

## Healthy aging attenuates task-related specialization in the human medial temporal lobe

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### Abstract

Recent research on aging has established important links between the neurobiology of normal aging and age-related decline in episodic memory, yet the exact nature of this relationship is still unknown. Functional neuroimaging of regions such as the medial temporal lobe (MTL) have produced conflicting findings. Using functional magnetic resonance imaging (fMRI), we have recently shown that young healthy individuals show a stronger activation of the MTL during encoding of objects as compared with encoding of positions. Using the same encoding task, the present study addressed the question whether this greater MTL activation during encoding of objects varies with age. Fifty-four healthy individuals aged between 18 and 81 years underwent functional magnetic resonance imaging while they encoded and subsequently made new-old judgments on objects and positions. Region of interest (ROI) analysis of task related changes in the blood oxygen level-dependent (BOLD) signal was performed in native space after correction for gender effects and individual differences in cerebral blood flow. The hippocampus, amygdala, and parahippocampal, perirhinal, entorhinal, and temporopolar cortices of right and left hemisphere were defined as ROIs. Aging had an adverse effect on memory performance that was similar for memorizing objects or positions. In left and right MTL, relatively greater activation for object stimuli was attenuated in older individuals. Age-related attenuation in content specificity was most prominent in the recognition stage. During recognition, the larger response to objects gradually decreased with age in all ROIs apart from left temporopolar and entorhinal cortex. An age-related attenuation was also present during encoding, but only in right parahippocampus and amygdala. Our results suggest that memory-related processing in the MTL becomes gradually less sensitive to content during normal aging.

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### 1. Introduction

Episodic memory, the memory of unique personal experiences (Tulving, 2002), is among the cognitive functions most affected by aging (Mitchell et al., 2000). A number of studies have demonstrated that the medial temporal lobe (MTL) region is crucial for episodic memory function and

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related working memory functions (Campo et al., 2005; Habeck et al., 2005; Hannula and Ranganath, 2008; Hayes et al., 2004; Piekema et al., 2006; Ranganath et al., 2004; Yonelinas et al., 2007). In the MTL, distinct subregions have been shown to make different contributions to object and spatial memory processes (Pihlajamäki et al., 2003, 2004, 2005), in the binding of object and spatial information (Mitchell et al., 2000), in encoding and retrieval (de Zubicaray et al., 2001; Kirwan and Stark, 2004; Tsukiura et al., 2005), as well as in familiarity and recognition judgments (Daselaar et al., 2006; Gonsalves et al., 2005; Henson, 2005; Henson et al., 2005).

Further evidence for distinct roles of individual MTL regions come from the study of age-related disorders that affect episodic memory, such as Alzheimer's disease (AD) and its precursor, mild cognitive impairment (MCI). Studies have consistently related these disorders to changes in MTL morphology and metabolism (Barnes et al., 2008; Baron et al., 2001; Chetelat et al., 2003; Convit et al., 1995; De Santi et al., 2001; Du et al., 2007; Fischl et al., 2002; Frisoni et al., 2002; Herholz et al., 2002; Ishii et al., 2005). More recently, studies employing multimodal imaging approaches have reported differential contributions of individual MTL regions to memory performance. For example, by comparing memory scores with a combination of fluorodeoxyglucose (FDG)-positron emission tomography (PET), magnetic resonance (MR) morphometry, and apolipoprotein E (APOE) genotype, Walhovd et al. (2010) found that in healthy older subjects, hippocampal metabolism predicted learning and recall, while entorhinal metabolism predicted recognition. By comparison, in MCI patients, entorhinal and precuneus volumes predicted learning, while parahippocampal metabolism predicted recognition. In AD, the volume of the posterior cingulate predicted learning, while apolipoprotein E genotype predicted recognition. In a similar vein, Jhoo et al. (2010) recently demonstrated that a model that optimally discriminated between healthy aging, MCI, and AD was found by using a combination of measures of regional metabolism, volumetry and fractional anisotropy (white matter homogeneity). Taken together, this further emphasizes the role of individual MTL regions in healthy and disrupted episodic memory function.

Functional neuroimaging studies on the impact of aging on MTL function have provided mixed results. Some studies have reported evidence of age-related activation decreases in the MTL and adjacent ventral temporal regions during visual perception and encoding (Park et al., 2004), in working memory function (Mencl et al., 2000; Vandenbergue et al., 2004), and in the binding of visuospatial information (Mitchell et al., 2000). These results have generally been interpreted as an age-related regional loss of function or specialization. Other studies have reported age-related activation increases, such as increased bilateral activation in temporal, prefrontal, and parietal regions during a wide range of cognitive tasks (Cabeza, 2002; Cabeza et

al., 2004; Dolcos et al., 2002; Frings et al., 2010; Grady and Craik, 2000; Rodrigue and Raz, 2004; Townsend et al., 2006; Ward, 2006). A more bilateral activation pattern, also found in the MTL region, was found to correlate with improved memory performance in old adults (Cabeza, 2002). Therefore, it was suggested that an attenuation of interhemispheric asymmetry may mediate a preservation of function during aging.

While differences in the experimental design, types of stimuli, and contrasts of interest might explain, to some extent, the discrepant results across studies, biological and technical factors also need to be taken into account, such as age-related changes in cerebral blood flow (CBF; Biagi et al., 2007; Parkes et al., 2004; Restom et al., 2007). Furthermore, the complex anatomy of regions such as the MTL has been shown to be poorly registered to a brain template using standard spatial normalization procedures (Kirwan et al., 2006; Salmond et al., 2002). This suggests that differences between studies in MTL activations may in part be due to displacement of MTL structures caused by spatial normalization methods and individual variance in MTL anatomy.

Using a region of interest (ROI) approach based on MR images in native space, we have recently shown with blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) that encoding of objects, compared with encoding of positions, recruits large portions of the MTL in young healthy individuals (Ramsøy et al., 2009). Here, we applied the same fMRI paradigm to healthy subjects in the age range from 18 to 81 years to examine how age influences this encoding-related specialization in the MTL region. If, as suggested, aging leads to reduced specialization in regions involved in certain functions, one would expect a similar process to occur in the MTL. Based on this, we hypothesized that during encoding, regional specialization for objects and positions in MTL regions would gradually decrease with age. The effects of age on MTL specialization were also examined during preparation, rehearsal, and recognition, to see whether any age-related alterations during encoding would also be present during related processing stages. The data acquisition protocol was optimized for BOLD fMRI of the MTL region. Separate CBF measurements were performed and included as a covariate in the fMRI analysis.

