

FEATURE ARTICLE

Structure–Function Correlates of Cognitive Decline in Aging

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To explore neural correlates of cognitive decline in aging, we used longitudinal behavioral data to identify two groups of older adults ($n = 40$) that differed with regard to whether their performance on tests of episodic memory remained stable or declined over a decade. Analysis of structural and diffusion tensor imaging (DTI) revealed a heterogeneous set of differences associated with cognitive decline. Manual tracing of hippocampal volume showed significant reduction in those older adults with a declining memory performance as did DTI-measured fractional anisotropy in the anterior corpus callosum. Functional magnetic resonance imaging during incidental episodic encoding revealed increased activation in left prefrontal cortex for both groups and additional right prefrontal activation for the elderly subjects with the greatest decline in memory performance. Moreover, mean DTI measures in the anterior corpus callosum correlated negatively with activation in right prefrontal cortex. These results demonstrate that cognitive decline is associated with differences in the structure as well as function of the aging brain, and suggest that increased activation is either caused by structural disruption or is a compensatory response to such disruption.

Keywords: aging, compensation, corpus callosum prefrontal diffusion-tensor imaging, fMRI, hippocampus, longitudinal, memory

Introduction

In vivo structural neuroimaging data and post-mortem examination of brain tissue have revealed a diverse array of age-related changes in the brain. Changes in brain morphology include a decline in total brain volume, cortical thinning and gyral atrophy (Uylings and de Brabander, 2002; Raz *et al.*, 2004). Several neuroimaging studies have confirmed that there are age-related changes in morphological characteristics of the brain (e.g. Pfefferbaum *et al.*, 1994; Blatter *et al.*, 1995; Raz *et al.*, 1997; Good *et al.*, 2001; Jernigan *et al.*, 2001; Sowell *et al.*, 2003), and that these changes are prominent in the prefrontal cortex (PFC) (Raz *et al.*, 1997). White-matter degradation, in the form of hyperintensities, reduced white-matter integrity and volume loss, is also commonly observed (e.g. Ylikoski *et al.*, 1995; Gunning-Dixon and Raz, 2000; O'Sullivan *et al.*, 2001; DeCarli and Scheltens, 2002; Bartzokis *et al.*, 2004; Head *et al.*, 2004, 2005; DeCarli *et al.*, 2005). Furthermore, the hippocampal formation, a structure important to declarative memory, experiences volume loss in advanced aging that is significantly accelerated in early stages of Alzheimer's disease (for reviews, see Jack and Petersen, 2000; Raz *et al.*, 2005).

In terms of cognitive performance, advanced aging is often associated with decline in declarative memory, prominently including episodic memory, probably as a result of both normal

aging processes and those associated with preclinical stages of Alzheimer's disease (Albert, 1997; Buckner, 2004; Hedden and Gabrieli, 2004). Both age-associated influences on frontal-striatal networks and the medial temporal lobe (MTL) have been proposed as important factors in memory decline. Cross-sectional studies of older adults that do not reach clinical criteria for mild dementia have found negative correlations between cognitive performance and the volume of hippocampus proper (Golomb *et al.*, 1994) and associated MTL structures (Rodrigue and Raz, 2004). For example, Rodrigue and Raz (2004) found that longitudinal changes in entorhinal cortex predicted memory performance. Taken together, even though several studies have failed to find significant relationships between hippocampus volume and behavioral performance (for a recent review, see Van Petten, 2004), these prior findings suggest that decline in episodic memory relates to structural changes in the hippocampus and related MTL structures. While not consistent across all studies, several studies have observed associations between measures of white-matter integrity and others aspects of frontal-striatal anatomy and memory and executive performance (Gunning-Dixon and Raz, 2000; O'Sullivan *et al.*, 2001; Madden *et al.*, 2004).

More recently, a number of studies have examined age-related differences in functional brain activity during cognitive task performance. A noteworthy finding is that under certain conditions, some frontal regions are relatively more active in older than younger adults (e.g. Cabeza *et al.*, 1997; Madden *et al.*, 1999; Reuter-Lorenz *et al.*, 2000; Logan *et al.*, 2002; Rosen *et al.*, 2002). The functional significance of such alterations in brain activity in older age remains poorly understood. One possibility is that increased frontal recruitment is beneficial to performance in older age (Cabeza *et al.*, 2002). Another possibility is that increases in frontal activation reflect detrimental age-related changes (Kinsbourne, 1980; Buckner and Logan, 2002) or a dedifferentiation of cognitive functions in older age (Baltes and Lindenberger, 1997).

In the current study, longitudinal behavioral data were obtained from an ongoing prospective study (Nilsson *et al.*, 1997) to identify two groups of older adults that differed with regard to how their level of episodic memory performance changed over time (Fig. 1A). One group involved participants with a stable memory performance over time, and the other group involved participants with a declining memory performance over time. This selection was based on composite scores from three episodic memory tests at three time points over a decade-long period. Within the declining group the participants could be subdivided into those declining from an initial high level to a final intermediate level (decline high), and those

who declined from an initial intermediate level to a final low level (decline low) (Fig. 1B).

The central question of this study was whether stable or declining longitudinal performance was associated with atypical functional and structural measures of the brain. More specifically, we were interested in regions of the brain that have been associated with episodic memory functions, such as the hippocampus and the prefrontal cortex. Differences in white matter may also be important as multiple forms of white matter degeneration have been associated with cognitive decline in aging presumably through their connections with cortical and sub-cortical structures. To explore structural correlates of longitudinal performance, manual measures of hippocampal volume and diffusion tensor imaging (DTI) measures of white-matter integrity were obtained. To explore functional correlates, functional magnetic resonance imaging (fMRI) was used to assess brain activity while participants performed a semantic categorization task that promoted incidental encoding of a word list. This type of task has consistently been associated

with left-lateralized prefrontal activation in younger adults (e.g. Demb *et al.*, 1995; Wagner *et al.*, 1998) with older adults often showing increased and more extensive activation, including increased right PFC activation (Logan *et al.*, 2002; Lustig and Buckner, 2004; for a review, see Park and Gutchess, 2005). The imaging data were acquired in a separate scanning experiment ~2 years after the last longitudinal behavioral session.

