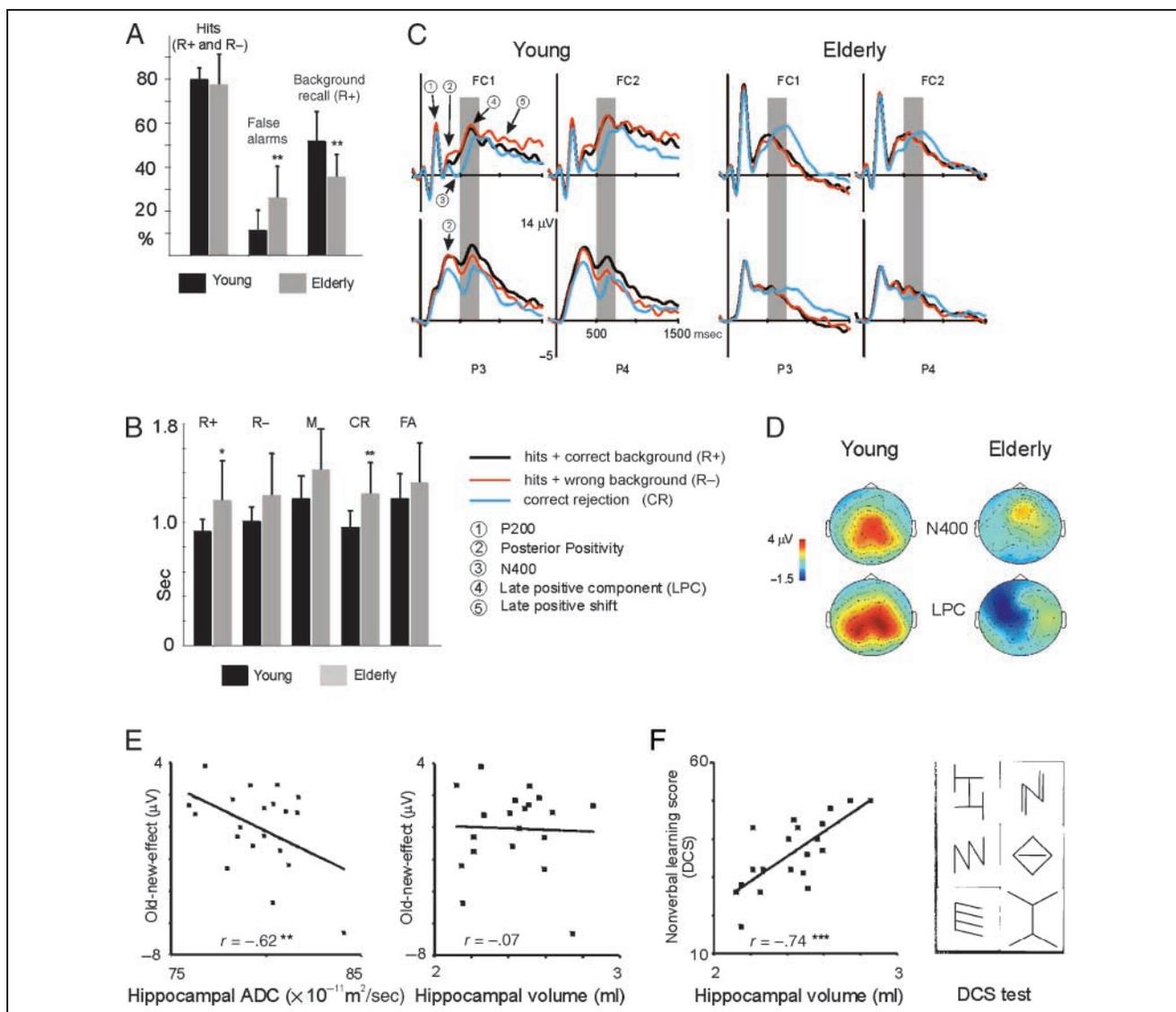
Figure 1. Behavioral and functional results of the ERP paradigm and correlations with hippocampal structure. (A) Correct recognition of studied faces (Hits), ''old'' responses to new faces (False alarms), correct background recall for hits. (B) Reaction time to all event classes (R+ = correct recognition of a studied face followed by correct background recall; R− = correct recognition of a studied face followed by wrong background recall; M = misses; CR = correct rejections; FA = false alarms). (C) ERPs elicited at frontocentral (FC1 and FC2) and parietal (P3 and P4) electrode sites. The gray bars mark the late positive component (LPC) time window (500–700 msec). (D) Topographical maps of the mean voltage difference between ERPs for hits + correct background recall and correct rejections (correctly identified new faces) in the early (N400, 400–500 msec, top) and the LPC (500–700 msec, bottom) time window for the young (left) and elderly (right). (E) Correlation of hippocampal diffusion (apparent diffusion coefficient [ADC]) and hippocampal volume and the left parietal (P3) ERP difference between hits + correct background recall and correct rejections in the LPC time window. (F) Correlation of nonverbal learning performance (DCS test) with hippocampal volume in the elderly (left) and six example configurations that have to be reproduced in the DCS test (right).

interest due to partial volume effects (i.e., smoothing with large kernels).

Voxelwise correlations of the LGM with hippocampal volume and hippocampal diffusion (apparent diffusion coefficient [ADC] values) were computed for the whole group and for the young and elderly subjects separately with both data sets. Additionally, two groups consisting of six subjects with the highest and six subjects with the lowest hippocampal volumes were formed and their

LGM was compared on a voxelwise basis by one-way ANOVA (2-mm data set).