## 2. Methods

### 2.1. Study population

Subjects were recruited through online advertisements ([www.forsoegsperson.dk](http://www.forsoegsperson.dk)) from the region of Copenhagen, Denmark. All subjects filled out a self-report questionnaire on medical history, and subjects were excluded in the case of self-reported claustrophobia, a history of neurological or psychiatric disorders, or a family history thereof, or hypertension. Exclusion criteria also included deviation of scores on the cognitive tests of more than 2 standard deviations

from the expected score of subject age, gender, and level of education (see below for further details on cognitive testing). No subject was excluded on such grounds. No medical examination was conducted, but all structural magnetic resonance imaging (MRI) scans of the brain were checked by a trained radiologist for signs of excessive atrophy or other anatomical abnormalities.

All participants signed an informed consent following the guidelines of the declaration of Helsinki. Subjects were paid for their participation. The study protocol was approved by the local ethics committee (KF 01–131/03). In all, 64 subjects underwent a comprehensive neuropsychological assessment (lasting approximately 1 hour), followed by a morphology scanning session (45 minutes). During a break subjects trained outside the scanner on 3 cognitive paradigms (the memory task reported here, a categorization task, and an emotion task, which will be reported elsewhere), after which they performed the 3 tasks in the same order during functional MRI scans. The second scanning session, which also included perfusion imaging, lasted for approximately 1 hour.

After visual inspection by a trained radiologist, 3 subjects were excluded from the study due to unexpected signs of neuropathology and were referred for further clinical assessment, and another subject was excluded from analysis due to a benign metal artifact. One subject aborted due to unexpected claustrophobia, 3 subjects were excluded from the analysis due to errors with the fMRI encoding paradigm, and 2 subjects were excluded because head movements during fMRI repeatedly exceeded a threshold criterion of  $> 3$  mm. In all, 54 subjects (age mean/SD/median: 41.9/18.8/40.5, range 18–81 years, 31 male, 46 right-handed, 7 left-handed, 1 ambidextrous) were analyzed in the present study. This study includes the data of 25 young subjects who have recently been reported (Ramsøy et al., 2009) in a study on the effects in young adults.

## 2.2. Neuropsychological testing

A comprehensive battery of neuropsychological tests was administered to all subjects, including tests of attention, working memory, long-term memory, and executive functions. The scores on the Danish Adult Reading Test (DART; a Danish version of the National Adult Reading Test; Andersen et al., 1997) and Wechsler Adult Intelligence Scale (WAIS) vocabulary (Harcourt Assessment, San Diego, CA, USA) were first normalized into  $z$ -scores based on Danish norms based on subject age, gender, and level of education (Mortensen et al., 1997). To test whether there were any age-related differences in estimated intelligence, the  $z$ -scores were analyzed with a multivariate general linear model (GLM) with each  $z$ -score as a dependent variable, and age and gender as independent variables. The  $z$ -scores were also used to assess general cognitive function in each subject. The effects of age on the neuropsychological tests are reported in Supplementary Table 1. In addition, we

tested for linear relationship between task performance and the size of the regions of interest (ROIs) in the MTL (more details are given below.)

## 2.3. Structural imaging protocol

All subjects were scanned using a Siemens Magnetom Trio 3T MR scanner (Erlangen, Germany) with an 8-channel head coil (Invivo, Gainesville, FL, USA). Consistent head positioning within the scanner was ensured by orienting the head to predefined reference marks on the scanner head coil. Movement was minimized by applying cushions to fixate the head in position. A scout scan was run to define the field of view (FOV) for the subsequent structural scan. The scans included: (1) a 3-D whole brain T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) scan with a voxel dimension of  $1 \times 1 \times 1$  mm<sup>3</sup>, FOV 256 mm, matrix  $192 \times 256 \times 256$ , repetition time (TR)/echo time (TE)/inversion time (TI) = 1540/3.93/800 ms, and a flip-angle of 9°; and (2) a 3-D whole-head T2-weighted sequence with a voxel dimension of  $1.1 \times 1.1 \times 1.1$  mm<sup>3</sup>, FOV 282 mm, matrix  $256 \times 256$ , TR/TE = 3000/354 ms, and a flip-angle of 28.5°.

## 2.4. Regions of interest

The N3 program (Sled et al., 1998) was used to correct images for nonuniformity artifacts due to radio frequency field inhomogeneities. Tissue classification was done using SPM2 (Wellcome Dept. of Imaging Neuroscience, London, UK) on the N3 bias-corrected images, with the SPM2 bias correction turned off. Careful editing of the gray matter tissue images ensured exclusion of non-MTL gray matter, and classified voxels that were outside of the brain but adjacent to the MTL. Six ROIs in each hemisphere were drawn on the MPRAGE structural image in native space using Montreal Neurological Institute (MNI) display (<http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC>). An ROI drawing protocol for the temporopolar cortex, perirhinal cortex, entorhinal cortex, and parahippocampal cortex was adapted from the Insausti et al. (1998a) protocol, neuroanatomic guidelines for the hippocampus and amygdala were adapted from those of Pruessner et al. (2000), and the atlas of Duvernoy (1991) was consulted (Fig. 1). The border between the perirhinal cortex and entorhinal cortex was set, in the coronal plane, at the top of the parahippocampal gyrus, making the perirhinal ROI cover the entire collateral sulcus down to the posterior border to the parahippocampal cortex. This differs from that of others (Insausti et al., 1998a) who have applied a more adaptive drawing protocol for the perirhinal-entorhinal border, based on the depth of the collateral sulcus. This deviation was made to reduce variability associated with subjective placement of the boundary within the collateral sulcus.

A reliability test of ROI drawing had previously been performed on a different data set consisting of 13 healthy young subjects (9 female, age range 19–31 years). This test



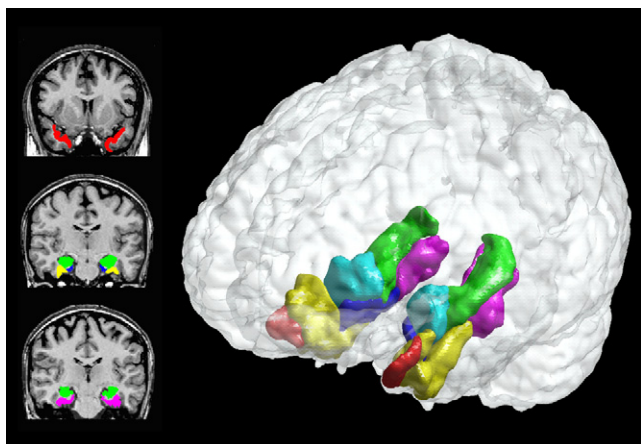


Fig. 1. The medial temporal lobe regions, illustrated by region drawings from 1 subject. Left: Coronal slices showing original region of interest (ROI) drawings including temporopolar cortex (red), entorhinal cortex (blue), perirhinal cortex (yellow), hippocampus (green), parahippocampal cortex (pink), and amygdala (cyan, shown only in glass brain). Right: 3-D reconstruction of the same ROIs, displayed within a transparent view of the native brain.

was performed by one of the authors (TZR), who also drew the ROIs in the full aging data set. Here, all subject data including file headers were anonymized and an extra set for each subject was right-left flipped. These procedures were implemented to ensure full anonymity of the individual MRI scans. Thus, ROIs in a total of 26 structural scans were drawn for intrarater comparison. An intraclass correlation test (Rousson et al., 2002) on each ROI volume showed a mean  $r = 0.884$  for all regions (range 0.615–0.916). The lowest values were for the bilateral temporopolar cortex, all other correlations exceeded 0.8.