Materials and Methods

Participants

Informed consent was obtained from 40 participants who were paid for participation in accordance with the guidelines of the Swedish Council for Research in the Humanities and Social Sciences. All participants were recruited from 'The Betula Prospective Cohort Study: Memory, Health, and Aging' (Nilsson *et al.*, 1997). They were divided in two groups based on longitudinal memory performance. The following three tasks were used. (1) Yes/no recognition of faces. Each of the 16 pictures was presented for 8 s. During retrieval, participants were presented with a sequence of faces, 12 of which were new, and 12 previously presented. Target and distracter pictures were shown one by one in a random order (15 s/face). (2) Free recall of subject-performed tasks. Sixteen sentences in imperative form were presented and participants were asked to try to remember them. Each sentence, consisting of a verb and a noun, was presented visually for 8 s. The participants were instructed to perform the action presented on the card. If the action included an external object, the object was provided by the experimenter. Task (3) was similar to task (2) but the participants were instructed to remember the sentence without enactment. Following each of the encoding conditions (2 and 3) the participants were given a free recall test. List order and materials were counterbalanced across participants.

Mean memory score (SEM) for the stable group ($n = 20$) was 22.5 (1.10) at T1, 22.3 (1.09) at T2 and 22.2 (1.09) at T3; and for the declining group ($n = 20$) 26.3 (0.91) at T1, 20.7 (0.89) at T2 and 18.0 (1.00) at T3. In order to ensure that longitudinal change and between-group differences were not attributable to regression-to-the mean artefacts, we made sure that (i) the declining group did not start out with considerably higher memory performance than the total group from which the participants were initially selected (declining = 26.3; total sample = 24.1; effect size of the difference = 0.47, which is <1 SD from the distribution of the total sample, and suggests that the groups did not differ on overall performance); (ii) that the decline in performance was significant from T1 to T2 [paired-samples t -test $t(19) = 6.27, P < 0.001$], as well as T2 to T3 [$t(19) = 2.64, P < 0.05$]; and (iii) that performance for the declining group was below the average for the total sample at T3 (declining = 18.0; total sample = 20.2). All participants scored 25 or above on the mini-mental state examination (MMSE) (Folstein *et al.*, 1975).

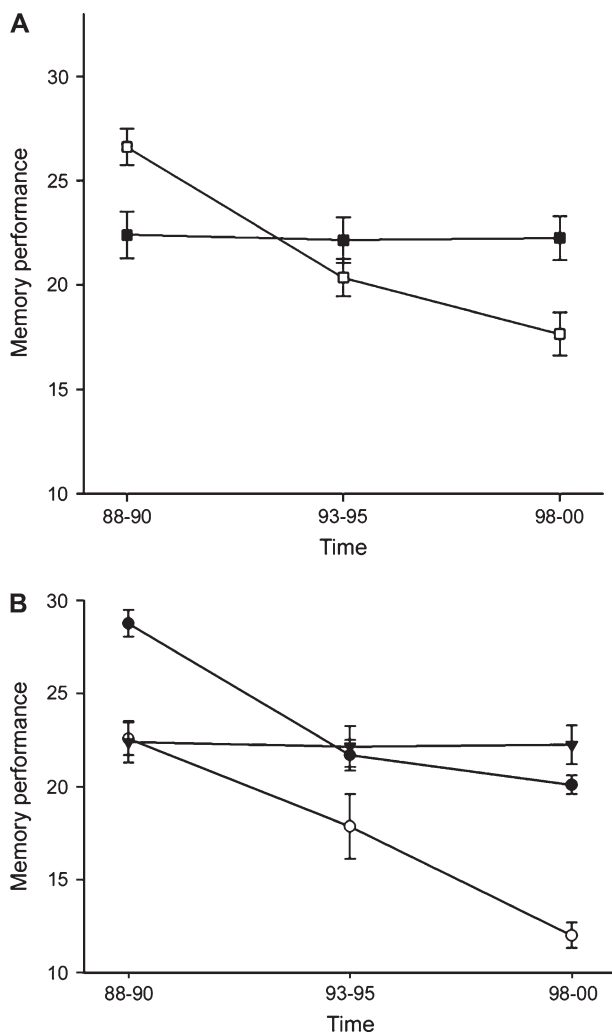


Figure 1. Memory performance over time (assessed by the sum of three episodic memory tests). Groups were divided into individuals showing either stable memory performance over time or declining memory performance over time (A). The declining group was further subdivided into individuals declining from a high to a moderate level of performance, and individuals declining from a moderate to low level of performance (B). Error bars show SEM.

Table 1

Demographic characteristics and behavioral performance

	Longitudinal memory performance		P
	Stable	Decline	
n	20	20	
Age	66.05 (5.66)	65.34 (7.14)	NS
Sex (M/F)	7/13	7/13	
Education	10.0 (3.4)	10.4 (3.9)	NS
MMSE	28.1 (1.3)	27.8 (1.5)	NS
SRB	23.0 (5.1)	24.5 (4.3)	NS
Recognition — accuracy	97.7 (17.7)	99.9 (20.8)	NS
Recognition — RT	2234.2 (296.2)	2208.8 (288.6)	NS

Mean scores are shown (SD). Age range for both groups was 49–74 years. MMSE = Mini-Mental State Examination (maximum = 30). SRB = Word Comprehension (maximum = 30). Edu = Education (years). Recognition - accuracy = delayed yes/no recognition at fMRI session (hits - false alarms). Recognition - RT = delayed yes/no recognition at fMRI session (reaction time in ms).