MR Diffusion-weighted Imaging

Twenty-four coronal diffusion-weighted spin-echo prepared echo-planar images of the temporal lobes were acquired (slice thickness 3 mm, echo time 133 msec, repetition time 7600 msec, matrix 128 × 128). Eight

equidistant b values increasing from 0 to 1050 sec/mm^2 in three orthogonal directions were applied. Postprocessing of the diffusion-weighted imaging began with a correction of eddy-current-induced artifacts using a cross correlation algorithm (Haselgrove & Moore, 1996). ADC maps were calculated voxel by voxel. First, mean hippocampal ADC was assessed. Determining the hippocampal voxels, special care was taken to exclude cerebrospinal fluid by a segmentation strictly within the hippocampal borders. For this purpose, 48 coronal T2-weighted images (slice thickness 1.5 mm, TE = 80 msec, TR = 3000 msec, bandwidth 10.42 kHz, field of view = 250 × 182.5 cm, matrix 256 × 192 pixels) were acquired additionally that allowed for the orientation of the diffusion-weighted images. Thus, exclusive selection of hippocampal tissue could be achieved. Clear identification of hippocampal structures was possible on 5 to 10 coronal slices. Segmentation was done by one rater blinded to the subjects' identities. Additionally five randomly chosen data sets were segmented by three raters, and interrater variability was assessed as above (κ = 0.96).

Additionally, extrahippocampal diffusion was assessed on spatially normalized ADC maps. To allow for voxelwise assessment of extrahippocampal ADC, the T2-weighted images were coregistered to the T1-weighted images used in the VBM analysis (acquisition and processing described below) and the resulting coregistration parameters were reapplied to the ADC maps. Finally, normalization parameters as obtained from the VBM analysis were reapplied to the ADC maps yielding resliced ADC maps (voxel dimensions 2 × 2 × 2 mm) in stereotactic MNI space.

Partial Least Squares Analysis

Partial least squares analysis was introduced post hoc as a multivariate tool to detect a possible relationship between hippocampal volumes and ERPs given that there was no correlation between hippocampal volumes and the early and late ERP old/new effects. ERPs elicited by R+, R−, and CR were submitted to a partial least squares (PLS) analysis. A second PLS used normalized ERPs (ERPs to R+, R−, and CR, respectively, minus the mean of R+, R−, and CR). The PLS procedure consists of three steps: (1) the computation of a correlation matrix between hippocampal volumes and ERP values (Electrode × Time) across subjects and tasks. This cross-correlation procedure produces one correlation map (consisting of Electrode × Time number of columns) per condition or contrast vector. (2) The correlation maps generated in Step 1 are combined into a matrix and decomposed with singular value decomposition (SVD). SVD produces df number of mutually orthogonal variables (latent variables [LVs]), each consisting of a singular image (electrode salience) and a singular profile (design salience). The singular image identifies electrodes at particular points in time whose ERP value covaries, as a whole, with hippocampal volumes. The singular profile identifies the components of the experimental design that are most strongly related to the pattern revealed in the singular image. (3) Multiplication of the singular image by the raw electrode spatiotemporal data (dot product) for each subject results in individual brain scores. The brain score is an indicator of how much of the pattern represented in a singular image is expressed by a subject within a condition and is conceptually similar to a factor score in factor analysis. For a detailed description of PLS, see McIntosh, Bookstein, Haxby, and Grady (1996); for a description of the application to EEG, see Lobaugh et al. (2001); and for a description of the time-frequency analysis of electromagnetic effects in an explicit word recognition paradigm, see Duzel, Habib, et al. (2003).

To determine the stability of the saliences identified on the LVs, the standard errors of the saliences were estimated through bootstrap resampling as described elsewhere (Duzel, Habib, et al., 2003). To test the statistical significance of each latent variable, each subject's data were randomly reassigned without replacement to different experimental conditions, and the entire PLS procedure was repeated. Following 500 such randomizations, the number of times the singular value from the randomized PLS analysis exceeded the singular value from the original PLS analysis was noted, thus providing an exact probability. In order to provide an estimate of how much the identified pattern of covariation between hippocampal volumes and ERP values is represented in the different event classes, correlations of the brain scores for every event class and hippocampal volumes were calculated.

RESULTS

ERP Study—Impaired Associative Recognition and Increased False Alarms in the Elderly

We measured response accuracy and reaction time in an associative face recognition task (see Methods, ERP study). Behaviorally, young and elderly subjects did not differ in their overall recognition rate of studied faces [studied faces: R+ responses (correct old response, hit, followed by recall of the correct background) and R− responses (hit followed by recall of the incorrect background) collapsed], but the elderly subjects had higher false alarm rates to new faces (Figure 1A). The recognition rate corrected for false alarms (recognition rate − false alarm rate) was therefore significantly higher for young, 68.5%, SD 11.0, versus elderly, 51.3%, SD 13.0, $t(27) = 3.45$, $p < .002$. In accord with previous findings (Harkins, Chapman, & Eisdorfer, 1979), the response criterion was significantly more liberal in the elderly than in the young: young 1.32, SD 0.46; elderly 0.71, SD 0.48, $F(1,27) = 10.29$, $p < .003$. The young were also more

likely to make an R+ response than the elderly: R+ / (R+ and R− and M), where M = incorrect new responses, 51.9%, SD 13.4, versus elderly 35.6%, SD 10.3, $t(27)$ = 3.59, $p < .001$. Response rates for all response classes are available as an additional table from the authors (Supplementary Table S1).