The volume of the resulting ROIs were used to estimate mean BOLD signal changes in each ROI during the various stages of the 2 memory tasks. In addition, the regional volumes of each ROI were used to test for a correlation between interindividual variations in regional volume and interindividual variations in task performance as well as task-specific BOLD signal changes.

### 2.5. Perfusion MRI

Increasing age is associated with changes in CBF (Biagi et al., 2007; Parkes et al., 2004), which have been shown to influence BOLD fMRI results (Restom et al., 2007). In particular, age-related increases in the BOLD signal may be partly explained by regional reductions in CBF. The failure to include CBF as a covariate may therefore lead to erroneous estimates of age-related changes using BOLD fMRI.

Regional CBF was assessed with an arterial spin labeling (ASL) protocol. A proximal inversion with a control for off-resonance effects (PICORE) sequence (Wong et al., 1997) with gradient echo (GE)-planar imaging (EPI) read-out and presaturation was used ( $TE/TR = 24/2600$  ms; TIs of 200, 400, 600, 800, 1000, 1200, 1400, 1600, and 1800 ms

in a fixed pseudorandom order). Multiple TIs were used to take possible age-related changes in vascular delay into account. Fourteen contiguous slices with 5-mm slice thickness were acquired. The slices were oriented  $20^\circ$  oblique to the transverse plane, so that the slices were roughly parallel to the long axis of the temporal lobe, with a  $3 \times 3$  mm in-plane resolution ( $64 \times 64$  matrix). The time between subsequent slices ( $\Delta TI$ ) was 50 ms, acquired in ascending order with 72 repetitions (36 pairs) at each TI. We used a flow crusher gradient with  $b = 5$  seconds per  $\text{mm}^2$  and a bandwidth of 2604 Hz per pixel.

For the analysis of the ASL data the first image of each TI series was coregistered to the first image in the TI = 200-ms series using SPM2 with normalized mutual information. Then, all subsequent images within each TI series were realigned to the first image of that series using SPM2 with least squares. The 3-D T1-weighted structural image was then coregistered to the ASL image. The ROIs drawn on the 3-D T1-weighted structural images were resliced into the ASL image orientation and position, and tag and control values were averaged for each ROI at each TI. T1 relaxation curves were fitted for each ROI to tag and control values acquired at multiple inversion times. A general kinetic model (Buxton et al., 1998) was fitted to the difference of magnetization (control-tag) signals at multiple TI values giving estimates of perfusion, transit delay, and bolus width. The following assumptions were used in the model: T1 of blood = 1600 ms and blood-brain partition coefficient = 0.9.

Within the individual subjects, regions where either the T1 relaxation curve or the kinetic model gave a nonphysiological fit were subsequently excluded. Only T1 values fulfilling  $600 \text{ ms} < T1 < 2500 \text{ ms}$  and model fits giving positive transit delays were considered physiological. We then tested whether there were significant differences in perfusion between regions, by applying a 1-way analysis of variance (ANOVA), and found no significant effect of region on perfusion (calculation of normal distribution of scores was performed using the Shapiro-Wilk  $W$  test, where the mean score for all ROIs was 0.37, range 0.13–0.93). Thus, we chose to calculate the median MTL perfusion value for each subject, in order to produce a more robust estimate of perfusion. Using a univariate GLM, we first tested whether age had an effect on this perfusion value. We then included the median MTL baseline perfusion for each individual as a covariate in the multivariate analysis of the fMRI data.

### 2.6. BOLD imaging

We used an EPI sequence with the parameters  $TR/TE = 2000/30$  ms,  $64 \times 64$  matrix. The method described by Deichmann et al. (2003) was used to optimize the signal-to-noise ratio of the EPI sequence with respect to BOLD fMRI of the MTL region. This was done in a separate scan in which different slice orientations and z-shimming gradi-

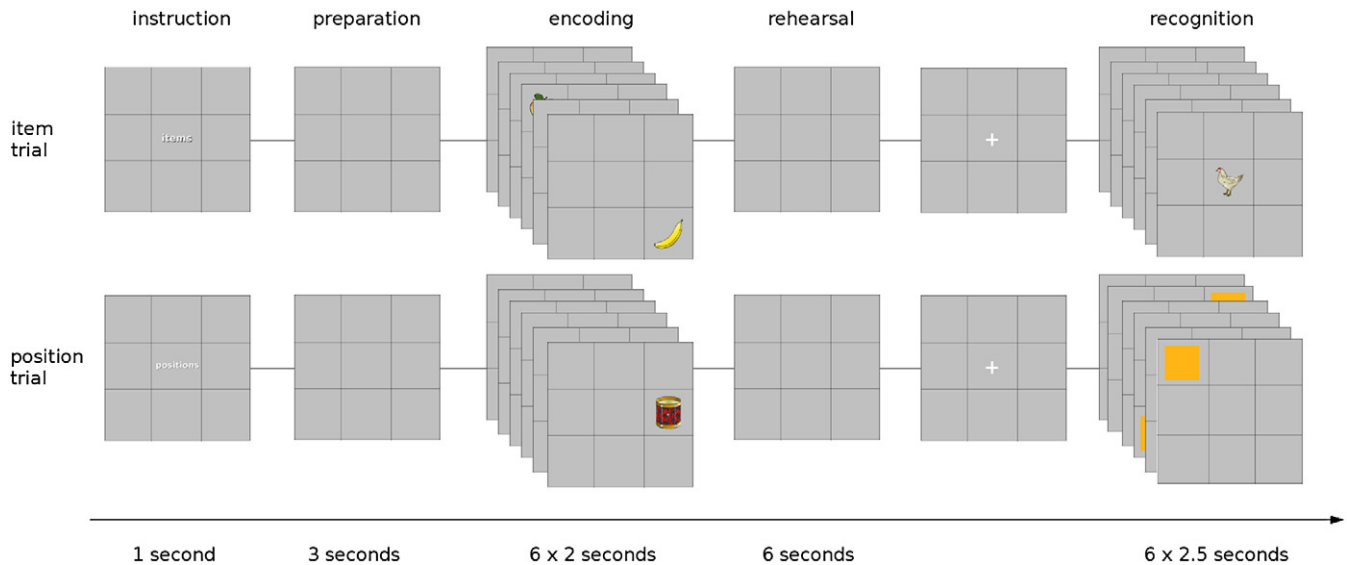


Fig. 2. The memory paradigm. Object and position trials consisted of an instruction cue; a preparation phase; an encoding phase with 6 trial-unique objects and positions; a rehearsal phase; and a recognition phase with old-new judgments. Only the instruction cue and recognition phases were visually different between the conditions. Numbers at the bottom indicate block duration.