Participants were closely matched in terms of demographic characteristics and behavioral performance (see Table 1 for group characteristics). Data on MMSE and word comprehension (SRB) were acquired at T3, and recognition data were acquired after the scanning session. Given the possible effects of vascular conditions, such as hypertension, on brain function and anatomy, we compared the two groups on markers for vascular problems. These measurements included blood pressure, self-reported use of blood-pressure-lowering medication and self-reported history of vascular conditions. There were no differences between the stable or declining individuals on either systolic [decline = 139.0, stable = 139.5; $t(38) < 1$] or diastolic [decline = 87.8, stable = 84.8; $t(38) = 1.02$, $P = 0.32$] blood pressure. Also, there were no differences between the groups on self-reported use of blood-pressure-lowering medication or history of vascular conditions. For the declining low versus declining high comparison, 7 participants were categorized as declining from a moderate to a low level of memory performance, and 13 as declining from a high to a moderate level of memory performance. Importantly, there was minimal age difference between the groups (age - low decline = 67.4; age - high decline = 64.4). All subjects were native Swedish speakers, and had no reported neurological problems that might cause dementia. Vision was normal or corrected to near normal using scanner-compatible glasses or contact lenses.

The MRI data were acquired in a separate experiment in 2002 and 2003. There was variation in the temporal lag between the last behavioral session (T3) and the scanning experiment since data for the behavioral sessions were collected over an extended time. This, together with the temporal lag between the behavioral assessments and the MRI session, could have implications for the interpretation of the temporal relationship between the behavioral and MRI results.

fMRI Data Acquisition

A Philips Intera 1.5 T scanner (Philips Medical Systems, The Netherlands), equipped for echo-planar imaging (EPI), was used for magnetic resonance imaging. To acquire blood-oxygen level-dependent contrast images a T_2^* -weighted single-shot gradient echo EPI sequence was used with the following parameters: T_R 3000 ms, T_E 50 ms, flip angle 90° , field of view 22×22 cm, 64×64 matrix and 3.9 mm slice thickness. Thirty-three contiguous transaxial slices positioned to include the whole brain volume were acquired every 3.0 s. To avoid signals resulting from progressive saturation, five 'dummy scans' were acquired and discarded prior to the image acquisition. In the scanner, cushions inside the head coil were used to reduce head movement, and headphones were used to dampen the scanner noise. Responses were collected with a fiber-optic response box held in the right hand (Lumitouch Reply System, Lightwave Medical Industries, Canada). Stimuli were projected on to a semi-transparent screen at the head of the bore, viewed by the subject via a mirror mounted on the head coil. Sixty-nine functional volumes per run were collected across four separate runs for each participant. Structural high-resolution T_1 - and T_2 -weighted images were also acquired.

fMRI Behavioral Tasks

During the functional runs, a blocked-task paradigm was used, alternating between categorization task blocks in which the participants were asked to categorize words as either abstract (e.g. democracy) or concrete (e.g. hammer) that served as incidental word encoding (30 s) and fixation blocks (21 s) (Demb *et al.*, 1995). Each functional run started and ended with brief fixation blocks (12 s). Four identical runs were performed that each consisted of four categorization blocks containing 10 words. Two of the blocks included words that had been presented twice prior to scanning and the other two blocks included novel words (i.e. words that had not been presented previously during the study). For the purpose of the present analyses, data were collapsed across novel and previously presented words. The words were abstract and concrete nouns presented in lowercase Courier New font (font size 60 points). After the scanning session, memory performance was tested using a self-paced old/new recognition test.

fMRI Data Analysis

All functional images were pre-processed and analyzed using SPM99 (Wellcome Department of Cognitive Neurology, London) implemented

in Matlab 6.1 (Mathworks Inc.). Prior to analysis, all image volumes were realigned with respect to the first image volume using sinc interpolation. The images were then normalized using affine and smooth nonlinear transformations to an EPI template in the Montreal Neurological Institute (MNI) space. Finally, all normalized images were spatially smoothed with a 6.0 mm full-width at half-maximum Gaussian kernel. Within-participant statistical contrasts used the general linear model. The encoding condition was modeled as a fixed response (boxcar) waveform convolved with the hemodynamic response function. Statistical parametric maps (SPMs) were generated using t -statistics to identify regions activated according to the model. Group data were analyzed using a random-effects model. All reported activations passed a whole-brain false discovery rate (FDR) (Genovese *et al.*, 2002) of $P < 0.05$ with an extent threshold of 20 contiguous voxels. For the region-of-interest (ROI) analyses, we selected peak coordinates that have both been associated with incidental encoding in previous neuroimaging studies and were activated during incidental encoding in the group analysis that included all participants (Figs 2 and 3). In this manner, ROIs were defined without bias to the subsequent tests that explored differences between groups. The ROI in each case was defined as an 8.0 mm radius sphere surrounding the specific coordinates. Regions are discussed in reference to their approximate Brodmann area (BA). These ROIs were located in left dorsal frontal cortex (BA 6/44: -42, 4, 32), left inferior frontal cortex (BA 45/47: -48, 20, -6), right dorsal frontal cortex (BA 6/44: 48, 4, 32), and right ventral frontal cortex (BA 47: 50, 20, -12).