Reaction times showed a pattern that was similar in both groups. For studied faces, R+ responses were fastest, followed by R− and M. The young made faster R+ and CR (correct new responses) decisions than the elderly, whereas there was no group difference for R−. CRs were made significantly faster than FA by the young but not the elderly (Figure 1B and Supplementary Table S1B).

ERP Differences between the Young and the Elderly

In the young, ERPs were characterized (in the temporal order of occurrence) by a negative deflection between 150 and 200 msec (N170), a positivity between 200 and 300 msec (P200), a posterior positivity between 250 and 400 msec, a negative deflection between 300 and 500 msec, a positive deflection between 500 and 700 msec (late positive component [LPC]) and a long-lasting positive shift, between 600 and 1500 msec, which partly overlapped with the LPC (Figure 1C and D).

In the elderly, the P200 was more positive than in the young over frontocentral and parietal sites for all stimulus and response classes, $F(1,27)$ = 4.44, $p < .05$. This difference was more pronounced over frontocentral sites irrespective of stimulus and response class: Age × Electrode Site: $F(1,27)$ = 9.12, $p < .005$; Age × Electrode Site × Response Class, $F(2,26)$ = 2.70, $p > .08$. The posterior positivity between 250 and 400 msec had a smaller amplitude in the elderly than in the young over parietal electrodes, again irrespective of stimulus and response class: age, $F(1,27)$ = 6.08, $p < .02$; Age × Response Class, $F(2,26)$ = 2.65, $p > .09$. Also irrespective of stimulus and response class, the LPC was of lower amplitude in the elderly than in the young: 500–700 msec, parietal sites P3 and P4: $F(1,27)$ = 5.36, $p < .03$. Furthermore, the late positive slow shift had a lower amplitude in the elderly for R+ and R− responses over parietal and frontocentral sites, 600–1000 msec, $F(1,27)$ = 6.6, $p < .02$. CRs, on the other hand, elicited more positive ERPs than R+ and R− over parietal and frontocentral sites in the elderly in this late time window resulting in an inverted voltage difference compared to the young, R+/CR × Age: $F(1,27)$ = 12.35, $p < .002$; R−/CR × Age: $F(1,27)$ = 6.24, $p < .02$.

## Effects of Age on the ERP Indices of Familiarity and Recollection

We assessed the well-known early (400–500 msec, N400 time window) and late (500–700 msec, LPC time win-

dow) ERP old/new effects in the young and elderly (Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997; Wilding & Rugg, 1996). In the young, ERPs showed the early and late old/new effects (Figure 1C, D). In the N400 time window, ERPs to both R+ and R− responses were more positive than ERPs to CRs over frontocentral sites both in the young, R+/CR: $F(1,8)$ = 39.32, $p < .001$; R−/CR: $F(1,8)$ = 5.5, $p < .05$, and in the elderly, R+/CR: $F(1,19)$ = 9.93, $p < .005$; R−/CR: $F(1,19)$ = 7.82, $p < .02$. There were no reliable group differences, indicating a relatively intact electrophysiological index of familiarity-based recognition in the elderly, Age × R+/CR: $F(1,27)$ = 1.6, $p > .2$; Age × R−/CR: $F(1,27)$ = 4.21, $p > .1$.

In the LPC time window, as expected, old/new effects were evident in the young only for R+ at frontocentral and parietal sites, frontocentral: $F(1,8)$ = 13.97, $p < .006$; parietal: R+/CR: $F(1,8)$ = 24.99, $p < .001$, but not for R−, frontocentral: $F(1,8)$ = 2.73, $p > .1$; parietal: $F(1,8)$ = 3.44, $p > .1$. More importantly, in the young, ERPs to R+ were significantly more positive than those to R− over parietal, $F(1,8)$ = 8.99, $p < .02$, but not over frontocentral sites, $F(1,8)$ = 0.006, $p > .9$. In the elderly, on the other hand, none of the old/new effects was evident at either frontocentral or parietal sites: frontocentral, R+/CR: $F(1,19)$ = 0.8, $p > .3$; R−/CR: $F(1,19)$ = 1,72, $p > .2$; parietal, R+/CR: $F(1,19)$ = 0.47, $p > .5$; R−/CR: $F(1,19)$ = 0.58, $p > .4$. Indeed, for R+, there were significant group differences of the old/new effects in LPC time window at both sites: frontocentral, Age × R+/CR: $F(1,27)$ = 12.51, $p < .001$; parietal, Age × R+/CR: $F(1,27)$ = 7.61, $p < .01$. For R−, group differences were significant only at frontocentral sites: frontocentral, Age × R−/CR: $F(1,27)$ = 6.78, $p < .02$; parietal, Age × R−/CR: $F(1,27)$ = 2.0, $p > .1$. Moreover, the elderly subjects showed no difference between R+ and R− in the LPC time window at frontocentral or parietal sites, frontocentral, $F(1,19)$ = 0.1, $p > .7$; parietal, $F(1,19)$ = 0.02, $p > .8$. For this contrast, there was a significant group difference parietally but not frontocentrally: parietal, Age × R+/R−: $F(1,27)$ = 4.86, $p < .04$; frontocentral, Age × R+/R−: $F(1,27)$ = 0.05, $p > .8$. The well-preserved frontocentral N400 old/new effect in the face of a clearly reduced parietal LPC old/new effect especially for associative information is consistent with a relatively preserved familiarity-based recognition and a more severe impairment of episodic recollection in the elderly (Grady & Craik, 2000).