ents were tested for optimal signal-to-noise ratio in the MTL region, fixated at the perirhinal cortex in each hemisphere. The block of 33 slices was oriented  $20^\circ$  oblique to the transverse plane. The voxel size was  $3 \times 3 \times 2$  mm with no interslice space. The 2-mm slice thickness was applied to further reduce susceptibility artifacts. The total scanning time was 702 seconds. Pulse and respiration were recorded using an MR-compatible pulse oximeter and a respiration belt, sampled at 50 Hz.

### 2.7. Cognitive paradigm

The encoding task involved 18 blocks, divided into 9 blocks each for object and position processing. The object and position blocks were presented pseudorandomly, with no more than 2 repeats of the same block type. The scan originally included an additional object block that was discarded to obtain an equal number of blocks. Each block included a 1-second instruction cue; a 3-second preparation epoch; 6 stimuli presented serially 2 seconds each for encoding; a 6-second rehearsal epoch; and 6 stimuli presented serially, 2.5 seconds each, for old/new recognition judgments (Fig. 2). Each encoding stimulus was a unique, colored Snodgrass and Vanderwart-like drawing of a living or nonliving object (Rossion and Pourtois, 2004) presented in a trial-unique location among 9 positions in a  $3 \times 3$  spatial grid. No objects were repeated across trials. During preparation and rehearsal, an empty grid was displayed. Just prior to the instruction cue and recognition phase a white cross appeared at the middle of the grid for 1 second, signaling the onset of the encoding or recognition phase. In the object memory trials, recognition stimuli were 3 previously shown and 3 novel objects presented in a fixed pseudorandom order. In position memory trials, recognition stimuli con-

sisted of an orange square that appeared in 3 old and 3 novel positions within the grid, presented in a pseudorandom order. The verbal instruction cue at the beginning of each trial indicated whether the subjects were to encode (and rehearse and recognize) objects or grid positions in the subsequent series of stimuli. Subjects were asked to try to keep the objects or grid positions in mind during the rehearsal epoch. Behavioral responses during the recognition phase were recorded using a button box with the right hand, where index finger presses indicated “seen” responses and middle finger presses “not seen” responses. Behavioral data included reaction time and response accuracy. Training outside the scanner was performed using a different set of objects.

Stimuli were presented using E-prime ([www.pstnet.com](http://www.pstnet.com)) and IFIS-SA System software (MRI Devices Corp., Gainesville, FL, USA), in a Windows 98 environment (Microsoft Corp., Redmond, WA, USA). Visual stimulation was provided by means of a liquid crystal display (LCD) projector (Canon LV740, Lake Success, NY, USA), located outside the scanner room, and a zoom lens (Buhl Optics 849MCZ087, Navitar, Rochester, NY, USA) projected the image ( $800 \times 600$  pixel resolution) through a wave guide onto a screen behind the subject’s head. The screen covered  $24 \times 18$  degrees of the visual field, and was visible to the subject through a mirror mounted on the head coil. The following settings were used: full brightness = 3700 American National Standards Institute (ANSI) lumens, setting = 10; contrast = 800:1, setting = 32.

### 2.8. Analysis of behavioral data

We analyzed the effects of age on accuracy and reaction time, using a multivariate GLM in Statistica 7.0 (StatSoft,

Inc., Tulsa, OK, USA) with accuracy (object: ACC-o, position: ACC-p) and reaction time (object: RT-o, position: RT-p) as dependent variables, and age and gender as independent variables. To study whether accuracy on either of the 2 tasks was significantly more affected by age, we further analyzed the ratio between the 2 scores (ACC-o/ACC-p). The effect of age on this ratio (ACC) was performed with a univariate regression analysis with age and gender as independent variables. We also tested whether interindividual variations in regional volume of each ROI in MTL correlated with interindividual variations in task performance.

### 2.9. Analysis of BOLD signal changes

To avoid anatomical uncertainty following spatial normalization, EPI data analysis was performed in native space using SPM5 (Wellcome Dept. of Imaging Neuroscience, London, UK). Images were realigned without smoothing. The EPI image series was coregistered to each individual's anterior commissure-posterior commissure (AC-PC) aligned structural image, using mutual information, trilinear interpolation without warping, and subsequently manually checked (by TZR). For each content condition (object and position) preparation, encoding, rehearsal, and recognition were entered as separate regressors in the design matrix, leading to a total of 8 regressors of interest. The regressors were convolved with a canonical hemodynamic response function. Nuisance regressors for respiration, heartbeat, and motion were included in the analysis (Lund et al., 2006). For each ROI the average value for the contrasts of interest (e.g., object encoding minus position encoding) was fed into a second level analysis. This provided a contrast value for each ROI, where positive values were indicative of higher involvement in object encoding compared with position encoding, and negative values would indicate higher involvement in position encoding compared with object encoding. Values around zero would indicate that the structure did not differentiate between the 2 types of content.

To study the effects of age upon regional contrast values, we first applied a multivariate GLM with ROI contrast values for encoding as the dependent variables, and with age, gender, and perfusion as covariates. Second, we applied the same GLM analysis to test whether age had an impact on other processing stages, including preparation, rehearsal and recognition.