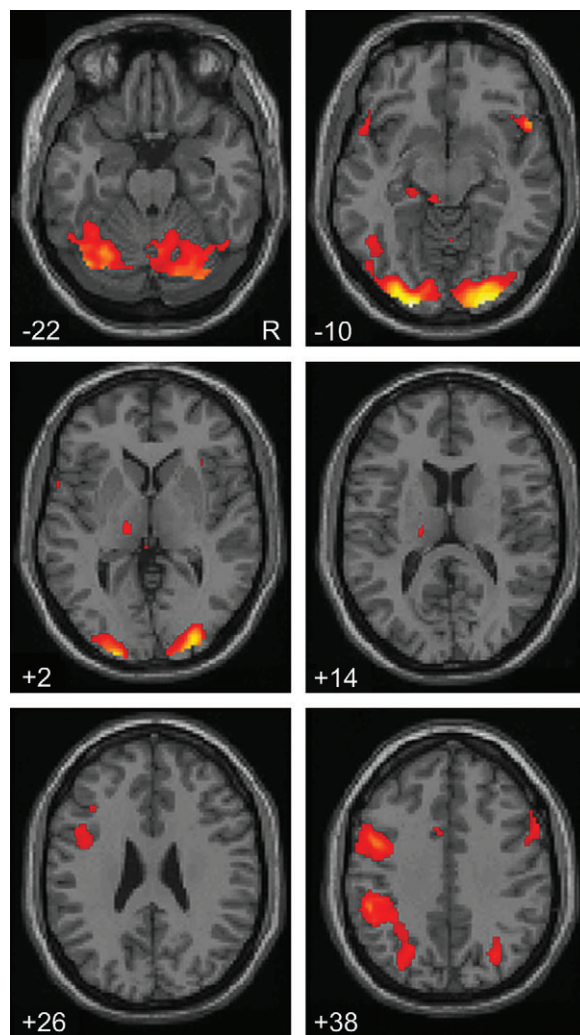
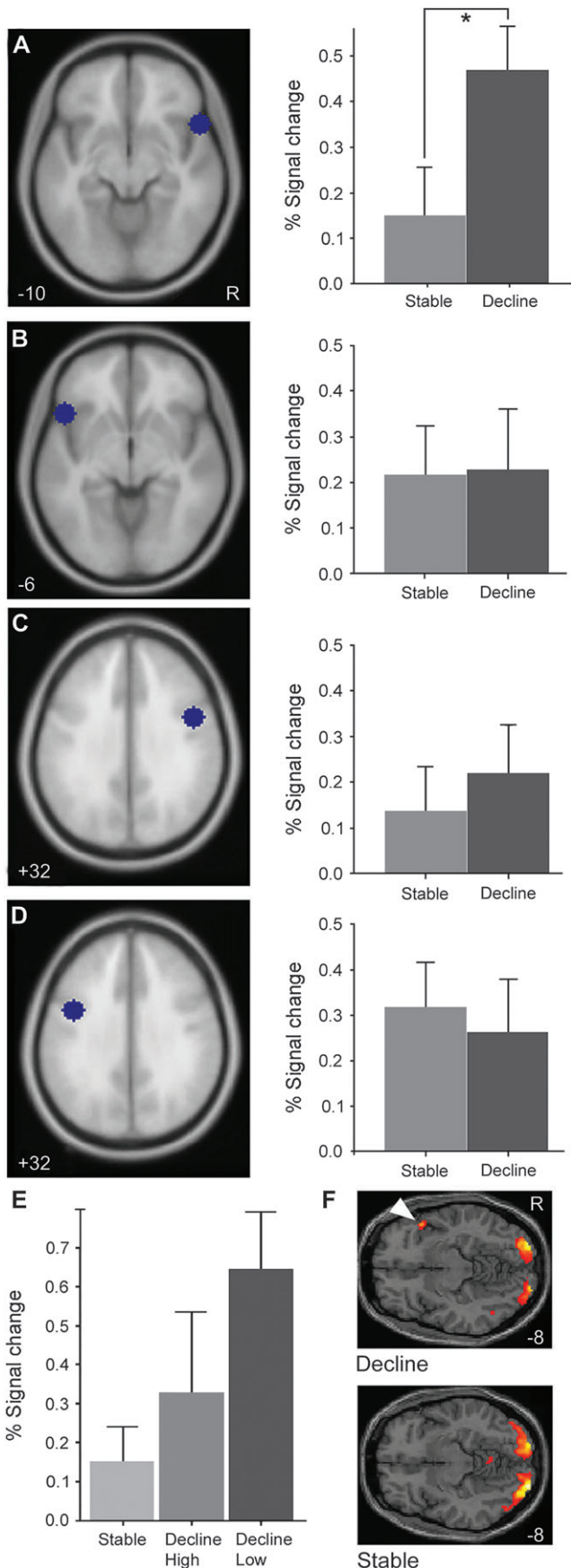


Figure 2. Transverse sections show significant activation during semantic categorization (incidental encoding) as compared to fixation baseline (FDR corrected threshold at $P < 0.05$). The anatomical template is used as the backdrop.



To create the ROIs and extract percent signal change we used the SPM ROI toolbox (<http://sourceforge.net/projects/spm-toolbox>).

Volumetric Image Analysis

For the volumetric measurements, a T_1 -weighted 3D gradient echo sequence was used with the following parameters: T_R 24ms, T_E 6ms, flip angle 35° and field of view 18×18 cm. One hundred and twenty-four coronal slices with a slice thickness of 1.8 mm were acquired in 160×160 matrices and reconstructed to 256×256 matrices. Two averages were used. After acquisition, the T_1 -weighted images were aligned to correct for undesirable effects of head tilt (to the left or right shoulder), pitch (forward or backward) and rotation (to the right or to the left) using BrainImage 5.2.5, public domain software (<http://www.stanford.edu/group/cap/research/neuroimaging/imageanalysis>). The alignment is facilitated if the image volume can be viewed with equal dimensions in all directions, and bicubic interpolation between the slices was performed to obtain volumes with slice thickness equal to the pixel size. To correct for head pitch, the axial plane was tilted so it passed through the long axis of the right hippocampus, visualized on a parasagittal section. From that operation, the alignment proceeded as previously described by Raz *et al.* (2004).