Neuropsychology

Scores in neuropsychological tests of declarative memory, attention, and set shifting were obtained in the elderly subjects. The scores were comparable to those reported in the literature for this age range. In some of the tests, our subjects performed better than the appropriate age range. The z-normalized data are summarized in Figure 2. None of the elderly showed a performance
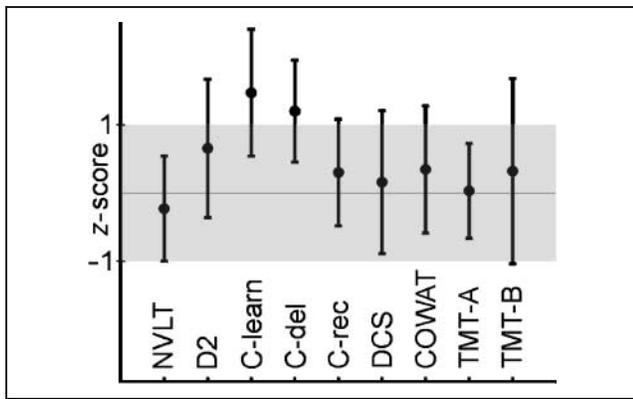
Figure 2. Neuropsychological performance of the elderly subjects. Depicted are group mean and standard deviation for every test after *z* transformation with respect to the appropriate norms (adjusted for age and education). Tests: Non Verbal Learning Test (NVLT), D2 Test of Attention (D2), California Verbal Learning Test (C-learn, C-del, C-rec), "Diagnosticum für Cerebralschädigung" (DCS), Controlled Oral Word Association Test (COWAT), Trail Making Test Part A and B (TMT-A, TMT-B).

of more than 1.5 *SD* below the appropriate age norm in more than one of the neuropsychological tests.

Hippocampal Structure

Hippocampal water diffusion (ADC in 10^{-11} m²/sec; see Methods section) did not differ between young and elderly: left, young 79.8, *SD* 2.9 vs. elderly 80.6, *SD* 3.1, $F(1,27) = 0.56$, $p > .4$; right, young 79.8, *SD* 2.7 vs. elderly 78.6, *SD* 2.2, $F(1,27) = 1.7$, $p > .2$.

Hippocampal volumes were assessed by MR volumetry (Pruessner et al., 2000). Volumes also did not differ between groups on either side and the variance of the volumes did not significantly differ (Levene's test of equality of variance) on either side, left: young 2.39 ml, *SD* 0.25 vs. elderly 2.35 ml, *SD* 0.29, mean: $F(1,27) = 0.19$, $p > .6$, variance: $F(1,27) = 0.47$, $p > .8$; right: young 2.37 ml, *SD* 0.18 vs. elderly 2.23 ml, *SD* 0.26, mean: $F(1,27) = 2.4$, $p > .1$, variance: $F(1,27) = 2.34$, $p > .1$.

Hippocampal volume and diffusion did not correlate in either the young or the elderly on any side (all $p > .5$).

Correlation of Hippocampal Structure with Electrophysiology and Neuropsychology

Correlations of hippocampal diffusion and volume with behavior and electrophysiology were calculated separately for the young and the elderly. A strict statistical criterion of $p < .005$ was adopted for the analyses to account for multiple comparisons.

In the elderly, the mean diffusion of both hippocampi correlated inversely with the left parietal LPC old/new effect (R+ vs. CR, electrode P3: $r = -.62$, $p < .005$, Figure 1E). This finding was not evident in the young ($p > .8$). There were no correlations between hippocampal diffusion and the N400 old/new effect or the R+/R− difference in the LPC time window in either group (all $p > .2$).

In contrast to hippocampal diffusion, hippocampal volumes did not correlate with the magnitude of either the N400 or the LPC old/new effects over frontocentral or parietal sites for the elderly or the young (all $p > .2$). There was also no correlation between hippocampal volumes and the parietal R+ / R− difference in the LPC time window ($p > .3$).

Behaviorally, corrected hit rates, false alarm rates, and background recall performance and the respective reaction times did not correlate with either hippocampal volumes or diffusion in any group. Additionally, there were no group differences between the six elderly subjects with the highest and lowest volume and diffusion, respectively.

In the neuropsychological testing obtained from the elderly subjects, both hippocampal volumes correlated with nonverbal learning performance in the DCS test that requires subjects to recall and manually rearrange nine 2-D configurations of five identical bars and can be viewed as a figural pendant to the CVLT (Figure 1F, left hippocampus, $r = .72$, $p < .001$; right hippocampus, $r = .66$, $p < .002$. Exemplary configurations are available in Supplementary Figure S5. This result was corroborated by a direct comparison of the six individuals with the smallest and largest hippocampal volumes yielding a significant difference in the nonverbal learning performance in the DCS test, $F(1,10) = 15.2$, $p < .003$. Scores in all other tests were neither correlated to hippocampal volume nor did they show a group difference (Supplementary Table S2). There were no significant correlations between hippocampal diffusion and neuropsychological test performance and there were no group differences in any test between the six elderly subjects with the highest and lowest hippocampal diffusion.

Partial Least Squares Analysis

In order to characterize the relationship between hippocampal volumes and ERPs more completely, we applied a multivariate analysis, PLS (Lobaugh et al., 2001).

PLS analysis revealed relations of ERP amplitudes (R+, R−, and CR) with hippocampal volumes at electrode sites that were not part of the conventional statistical assessment described above. The identified pattern showed that larger hippocampal volumes were associated with more positive early (275 to 325 msec) ERPs over parieto-occipital areas irrespective of stimulus class. It ($p < .02$) was reliably correlated with hippocampal volume in the elderly but not in the young and accounted for 70% of variance in the data (Figure 3A shows correlations, distribution and grand mean ERPs).