Following these hypothesis-specific tests, we performed post hoc analyses where handedness, DART score, and performance (ACC-o and ACC-p, or ACC) were included as additional covariates, either as individual regressors or interaction effects with age. We then tested the relationship between regional contrast values and performance on the object and position tasks using multivariate analyses with age, gender, and perfusion as covariates. When testing the effect on performance for 1 task type (e.g., accuracy for memorizing objects) we included the performance measure

Table 1

The effects of age on cognitive function, task performance, and CBF

| Test                      | <i>F</i> | <i>p</i> |
|---------------------------|----------|----------|
| DART raw score            | 0.54     | 0.935    |
| DART z-score              | 0.97     | 0.331    |
| WAIS vocabulary raw score | 1.09     | 0.421    |
| WAIS vocabulary z-score   | 0.46     | 0.503    |
| CBF                       | 0.39     | 0.535    |
| RT objects                | 0.40     | 0.531    |
| RT positions              | 0.00     | 0.921    |
| ACC-o                     | 14.00    | <0.001   |
| ACC-p                     | 14.74    | <0.001   |
| ACC ratio                 | 1.00     | 0.322    |

Results from multivariate GLM analysis of the effects of age on cognitive, behavioral, and physiological scores (effects of age: effect *df* = 2, error *df* = 46). See text for details.

Key: ACC-o, accuracy for object memory; ACC-p, accuracy for position memory; CBF, cerebral blood flow; DART, Danish Adult Reading Test; RT, reaction time; WAIS, Wechsler Adult Intelligence Scale.

for the other task type (e.g., accuracy for memorizing positions) as a covariate in the analysis.

Finally, we also performed additional analyses in which the relative ROI volume was used as a regressor for the analysis of task-specific BOLD signal changes during the different stages of the experimental tasks (i.e., preparation, encoding, rehearsal, and retrieval stage). Here, we used the right and left hippocampus as our model. This analysis was computed to test whether age-related volume changes were collated with age-related changes in functional differentiation regarding object or spatial memory.

## 3. Results

### 3.1. Demographic data

There were no effects of age upon estimated IQ levels, as measured by the derived z-scores on DART and WAIS vocabulary, as shown in Table 1 and Figure 3. As these scores are related to general intelligence estimates, this result suggests that the general cognitive level was comparable across the age cohort.

### 3.2. Perfusion MRI

The percentage of ROIs with valid ASL values was 79.1/13.7 (mean/SD), but these were not systematically related to specific regions. To test for potential effects of age on this value, we ran a regression analysis with the percentage of valid ROIs as the dependent variable and age as independent variable. Here, we found a significant effect of age ( $F = 4.22$ ,  $p = 0.045$ ,  $R^2 = 0.075$ ), which demonstrated a positive relationship between age and the percentage of valid ROIs. Consequently, we included the percentage of valid ROIs as a regressor in the perfusion analysis. Age had no overall effect on regional CBF in the MTL, even when correcting for the effects of age on the percentage of ROIs with valid ASL fit (Table 1, Fig. 3). Because there were large individual differences in MTL perfusion, and those

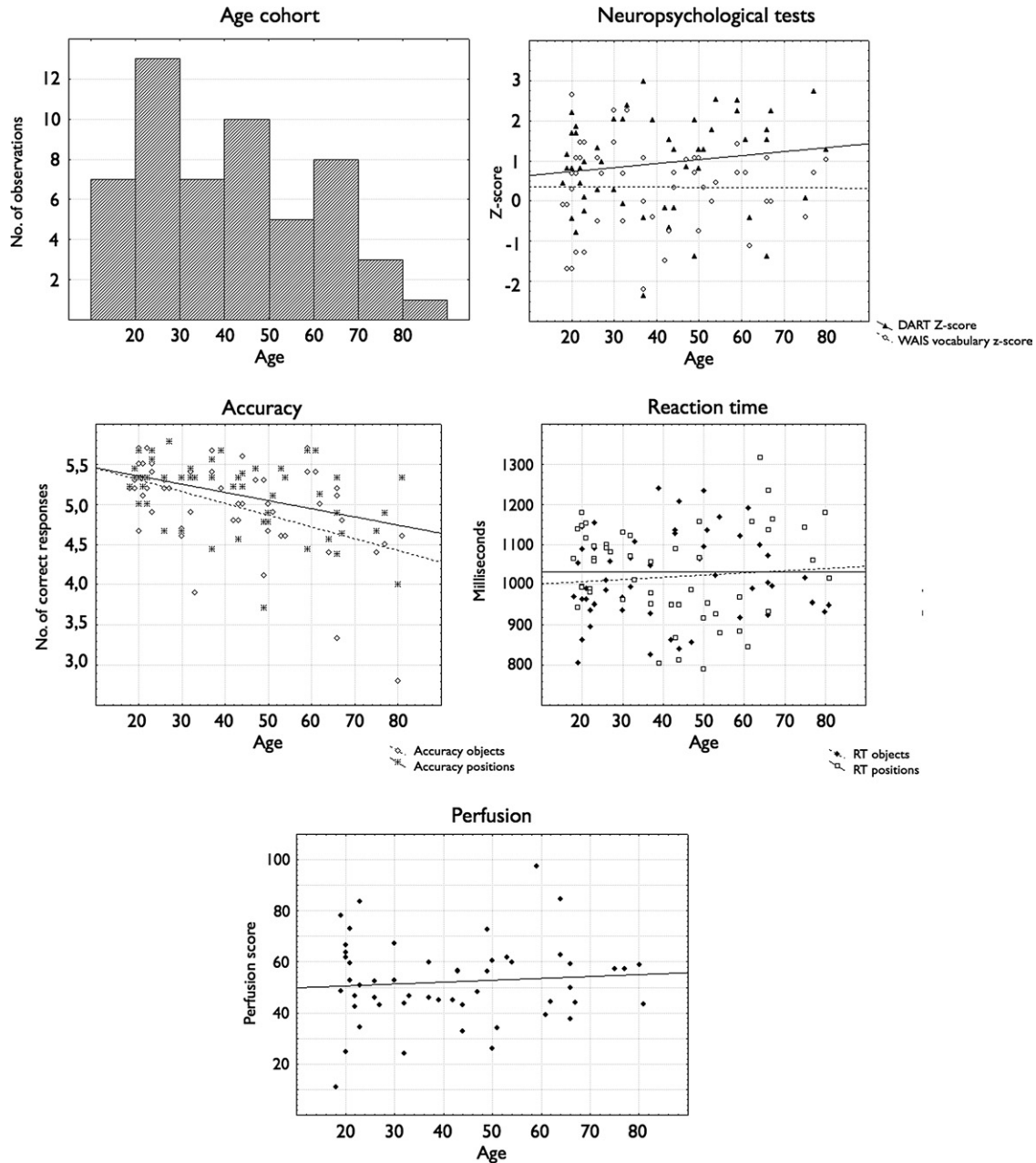


Fig. 3. Descriptive figures of age cohort, and plots of age-effects on neuropsychological tests (Danish Adult Reading Test [DART], black triangles, solid line; Wechsler Adult Intelligence Scale [WAIS] vocabulary, open circles, stippled line), accuracy (object, open circles, stippled line; position, star, solid line), reaction time (object, black triangle, solid line; position, open square, stippled line), and medial temporal lobe (MTL) perfusion. See text for further details.

effects were not related to individual differences in ASL fit ( $F = 1.18$ ,  $p = 0.33$ ), we included the MTL CBF value for each subject as a regressor in our BOLD fMRI analysis.