The hippocampal formation (hippocampus) was manually traced on every other interpolated coronal slice, using a computer mouse, and measured with NIH Image public domain software (version 1.60; <http://rsb.info.nih.gov/nih-image/>). The left and right hippocampus were measured separately, and volumes were computed by multiplying the total number of voxels for each hippocampus by the voxel size of 0.695 mm^3 . The total number of coronal slices used to outline the hippocampus varied between 17–23 per participant.

Beginning rostrally, the first slice used was the one where the mammillary bodies were clearly visible, whereas the caudal boundary was marked by the slice showing the fornices rising from the fimbria. As previously noted by Raz *et al.* (2004) this definition of the hippocampus is a conservative one. To outline the rostral part of the hippocampus and separate this part from the adjacent amygdala, the temporal horn of the lateral ventricle was used as a landmark. Laterally, the white matter of the temporal lobe was used as a border, and medially, the subiculum was demarcated from the cortex of the parahippocampal gyrus by tracing the subiculum to its most medial position and draw a horizontal line at its medial curve. Any part of the subiculum above this line was included as a part of the hippocampus. In the caudal slices, the white matter of the temporal lobe was used as the ventral border. In applying the rules of demarcation, questionable cases were resolved by consulting correlative and general brain atlases.

All volumetric measurements were performed by the same operator (J.L.), who was blind to the demographic characteristics of the participants. To ensure reliability of the tracing, the operator underwent an extensive training program. In this process, the novice operator traced a set of previously measured brains, together with an experienced operator, side-by-side. The training proceeded until the measures of the hippocampus areas did not differ by more than 10% from the previously trained operator ensuring that they were following the same tracing conventions. The final reliability estimate (ICC; measured on a new set of five brains) for this operator was 0.97. Since head and body size is highly correlated with total intracranial volume, correction for overall differences in body size was performed (similar to Rodrigue and

Figure 3. Transverse sections show the location of the four frontal ROIs used for analysis. Bars show average percent signal change for participants with a declining and stable memory performance over time. Error bars show standard error of the mean. The regions include right ventral frontal cortex (BA 47, A), left inferior frontal cortex (BA 45/47, B), right dorsal frontal cortex (BA 6/44, C), and left dorsal frontal cortex (BA 6/44, D). Brodmann area labels should be considered approximate. (E) Average percent signal change in the right ventral frontal ROI for participants in relation to memory performance over time (high and low decline and stable). (F) Brain responses (FDR corrected threshold at $P < 0.05$) during semantic categorization compared to fixation baseline for participants with stable memory performance (bottom) and declining memory performance (top). Activations are displayed on transverse sections of an anatomical template brain. A blue arrow points to the region being highlighted.

Raz, 2004). We used height to adjust for differences in body size via the analysis of covariance according to the formula: adjusted volume = raw volume - $b \times (\text{height} - \text{mean height})$, where b is the slope of regression of the appropriate ROI volume on height. This procedure removes variance associated with body (and head) size, and redefines data points as the difference between an individual's measures and others of similar size in the sample.

Diffusion Tensor Imaging

Participants were imaged using a single-shot spin echo EPI sequence, and cardiac gating was used to reduce motion artefacts due to pulsation of blood and cerebro-spinal fluid. The following imaging parameters were used: T_R shortest, T_E 77 ms, field-of-view 23×23 cm, acquisition matrix 96×96 reconstructed to 128×128 and flip angle 90° . Fifty-four 3.0 mm thick contiguous axial slices were acquired. The DTI sequence was repeated four times, and the images were averaged using a script implemented in Matlab 6.1. The DTI sequence included six sets of diffusion gradients placed along non-collinear directions [$b = 1000 \text{ s/mm}^2$; gradient directions (x, y, z) = (1, 0, 0), (0, 1, 0), (0, 0, 1), ($1/\sqrt{2}, 1/\sqrt{2}, 0$), ($1/\sqrt{2}, 0, 1/\sqrt{2}$), (0, $1/\sqrt{2}, 1/\sqrt{2}$)] and one set without diffusion weighting ($b = 0 \text{ s/mm}^2$).

The averaged images were processed using a custom toolbox in SPM99 that calculated the diffusion tensor eigenvalues in each voxel. Fractional anisotropy (FA) maps were then calculated. The non-diffusion-weighted image was normalized to a common template in MNI space, and the resulting affine and non-linear transformation parameters were applied to the anisotropy images. Finally, the FA maps were smoothed with a Gaussian kernel of 8 mm full width at half maximum. The ROIs were outlined on the non-diffusion weighted image and each ROI was manually outlined using MRICro (<http://www.psychology.nottingham.ac.uk/staff/cr1/micro.html>) by the operator (J.P.) who was blind to the participants' demographic characteristics. The ROIs included the genu, splenium and body of the corpus callosum. The ROIs were clearly visible on the non-diffusion-weighted images, and standard anatomical landmarks were used to define these regions (e.g. O'Sullivan *et al.*, 2001). The ROIs were then superimposed on the FA maps and mean values for each region and for each participant were calculated.

Results

fMRI Results

A random-effects analysis including all participants revealed task-sensitive brain regions. Consistent with previous findings (e.g. Demb *et al.*, 1995; Wagner *et al.*, 1998), increased activation was observed in multiple frontal regions, including bilateral dorsal (BA 6/44) and ventral (BA 45/47) frontal cortex (Fig. 2). Activated frontal regions in the overall analysis served as a basis for defining specific ROIs for group comparisons. Four spherical ROIs were used, and the mean signal change was computed for the declining and stable groups separately (Fig. 3).