Figure 3. Partial least squares (PLS) analyses of the relation of hippocampal volumes to ERPs in the elderly. (A) PLS with ERP voltages of the elderly elicited by all event classes. Bars on the left depict cross-correlation values of structural data and the topographic map displayed on the right. The topographical map displays the bootstrap ratios (BR, equivalent to z scores; absolute values higher than 1.96 can be considered reliable) for the brain salience of this pattern (latent variable [LV]). The parietal ERPs that are collapsed over all response and stimulus classes and that show the effect revealed in the PLS analysis are displayed on the right. (B) Equivalent to (A), but this time ERPs were normalized before being entered into PLS. The patterns separate CRs from R+ and R−.
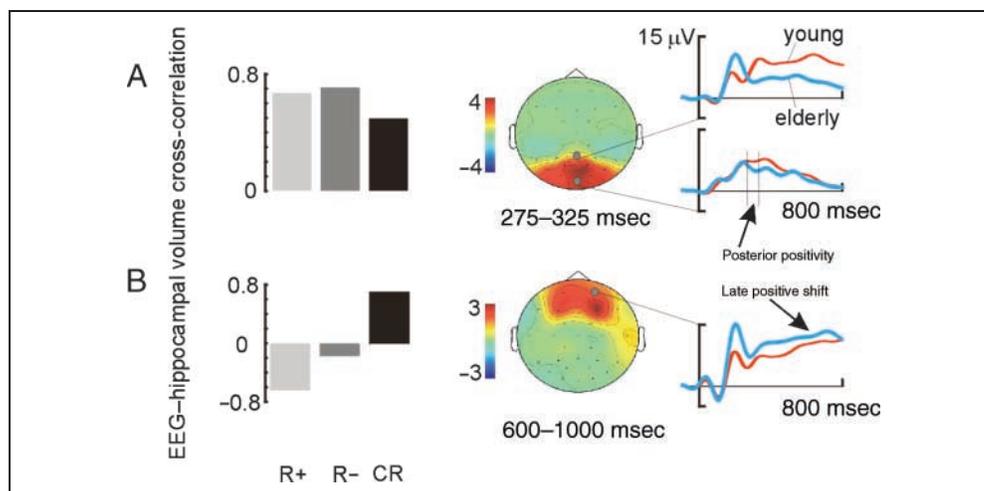
In order to examine whether the ERPs to the stimulus classes were affected differentially by hippocampal volume, we subtracted the grand mean across stimulus classes from every class to remove common effects and conducted a second PLS analysis. It revealed a pattern ($p < .003$) that reliably correlated with hippocampal volumes in the elderly but not in the young and accounted for 66% of the variance in the data (Figure 3B). Over frontopolar electrodes, in the time window between 600 and 1000 msec, larger hippocampal volumes were associated with more negative ERPs to R+ and more positive ERPs to CR. This pattern was surprising as it shows that, with larger hippocampal volumes, frontal ERPs of the elderly become more different from frontal ERPs of the young; that is, the inverted voltage difference between R+ and CR in the elderly becomes more pronounced.

Correlations between Hippocampal and Extrahippocampal Structure

The LGM amount was determined voxelwise throughout the brain using VBM (optimized protocol, Good et al., 2001; see Methods). There were no clusters of >18 voxels where extrahippocampal diffusion (in slices spanning $y = 21$ to -57 in MNI space) or clusters of >150 voxels where LGM correlated with hippocampal diffusion either in the entire group or in the young and the elderly separately. In contrast, hippocampal volume correlated with LGM of major parts of the limbic system (Figure 4, Table 1). In detail, correlated areas were the entorhinal cortex on the left side, the perirhinal cortex on the right side, the orbitofrontal cortex and basal forebrain with the gyrus rectus, the medial orbital gyrus (Brodmann's area [BA] 10 and 11), the subcallosal area, the septal region, the anterior, medial, mediodorsal, and midline thalamic nuclei, the medial pulvinar, and the ventral striatum (nucleus accumbens). Neocortical regions whose LGM also correlated with the hippocampus were the right insula (BA 13), right temporal pole (BA 20), right middle temporal gyrus (BA 21) and inferior temporal gyrus (BA 20), right precuneus (BA 7), left fusiform cortex (BA 37), and the retrosplenial cortex (BA 30). Additional analyses using less spatial smoothing to prevent the elimination of small clusters by partial volume effects (2-mm data set, Figure 4) confirmed this correlation pattern and additionally revealed correlations also in the amygdala bilaterally.

To assess whether these changes in LGM actually amounted to a significant difference between subjects with the highest and lowest hippocampal volumes, two groups of subjects ($n = 6$ each), one with the highest and another with the lowest hippocampal volumes, were sampled from the elderly and the young. The voxelwise group comparison of the LGM of the two groups yielded highly significant LGM differences at locations where a correlation of hippocampal volumes with cortical and subcortical gray matter volume changes had been evident in the correlation analyses (Table 2; Supplementary Figure S2).