### 3.3. Behavioral results

The behavioral analysis showed no age-effect on reaction time for either object or position responses, as shown in Table 1 and Figure 3. Age was associated with an overall decline in memory performance for both type of memories, as indexed by a decrease in recognition accuracy (ACC-o:

$r = 0.48$ ,  $F = 14.00$ ,  $p < 0.001$ ; ACC-p:  $r = 0.41$ ,  $F = 14.74$ ,  $p < 0.001$ ). The ratio between ACC-o and ACC-p was not influenced by age ( $F = 1.0$ ,  $p = 0.322$ ), indicating that the relative task performance between the 2 tasks was stable across the age cohort. We furthermore compared the 2 regression lines of ACC-o and ACC-p, using a common slope as correction, and found that there was no significant difference between the 2 slopes (difference in adjusted means =  $-0.1462$ , standard error [SE]<sub>diff</sub> =  $0.0897$ ,  $t = -1.63$ ,  $p = -0.1062$ ).



Table 2  
The effects of age on regional BOLD fMRI contrast values between object and position processing for different steps of the memory process

| Region                            | Age effect |                | T     | p                   |
|-----------------------------------|------------|----------------|-------|---------------------|
|                                   | $\beta$    | Adjusted $R^2$ |       |                     |
| Preparation (object vs. position) |            |                |       |                     |
| Right temporopolar cortex         | −0.26      | 0.06           | −1.82 | 0.075 <sup>b</sup>  |
| Encoding (object vs. position)    |            |                |       |                     |
| Right temporopolar cortex         | −0.24      | 0.19           | −1.99 | 0.052 <sup>b</sup>  |
| Right parahippocampal cortex      | −0.27      | 0.09           | −2.10 | 0.041 <sup>a</sup>  |
| Right hippocampus                 | −0.22      | 0.10           | −1.79 | 0.079 <sup>b</sup>  |
| Left amygdala                     | −0.24      | 0.21           | −1.99 | 0.052 <sup>b</sup>  |
| Right amygdala                    | −0.32      | 0.26           | −2.43 | 0.019 <sup>a</sup>  |
| Rehearsal (object vs. position)   |            |                |       |                     |
| Right parahippocampal cortex      | −0.22      | 0.17           | −1.83 | 0.074 <sup>b</sup>  |
| Recognition (object vs. position) |            |                |       |                     |
| Right temporopolar cortex         | −0.34      | 0.10           | −2.76 | 0.008 <sup>a</sup>  |
| Right entorhinal cortex           | −0.30      | 0.01           | −2.53 | 0.015 <sup>a</sup>  |
| Left perirhinal cortex            | −0.31      | 0.18           | −2.79 | 0.008 <sup>a</sup>  |
| Right perirhinal cortex           | −0.34      | 0.13           | −3.06 | 0.004 <sup>a</sup>  |
| Left parahippocampal cortex       | −0.38      | 0.08           | −3.23 | 0.002 <sup>a</sup>  |
| Right parahippocampal cortex      | −0.33      | 0.18           | −2.84 | 0.007 <sup>a</sup>  |
| Left hippocampus                  | −0.30      | 0.07           | −2.54 | 0.015 <sup>a</sup>  |
| Right hippocampus                 | −0.31      | 0.21           | −2.68 | 0.010 <sup>a</sup>  |
| Left amygdala                     | −0.36      | 0.11           | −3.20 | 0.002 <sup>a</sup>  |
| Right amygdala                    | −0.40      | 0.23           | −3.56 | 0.0009 <sup>a</sup> |

Values indicate results from multivariate GLM with each MTL region as dependent variable, and age, gender, and perfusion as regressors. Effects for each stage is shown separately.

Key: BOLD, blood oxygen level-dependent; fMRI, functional magnetic resonance imaging; GLM, general linear model; MTL, medial temporal lobe.

<sup>a</sup> Significant results, using a standard ( $p < 0.05$ ) threshold.

<sup>b</sup> Significant results, using a liberal ( $p < 0.1$ ) threshold.

We also tested for a relationship between the regional volume of MTL structures and individual variations in task performance (see Supplementary Table 2). There was a linear relationship between relative ROI size of the hippocampus and memory performance for either the object task, position task, or shared task performance. Further, the regional volume of left and right amygdala, right temporopolar, and parahippocampal cortex correlated positively with position memory. Likewise, the ROI volume of left parahippocampal, right ento- and perirhinal cortex were positively associated with performance in the object memory task.

### 3.4. fMRI results

As previously demonstrated in young subjects by Ramsøy et al. (2009), the present fMRI paradigm engaged the MTL region throughout the age cohort (Supplementary Table 3). Analysis of the regional BOLD signal during the encoding stage demonstrated a significant negative relationship between age and contrast value in the right parahippocampal cortex and right amygdala ( $p < 0.05$ ). Similar nonsignificant trends ( $p < 0.1$ ) were found in the right temporopolar cortex, right hippocampus, and left amygdala (Table 2, Fig. 4b). Figure 5 demonstrates this effect as a linear effect of age.

During the recognition stage, a number of regions in the right and left MTL showed a significant negative relationship between age and contrast value (see Table 2, Fig. 4d), indicating a gradual change in task-specificity with age. Age-related changes were present in the right temporopolar cortex, right entorhinal cortex, and bilaterally in the perirhinal cortex, parahippocampal cortex, hippocampus, and amygdala. Figure 6 shows the linear effects of age on the contrast values in these regions. Notably, while the other regions demonstrated a change in contrast values from positive values toward zero, the right entorhinal cortex contrast value (Fig. 6, top left) tended to go from positive to negative. For the right entorhinal cortex, we performed a post hoc 1 sample  $t$  test of contrast values for this region in the youngest and oldest adults separately, using predefined age groups (young = 18–35 years, old = > 55 years, middle-aged and excluded = 36–55 years). While young subjects ( $n = 25$ ) demonstrated a significant task effect ( $t = 2.35$ ,  $p = 0.028$ ), older adults ( $n = 15$ ) showed no such effect ( $t = -0.16$ ,  $p = 0.877$ ). This suggests that the age-related effect in right entorhinal cortex was comparable with the age-related effects seen in other medial temporal regions.