A significant between-group difference was observed in the right ventral prefrontal ROI [BA 47, $t(38) = 2.20, P < 0.05$] (Fig. 3A,F) with greater activity in the declining group. Response magnitudes did not differ between the groups for either of the two left frontal ROIs [BA 6/44, $t(38) = 0.37, P = 0.72$ (Fig. 3D); BA 45/47, $t(38) = 0.47, P = 0.64$ (Fig. 3B)] or the right posterior-dorsal ROI [BA 6/44, $t(38) = 0.49, P = 0.63$ (Fig. 3C)]. The level of right frontal recruitment was also analyzed as the residual magnitude after variance in left frontal activation was removed, and the declining group still showed greater residual activation in the right ventral prefrontal ROI [$F(1,39) = 4.71, P < 0.05$]. When the declining group was divided into subgroups, it was found that the magnitude of right ventral prefrontal activity was maximal for the declining-low group (Fig. 3E).

Hippocampus Volumes

Hippocampus volumes differed as a function of group. Both left and right hippocampus volumes were significantly smaller for individuals with declining compared to stable memory performance over time [left: $t(36) = 2.33, P < 0.05$; right $t(36) = 2.01, P < 0.05$] (Fig. 4A,C). When the declining group was

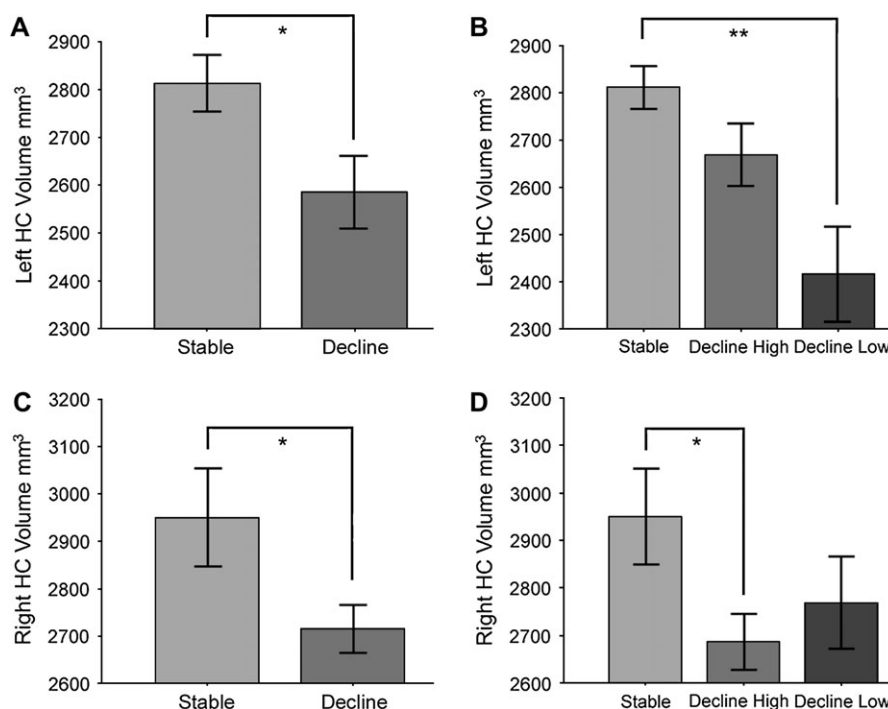


Figure 4. Mean height adjusted volume of the left (A, B) and right (C, D) hippocampus (in mm^3). (A, C) Mean hippocampus volume for individuals with stable (light gray) and declining (dark gray) longitudinal memory performance. (B, D) Mean hippocampus volume for individuals with stable (light gray), declining high (gray), and declining low (dark gray) longitudinal memory performance. Error bars show SEM.

divided into subgroups, it was found that the reduction in left hippocampus volume was most apparent for the declining-low group (Fig 4B), whereas the right hippocampus reduction was of a similar magnitude for both declining groups (Fig. 4D). There was no significant difference between the group that declined from a high to moderate performance level, and the group declining from a moderate level to a low level of performance in either left [$t(36) = 1.98, P = 0.17$] or right [$t(36) = -0.49, P = 0.62$]. The difference in left hippocampus

volume between the stable and the group declining from a moderate to a low level was significant [$t(36) = 2.98, P < 0.01$], as was the difference in right hippocampus volume between the stable group and the group declining from a high to a moderate performance level [$t(36) = 1.78, P < 0.05$, one-tailed]. As a *post-hoc* analysis we computed the correlation between volume in right and left hippocampus and fMRI signal change in the right ventral frontal ROI. No significant correlations were found.