This shows that LGM in these regions was not only correlated with hippocampal volume but actually showed

Figure 4. Correlation of hippocampal volume with local gray matter (LGM) amount based on voxel-based morphometry. Top, displays the data overlaid on a "glass brain," demonstrating the correlation of widespread limbic areas with hippocampal volume. Threshold $t = 2.74$ (corresponding to $p < .005$, uncorrected), cluster size > 150 suprathreshold voxels. Data set smoothed with a Gaussian kernel of 2 mm full width half maximum. BF = basal forebrain; CG = cingulate gyrus; HC = hippocampus; MO = medial orbitofrontal cortex; NA = nucleus accumbens; P = precuneus; PC = perirhinal cortex; SA = subcallosal area; TH = thalamus. All images in radiological convention (left is right).
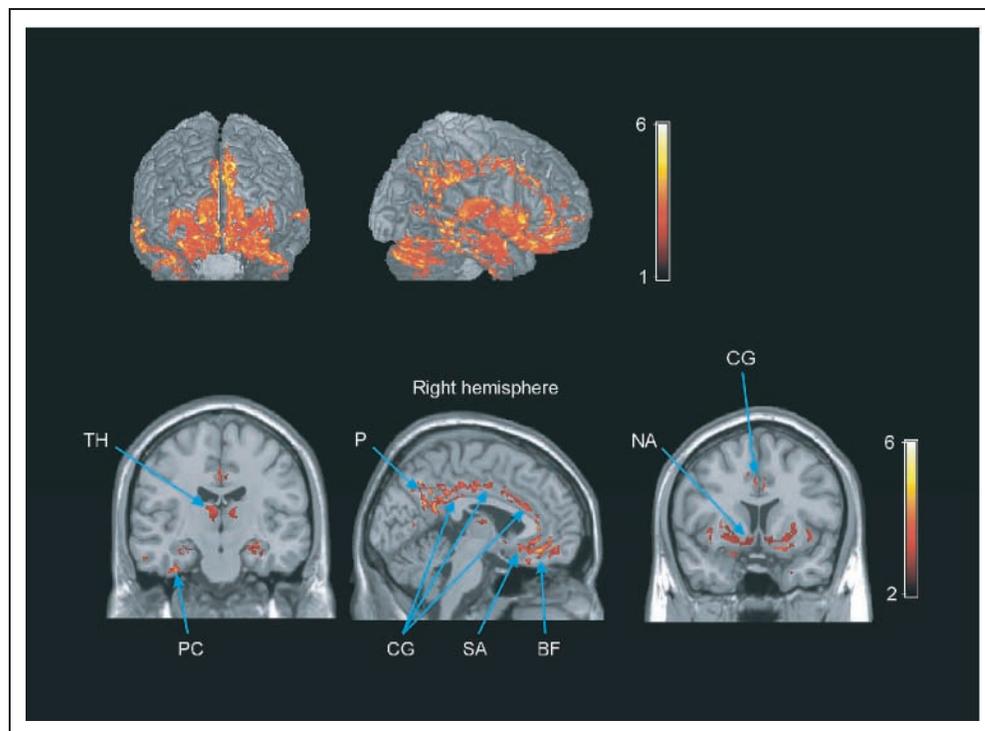
significant changes between individuals with small and individuals with large hippocampi. Whereas the low-volume group consisted of only elderly subjects, the high-volume group consisted of three young and three elderly subjects. Therefore, the correlated changes in LGM that accompany hippocampal volume might not be entirely age-related effects, but might partly reflect individual variability, although the variance of hippocampal volume in the elderly adults did not differ significantly from that in the young, mean total hippocampal volume in the elderly adults 2.28 ml, *SD* 0.27, vs. 2.4 ml, *SD* 0.21, in the young, Levene's test of equality of variance: $F(1,27) = 2.45, p > .1$.

To assess whether the structural correlation pattern between hippocampal volumes and limbic system LGM is age related or merely reflects individual variability of a limbic–cortical network independent of age, separate correlation of hippocampal volumes with LGM was conducted in the young and the elderly subjects. In the elderly, a pattern quite similar to that of the entire group emerged (Supplementary Figure S3A). In contrast, no such pattern emerged in the young (Supplementary Figure S3B). To rule out the possibility that a smaller variance of hippocampal volumes in the young was the reason why they did not show the same pattern as the elderly, we conducted an additional correlation analysis in a subgroup of 13 elderly subjects with hippocampal volumes matched to the young (mean volume in this subgroup 2.4, *SD* 0.21). This matched group of elderly subjects replicated most of the correlation pattern of the entire group of elderly subjects. This indicates that LGM changes related to hippocampal volume cannot be explained by differences in variance of hippocampal volumes between young and elderly.

DISCUSSION

Behavioral performance of the elderly showed the expected (Grady & Craik, 2000) two types of impairment in the ERP face recognition memory paradigm when compared to the young (Figure 1A, B): (1) lower background recall performance and slower reaction times for recalled backgrounds indicating impaired recollection and (2) a higher false alarm rate and slower reaction times for correct rejections indicating impaired discrimination of new items from studied items. This impairment of our elderly group can best be described as "age-associated memory impairment" (DeCarli, 2003) because none of them had lower performance in neuropsychological testing than their established age norm (Figure 2); that is, none of them suffered from "mild cognitive impairment" (DeCarli, 2003).

The ERP data of the elderly group showed several differences to those of the young. The most obvious changes were a prominent increase of P200 amplitude and a decrease of a posterior positivity (250 to 400 msec) for all stimulus and response classes, a strongly diminished parietal LPC effect, and negative shift of the ERPs elicited by recognized faces, leading to a reversed amplitude relationship between ERPs to new faces and ERPs to recognized faces over parietal and frontal electrode sites in the LPC time window. In a direct group comparison of the ERP old/new effects, there were changes that were clearly specific to recollection. Whereas the