To test whether these ROI results could be influenced by age-related atrophy, we included relative ROI size as a covariate in our analysis. We used the bilateral hippocampi during recognition as our model. Each ROI size was calculated as the raw ROI size divided by the intracranial volume (ICV). To calculate the ICV, the MPRAGE image was affine-registered to MNI152 space (Jenkinson and Smith, 2001; Jenkinson et al., 2002) to obtain a volumetric scaling factor, and to further be used as a normalization for head size. Intracranial volume was calculated by multiplying the volumetric scaling factor and the intracranial volume of the standard space brain. By running a regression analysis with contrast value as the dependent variable, and with perfusion, age- and ICV-corrected ROI size as independent variables, we found no additional effect of ROI size on contrast values in the left ( $t = 0.89$ ,  $p = 0.383$ ) or right hippocampus ( $t = 1.29$ ,  $p = 0.202$ ). Extending this analysis to other processing stages, we found that in the right hippocampus (HP), ROI size was significantly related to the contrast value during rehearsal ( $t = 2.48$ ,  $p = 0.0169$ ) but not during preparation ( $t = -0.43$ ,  $p = 0.672$ ) or encoding ( $t = 0.66$ ,  $p = 0.516$ ). For the left HP ROI size a trend was found during rehearsal ( $t = 1.99$ ,  $p = 0.052$ ) and encoding ( $t = 1.78$ ,  $p = 0.08$ ) but not during preparation ( $t = 0.42$ ,  $p = 0.680$ ). These analyses show that activation-related effects were unaffected by interindividual variations in the volumes of the hippocampal ROI, indicating that in contrast to memory performance, the age-related shift in task-specific BOLD activation was not directly related to regional atrophy.

For the preparation and rehearsal stages, the ROI analysis did not reveal any significant age-related changes at a corrected statistical threshold of  $p < 0.05$ . The right



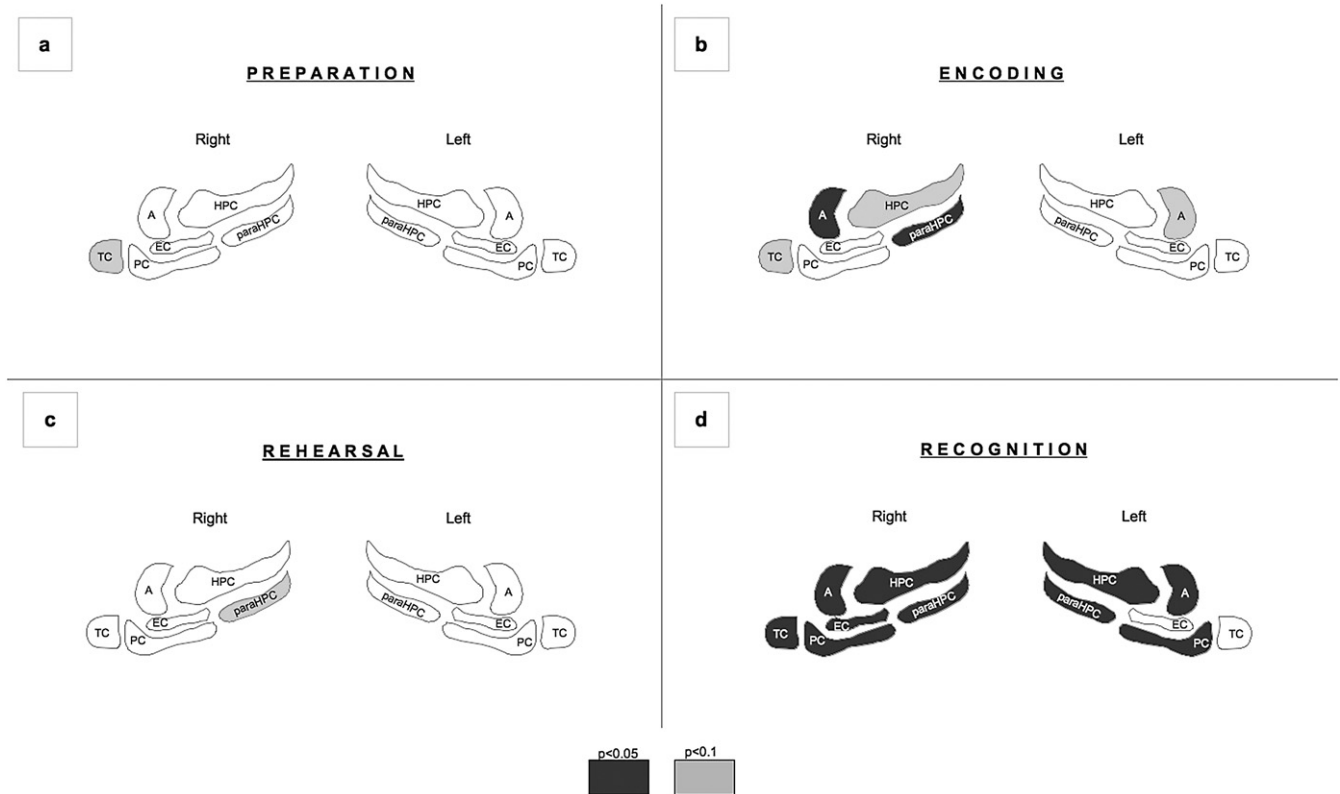


Fig. 4. Illustration of age-related changes in contrast value during the 4 processing stages. Colored regions show significant age-effects in blood oxygen level-dependent (BOLD) contrast at  $p < 0.05$  (dark gray) and  $p < 0.1$  (light gray). Regions are outlined and named, where A = amygdala, EC = entorhinal cortex, HP = hippocampus, paraHPC = parahippocampal cortex, PC = perirhinal cortex, and TC = temporopolar cortex.

temporopolar cortex and right parahippocampal cortex showed a trend toward age-related changes ( $p < 0.1$ ) for the preparation and rehearsal stages, respectively (see Fig. 4a and 4c).

Additional variables were originally included in a full model and were tested for added value using a stepwise regression with backward elimination procedure. Following this procedure, handedness and DART score did not improve the model, and were consequently excluded from the final model. We then attempted to predict the subjects' patterns of memory performance with the contrast values during different processing stages, using age, gender, and perfusion as covariates. In the preparation stage, performance on object memory (controlling for performance on position memory), showed a positive linear relationship with contrast values in specific MTL regions, namely left ( $t = 2.08$ ,  $p = 0.04$ ) and right temporopolar cortex ( $t = 2.59$ ,  $p = 0.01$ ) and right amygdala ( $t = 2.36$ ,  $p = 0.01$ ). The higher the preparatory BOLD signal level during the object memory task relative to the position memory task, the better participants performed the object memory task. This relationship was unaffected by gender- and age-effects. In the recognition stage, the contrast values in right parahippocampal cortex demonstrated a negative linear relationship with position memory performance

( $t = -2.34$ ,  $p = 0.02$ ). Increased BOLD signal during position recognition relative to object recognition, was related to better performance on the position memory task relative to the object memory task.