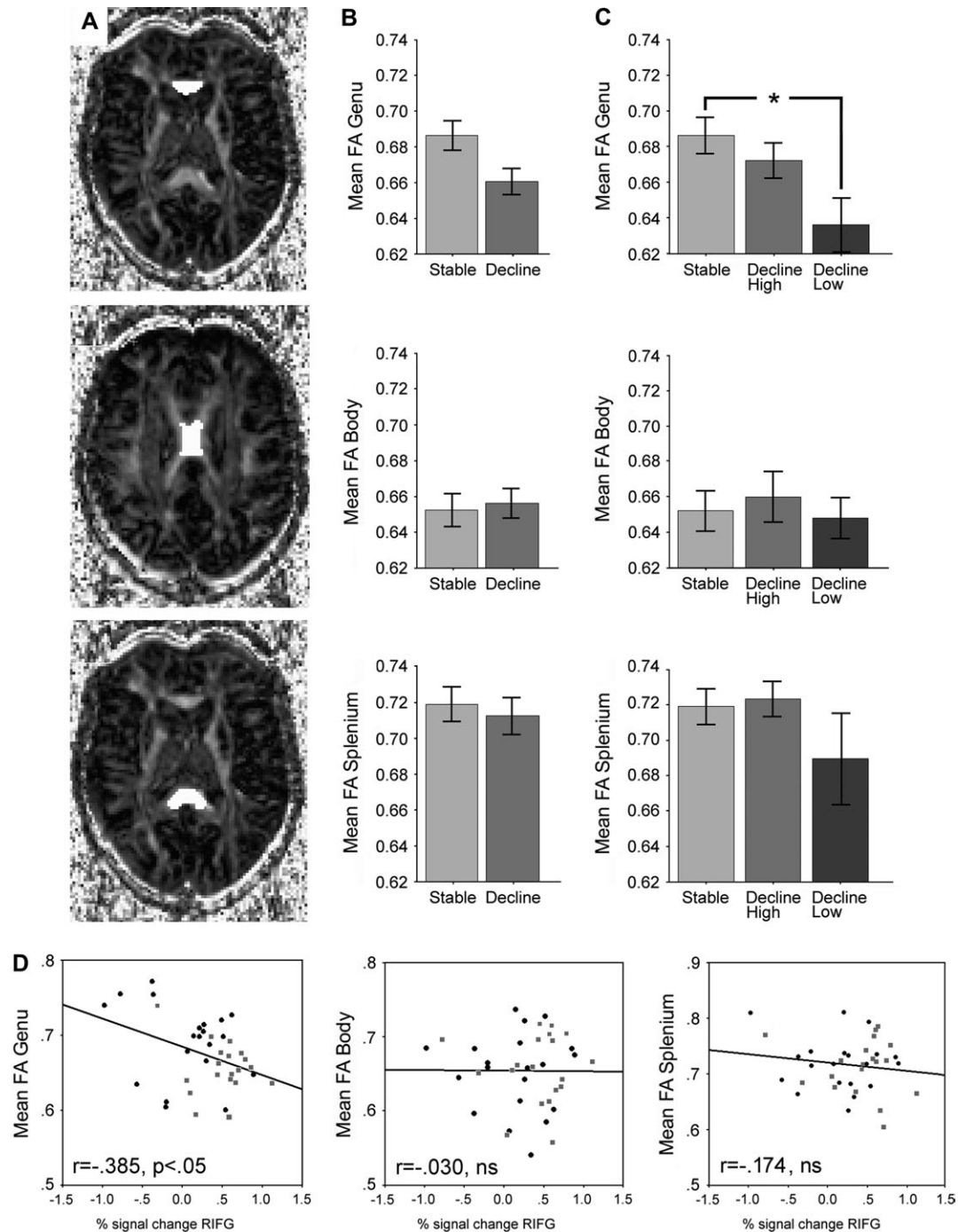


Figure 5. (A) ROIs (top, genu; middle, body; bottom, splenium) outlined on transverse slices of fractional anisotropy (FA) images. High signal intensity (brightness) reflects higher FA. (B) Mean FA as a function of longitudinal memory performance and ROI (light gray, stable; dark gray, declining). (C) Mean FA as a function of longitudinal memory performance and ROI (light gray, stable; gray, declining high; dark gray, declining low). (D) Scatterplots show a *post-hoc* correlation between mean FA in the ROIs and percent signal change in the right ventral frontal ROI (filled circle, declining group; filled square, stable group). Error bars show SEM.

Diffusion-tensor Imaging

Based on O'Sullivan *et al.* (2001) and Head *et al.* (2004), FA values for three regions of the corpus callosum were computed (anterior, middle, posterior; Fig. 5A). A group difference was apparent in the anterior region with a higher FA value in the stable group (Fig. 5B), and when the declining group was divided into subgroups, a significant difference between the stable and decline-low groups was found [$t(1,39) = 2.37, P < 0.05$] (Fig. 5B). As a *post-hoc* analysis we also computed the correlation between mean FA in anterior corpus callosum and fMRI signal change in the right ventral frontal ROI. A significant negative correlation between FA in anterior corpus callosum and brain activation was observed ($r = -.385, P < 0.05$) (Fig. 5D). No other correlations were significant. Thus, while provisional, the association between anterior white matter differences and functional activation is intriguing.

Discussion

The present study provides evidence for neuroanatomical and functional differences associated with longitudinal decline in episodic memory performance. The observed differences on multiple structural and functional measures is direct evidence for brain differences between cognitively declining and stable individuals, and is unlikely to be attributable to regression artefacts. Older adults with declining memory performance showed differences in DTI measures of anterior white matter as well as reduced hippocampus volume compared to older adults with preserved memory performance. The combination of hippocampal and anterior white-matter differences suggests that multiple factors are contributing to cognitive decline (Albert, 1997; Buckner, 2004; Hedden and Gabrieli, 2004). Moreover, differences in functional activation were noted in the form of increased recruitment associated with memory decline. This combination of associations is indicative of a structural and functional pattern of change in aging that may reflect detrimental processes, the emergence of compensation, or both.

Structural Relations

Our results support the hypothesis that the hippocampus plays a role in episodic memory in old age. These results are in line with evidence from cross-sectional studies (e.g. Golomb *et al.*, 1994; Rodrigue and Raz, 2004) that show a negative correlation between volume of hippocampus and structures of the MTL and cognitive performance, as well as extant data that suggest hippocampus volume decline is an early predictor of memory impairment associated with Alzheimer's disease (for a review, see Jack and Petersen, 2000). The observed link between cognitive performance and hippocampus volume is further supported by the finding of a correlation between longitudinal deterioration of cognitive performance and hippocampus volume (Golomb *et al.*, 1996).