Table 1. Peak Correlations of Hippocampal Volume with Local Gray Matter Amount

	MNI Coordinates	BA	t Value
Right inferior temporal gyrus	34 −8 −41	20	4.96
Right insula	43 −31 20	13	5.18
Left fusiform gyrus	−33 −39 −17	37	4.97
Left entorhinal cortex	−21 −19 −21	35	3.95
Right perirhinal cortex	37 −17 −32	20	4.8
Right superior temporal gyrus	30 19 −38	38	5.18
Right medial temporal gyrus	66 −40 −3	21	5.17
Right inferior temporal gyrus	64 −35 −20	20	5.17
Left medial temporal gyrus	−61 −32 3	21	4.33
Left nucleus accumbens	−9 14 −10		3.61
Right superior orbital gyrus	13 23 −18	11	4.33
Right subcallosal area	13 16 −11	25	4.22
Left subcallosal area	−12 15 −21	25	3.84
Right medial orbital gyrus	6 57 0	10	5.18
Left medial orbital gyrus	−4 57 −11	10	4.57
Right gyrus rectus	5 38 −14	11	4.57
Left gyrus rectus	−5 26 −19	11	4.05
	2 29 −7	11	4.84
Right anterior cingulate	5 29 25	32/24	4.28
	−8 30 27	32/24	5.67
Left anterior cingulate	−7 41 5	10/24	4.19
Right posterior cingulate	3 −51 25	23	4.3
Left posterior cingulate	−5 −39 30	23	4.75
Right precuneus (restrosplenial)	5 −50 12	30	4.33
Left precuneus (restrosplenial)	−7 −48 19	30	4.46
Right precuneus	4 −59 27	7	4.69
Left precuneus	−7 −54 39	7	5.29
Right gyrus rectus	8 16 −16	11	3.2
Left gyrus rectus	−3 19 −19	11	3.5
Right thalamus, mediodorsal nucleus	8 −13 14		3.56
Left thalamus, mediodorsal nucleus	−13 −21 13		3.42
Right thalamus, anterior nuclei	5 −10 12		3.3

Table 1. (continued)

	MNI Coordinates	BA	t Value
Right thalamus, medial pulvinar	15 −24 13		3.57
Left thalamus, medial pulvinar	−16 −28 3		4.11
Right caudate	15 17 −2		4.62

This table lists the voxels with highest t values for the correlation with hippocampal volume as identified with thresholding at t = 3.11, cluster size > 150 suprathreshold voxels. BA = Brodmann's area.

young showed the frontal familiarity effect in the N400 time window as well as the late parietal recollection effect in the LPC time window (Duzel, Habib, et al., 2003; Duzel, Vargha-Khadem, et al., 2001; Paller, Bozic, Ranganath, Grabowecky, & Yamada, 1999; Duzel, Yonelinas, et al., 1997; Wilding & Rugg, 1996), the elderly showed only the N400 effect, although their LPC effect was largely attenuated (Figure 1C, D). Furthermore, the parietal LPC effect in the young was increased when the study background could be recalled, but such an increase was absent in the elderly (Figure 1C). The pattern in the ERP old/new effects is compatible with the behavioral data from the ERP paradigm and with existing

Table 2. Group Comparison of Subjects with Highest and Lowest Hippocampal Volume

	MNI Coordinates	BA	t Value
Right hippocampus	34 18 −15	20	7.28
Left hippocampus	−29 −10 −20	20	5.47
Right entorhinal cortex	17 −14 −21	35	9.05
Right thalamus, mediodorsal nucleus	12 −28 −13		5.51
Left thalamus, pulvinar	−13 −28 0	27	5.59
Right medial orbital gyrus	5 46 −4	10	5.71
Left medial orbital gyrus	−1 32 −12	11	7.16
Right anterior cingulate	6 46 −3	10	5.76
Left anterior cingulate	−7 32 28	32	6.37
Right posterior cingulate	2 −36 35	23	10.58
Left posterior cingulate	−3 −34 33	23	6.54
Right precuneus	4 −54 26	23	7.61
Left superior orbital gyrus	−3 50 43	9	12.48

Listed are the voxels with highest t values in the group comparison of the six subjects with the highest and lowest hippocampal volume as identified thresholding at t = 4.14, cluster size > 100 suprathreshold voxels. BA = Brodmann's area.

evidence (Morcom & Rugg, 2004; Friedman, 2000; Grady & Craik, 2000; Jennings & Jacoby, 1993) that familiarity recognition is better preserved in the elderly than is episodic recollection.

Data from structural imaging showed that some of these ERP changes were accounted for by our measures of hippocampal integrity. As in previous studies, there was no correlation between hippocampal volumes and hippocampal diffusion, compatible with the notion that they measure different aspects of hippocampal structure (Duzel, Kaufmann, et al., 2004; Kantarci et al., 2002). Aside from being uncorrelated, volume and diffusion changes in the hippocampus also accounted for different aspects of the ERP changes observed in the elderly. Hippocampal diffusion selectively correlated with the LPC effect, hence with a functional measure of recollection (Figure 1E). Hippocampal volumes, on the other hand, did not show a correlation with the LPC effect. Instead, multivariate analyses revealed that they covaried with the amplitude of the posterior positivity between 250 and 400 msec and with the amplitude of the late frontal slow shift thereby being related to much of the observed unspecific ERP differences between the young and the elderly (with the exception of the P200, which was not related to changes in hippocampal volume or diffusion).