In the presence of an association with change in memory performance, the present study did not find significant differences between the two declining groups. This suggests that absolute performance *per se* may not be the most critical factor, but rather the decline of memory performance over time. A further important consideration regarding our observed associations with hippocampus volume is that participants with early stages of Alzheimer's disease are probably included in our sample of older adults. While clinical screening was performed

to rule out mild to moderate Alzheimer's disease, the low scores for global cognition in some individuals as well as the association between hippocampal volume and memory performance are suggestive of the earliest stages of preclinical Alzheimer's disease. R.L. Buckner *et al.* (in preparation) have shown that association between hippocampus volume and neuropsychological memory scores can largely be accounted for by the earliest stages of dementia, including individuals whose global cognition scores (e.g. MMSE) remain in the normal range at the beginning stages of the disease. It is presently unknown how many of the participants who displayed reduced hippocampus volume and memory performance are at the earliest stages of dementia, but early-stage Alzheimer's disease may be the cause of the observed association.

Older adults with a declining memory performance also showed reduced FA in the anterior part of the corpus callosum compared to their stable counterparts. The finding of group differences in the anterior part of the corpus callosum is supported by previous DTI studies that indicate that this region is specifically susceptible to age-related atrophy, while posterior regions are relatively spared (Pfefferbaum *et al.*, 2000, 2005; O'Sullivan *et al.*, 2001; Head *et al.*, 2004; Madden *et al.*, 2004). The difference in FA was most evident between the stable group and the group declining from a moderate to a low level of performance, suggesting that white-matter integrity may contribute to memory dysfunction in old age. These results concur with findings of negative correlations between white-matter integrity and behavioral performance in anterior parts, but not for posterior parts of the corpus callosum in older adults (O'Sullivan *et al.*, 2001; Madden *et al.*, 2004).

In the context of other studies that have shown dissociation between hippocampus volume loss and age-associated differences in anterior white matter (e.g. Head *et al.*, 2005), the present data are most consistent with a heterogeneous sample of older individuals for whom damage to multiple brain systems is contributing to cognitive decline.

Functional Relations

Older individuals with cognitive decline showed increased recruitment of specific frontal regions. By combining longitudinal behavioral data with functional neuroimaging, this study provides evidence that the increases in frontal activation observed in aging are related to age-related decline in cognitive function. Specifically, increased right ventral frontal activation during semantic categorization was associated with a history of declining episodic memory performance, with the greatest activation level for the group of elderly individuals declining from a moderate to a low level of memory performance. Strong right frontal activation is atypical for this type of task in studies of younger adults (Cabeza and Nyberg, 2000) but previous studies have observed such right-lateralized activity in groups of older adults (Logan *et al.*, 2002). In some of these past studies increases in dorsal frontal regions has been emphasized, which were not robust here. Ventral regions have been less well characterized.

By associating increased recruitment of frontal cortex with declining memory performance our results are consistent with the possibility that such activity differences relate to age-associated disturbance in brain function (Kinsbourne, 1980; Buckner and Logan, 2002; Li and Sikström, 2002; Logan *et al.*, 2002). These results suggest that additional frontal activation

may be elicited by disruption of brain networks, and may be related to a noisier processing system associated with increasing age (Li and Sikström, 2002). Indeed, in the present sample of individuals, the presence of additional frontal activation may be a marker for cognitive decline. Further support for this possibility comes from findings of greater frontal activity in patients suffering from dementia, or at risk for dementia, compared to non-demented elderly (Becker *et al.*, 1996; Woodard *et al.*, 1998; Bäckman *et al.*, 1999; Bookheimer *et al.*, 2000; Grady *et al.*, 2003). In the present study, the *post-hoc* negative correlation between fractional anisotropy and right PFC activation tentatively suggests that differences in frontal white matter may associate with cognitive decline linked to activation increases.

At first glance, these results seem to contradict earlier findings that show positive correlations between additional frontal recruitment and behavioral performance (i.e. compensation). It is important to note that when the whole sample is considered, frontal recruitment reflects detrimental performance, but within the group of individuals with declining performance, additional frontal recruitment may still show positive correlations with performance (discussed by Cabeza *et al.*, 2002). Such complex interactions between activation and performance were found in a recent study by Grady *et al.* (2003). They noted that individuals in early stages of Alzheimer's disease showed higher frontal recruitment compared to healthy older adults. When the dementia group was considered in isolation, however, they found that performance was positively correlated with frontal activation. Within the present sample, this possibility was partly supported by the finding of a positive, although non-significant, correlation between memory performance during the imaging study and right ventral frontal activation in the group of individual declining from a moderate to a low level of performance (data not shown). The most likely explanation for the combination of results is that detrimental brain decline leads to the need for compensatory processes (Buckner, 2004).

It seems probable that there are limitations to functional compensation. Studies of individuals with severe cognitive impairment have found frontal under-recruitment rather than over-recruitment (Kato *et al.*, 2001; Elgh *et al.*, 2003). This indicates that patterns of frontal activity are not directly reflecting the relative need for compensation, as this should be greatest for the most cognitively impaired. Limitations to functional compensation may also explain previous findings of no additional frontal activity in low-performing older adults. The boundaries for functional compensation remain to be determined, but there is suggestive evidence that the nature of the cognitive task is one important factor (Burggren *et al.*, 2002).

Conclusions

By integrating structural, neuroimaging and behavioral measures we characterized cognitive aging at multiple levels. Between-group differences in hippocampus volume and anterior white-matter integrity suggest a relationship between structural disruption and cognitive decline in old age. Augmentation of frontal activation may be a productive response to such changes. Given the temporal lag between longitudinal behavioral and MRI assessments, the exact sequence of relationships between age-related changes in the structure and function of the brain, and behavioral performance has yet to be determined. In future longitudinal studies it will be interesting to further

explore the underlying structural and physiological changes that elicit age-related alterations in brain activation, and to explore the extent to which such alterations are able to moderate performance.

Notes

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