These structure/function relationships are better understood when considering to what extent changes in hippocampal volume or diffusion were regionally selective. Strikingly, hippocampal volume loss correlated with the LGM amount of the entire limbic system (Figure 4) including mostly brain regions that are known to have a close functional or anatomical link to the hippocampus, such as the orbital and medial frontal cortex (Barbas & Blatt, 1995), the septal region, the subcallosal area (Mesulam, Mufson, Levey, & Wainer, 1983), the nucleus accumbens (French & Totterdell, 2002), the medial dorsal (Bentivoglio, Aggleton, & Mishkin, 1997), anterior (Aggleton, Desimone, & Mishkin, 1986), and midline (Zhang & Bertram, 2002) thalamic regions, the medial pulvinar of the thalamus (Bentivoglio et al., 1997), and the perirhinal cortex (Suzuki & Amaral, 1994b). This finding shows an in vivo correlate of a structural limbic system alteration during aging. Aside from the limbic system, there were also a few neocortical areas with correlated LGM changes, and these were mostly areas that either have monosynaptic connections to the hippocampal formation or a close functional relationship to it such as BA 7, the inferior temporal region (Rockland & Van Hoesen, 1999), and the retrosplenial cortex (BA 30) (Suzuki & Amaral, 1994a). It should be noted, however, that figural learning and recall as measured by the DCS test were highly correlated with hippocampal volumes in the elderly (Figure 1F). The DCS task requires the learning and free recall of a list of nine abstract spatial arrangements of wooden sticks. It has been shown in multiple studies to be sensitive to resections of the hippocampus as well as adjacent (entorhinal, perirhinal, parahippocampal) cortex (Helmstaedter, Kurthen, Lux, Reuber, & Elger, 2003). The DCS task thus appears to be particularly sensitive to the regionally less selective volumetric changes of the hippocampus as opposed to the regionally more specific diffusion changes in the hippocampus.

In previous neuroimaging studies of memory using functional magnetic resonance imaging (fMRI), high-performing elderly adults have been reported to show enhanced bilateral prefrontal recruitment during memory retrieval thereby differing from a more unilateral activation pattern in young adults (Cabeza, Anderson, Locantore, & McIntosh, 2002), and the increased prefrontal activation has been related to a decreased medial temporal lobe activation (Gutchess et al., 2005). Reduction in asymmetry and increased prefrontal activity have been interpreted as successful compensation of age-related memory impairment in high-performing adults (Gutchess et al., 2005; Buckner, 2004; Cabeza et al., 2002). Our observations are compatible with a compensation account. Elderly adults with the larger hippocampal volumes had more discrepant ERPs from the young: They had a higher amplitude posterior positivity and an opposite amplitude relationship in the frontal slow shift for recollected faces and new faces (Figure 3B), and they were higher performing in a neuropsychological test of declarative learning and recall (Figure 1F). An opposite amplitude relationship, that is, a frontal negativity elicited by old items compared to new items, has been observed before in studies of source memory in elderly patients (Li, Morcom, & Rugg, 2004; Wegesin, Friedman, Varughese, & Stern, 2002; Trott, Friedman, Ritter, Fabiani, & Snodgrass, 1999; Trott, Friedman, Ritter, & Fabiani, 1997). Our data thus suggest that this negativity is likely to reflect intact compensatory mechanisms.

Our observations complement the previous hemodynamic data by suggesting that normal hippocampal volumes (together with a structurally intact limbic system) may promote successful compensation (Buckner, 2004). By the same token, the medial temporal hypoactivation observed previously (Gutchess et al., 2005) may be more related to functional age-related disturbances such as transmitter dysfunction (Backman et al., 2000) than to hippocampal atrophy. Finally, it is possible that compensatory processes might have obscured the expected relationship between hippocampal volume/diffusion and the behavioral performance in our ERP paradigm. Functional measures, especially if, as in the present study, they have been widely established as specific cognitive indices, might therefore be more reliable for the understanding of structure/function relationships than behavioral measures alone.

A remaining issue is whether the structural correlation pattern between hippocampal volumes and limbic system LGM is age-related or merely reflects individual variability of a limbic–cortical network independent of

age. Our analyses support an age-related account, because the structural correlation pattern was absent in the young (Supplementary Figure S3B). Furthermore, the pattern also partly emerged in a subgroup of the elderly whose hippocampal volumes were matched to that of the young thereby eliminating any differences in the variance of hippocampal volumes between the two groups. Finally, a direct comparison of the six elderly subjects with the smallest hippocampi and the six subjects with the largest hippocampi showed that there is a significant loss of LGM in the limbic system of the elderly subjects with the smaller hippocampi (Supplementary Figure S2), and that therefore the correlation between hippocampal volume and limbic systems LGM in the elderly is not a mere reflection of volumetric variability but indicative of true atrophy. Such atrophy is unlikely to reflect neuronal loss in the hippocampus (Hof & Morrison, 2004; Good et al., 2001; Rapp & Gallagher, 1996) but, instead, is more likely to be related to a decrease of synapse density (Hof & Morrison, 2004; Selkoe, 2002; Davies, Mann, Sumpter, & Yates, 1987). Future studies examining larger samples are necessary to characterize putative effects of gender and menopause on the findings reported here. Follow-up studies are also necessary to determine to what extent our findings stem from developing but yet undetected dementia or amnesic syndrome. However, since none of our elderly subjects suffered from mild cognitive impairment, it is likely that these findings reflect a normal fate in healthy aging rather than incipient pathology.

To summarize, our results provide evidence that both regional selectivity and pathological heterogeneity are relevant factors that affect how age-related hippocampal changes are related to behavioral and functional measures of memory. In a recent meta-analysis of 33 studies on the influence of age-related hippocampal volume changes on memory performance, Van Petten (2004) concluded that there is little support for a "more is better" hypothesis. She discussed the influence of methodological differences of these studies that might partly account for the inconsistency of the results. Our results show a more-is-better relationship between hippocampal volume and the ability to learn and recall figural spatial arrangements (DCS test). But, our results also indicate that regional selectivity and pathological heterogeneity of age-related hippocampal changes are two possible sources of inconsistencies across studies.

Acknowledgments

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