Further analyses were used to explore these effects in the youngest and oldest subjects, employing the predefined age groups described above. In the young subject group, we did not find any relationship between memory performance and BOLD fMRI values for any ROIs at either processing stage. In the oldest subjects, however, we did find significant relationships between ACC-o and regional BOLD fMRI in the right temporopolar cortex ( $t = 4.04$ ,  $p = 0.0049$ ) during object preparation, suggesting that more activation of this region during object preparation was associated with better object memory. Further significant results were found in the left entorhinal cortex during rehearsal of both objects ( $t = -2.50$ ,  $p = 0.0409$ ) and positions ( $t = 2.98$ ,  $p = 0.0204$ ). Notably, there was a negative relationship between object memory and entorhinal activation during rehearsal of objects, but a positive relationship between position memory and entorhinal activation during position rehearsal. This suggests that increased entorhinal cortex activation was related to good performance on position memory and bad memory for objects.

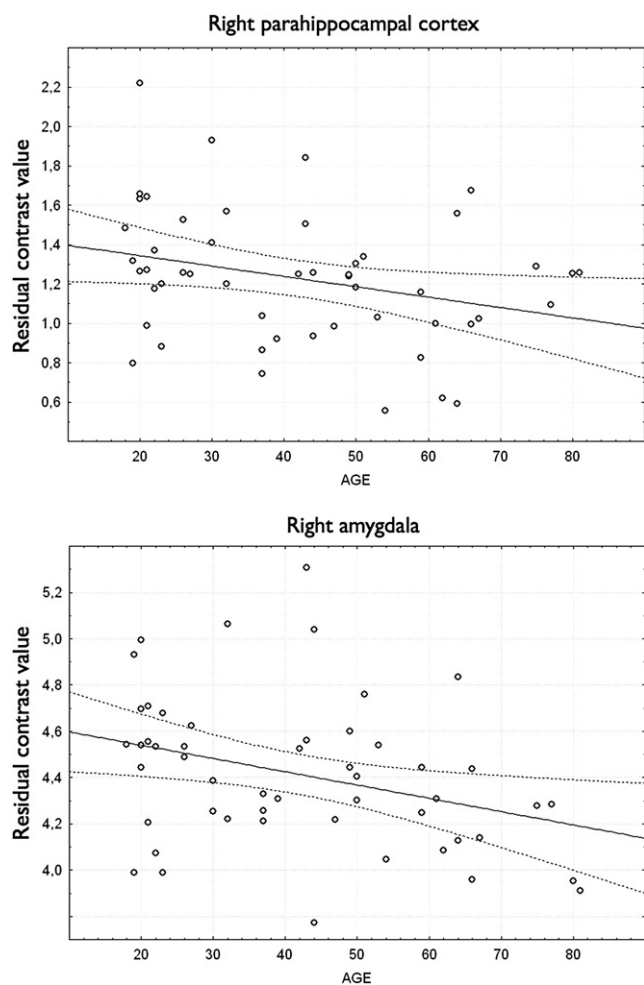


Fig. 5. Age-related changes in contrast value in affected regions during encoding. The plot shows each individual residual contrast value, after correction for the effects of gender and perfusion. The solid line shows linear regression line of the mean, and the dotted line demonstrates the 95% confidence interval.

#### 4. Discussion

The present study analyzed the effects of age upon task-related specialization in the MTL, operationalized as the difference in regional activation between object and position encoding. Recently, we showed that large portions of the MTL region were more strongly activated during object encoding relative to position encoding in young healthy individuals, pointing to a specialization within the MTL (Ramsøy et al., 2009). Following up on this, we now studied a continuous age cohort from ages 18 to 81 while they performed the same task during fMRI.

The analysis of the behavioral data revealed an age-related decline in memory performance. This subclinical impairment of working/episodic memory is in good agreement with a large body of research showing a gradual decline in both working memory and episodic memory during healthy aging (Cook et al., 2007; Henderson, 2007; Waters and Caplan, 2005; West and Bowry, 2005; Wing-

field and Kahana, 2002), including item and spatial memory (Fritsch et al., 2007; Luo and Craik, 2008). In our cohort, the age-related decline in memory performance was comparable for objects and positions. The comparable decline in object and position recognition with age indicates that both tasks were sensitive to the general age-related change in memory.

The adverse effect of age on memory performance has been linked to a decline in anatomical and functional integrity of the MTL with age. Structural MRI studies have consistently demonstrated age-related volumetric decline in the hippocampus (Geinisman et al., 1995; Jernigan and Gamst, 2005; Sowell et al., 2002), and in the entorhinal, perirhinal and parahippocampal cortex (Insausti et al., 1998b). At a structural level, age-related MTL atrophy has been correlated with a reduction in memory performance (Raz et al., 2000; Rodrigue and Raz, 2004). For example, Rodrigue and Raz (2004) demonstrated that annual shrinkage of the entorhinal cortex, but not the hippocampus or other MTL regions, was associated with reduced performance on both immediate and delayed memory performance.

The main finding derived from the fMRI data were an age-related gradual decline in task-related differences in MTL activity during encoding and recognition of objects or positions. This age-related attenuation of content differentiation in MTL regions indicates a reduced task-related specialization of MTL structures in memory function in elderly healthy individuals without recognizable clinical memory impairment. Because the age related decline in memory performance was comparable for objects and positions, the attenuated task differentiation in the MTL did not appear to be attributable to a differential effect of aging on task performance.

Most MTL regions displayed an age-related shift from positive contrast values (i.e., relatively stronger activation during object processing relative to location processing) toward zero (i.e., no content-related differentiation in activation). This was also the case for areas showing only little specialization in young subjects. For instance, the right entorhinal cortex displayed a lower degree of object specificity overall, yet this region still exhibited an age-related reduction in relative specialization. No region within the MTL showed a flip in task-related specialization from object-greater to location-greater preference.

The reduced task-related specialization in the MTL region represents a trait feature of normal aging without a clear link to age-related changes in memory function. Regression analyses failed to reveal a relationship between the age-related decline in performance (accuracy) and the age-related attenuation in MTL specialization, as revealed by relative differences in regional BOLD signal during the object and location memory task. It follows that the age-related decrease in content specificity in MTL regions cannot be used to predict age related memory impairment. The

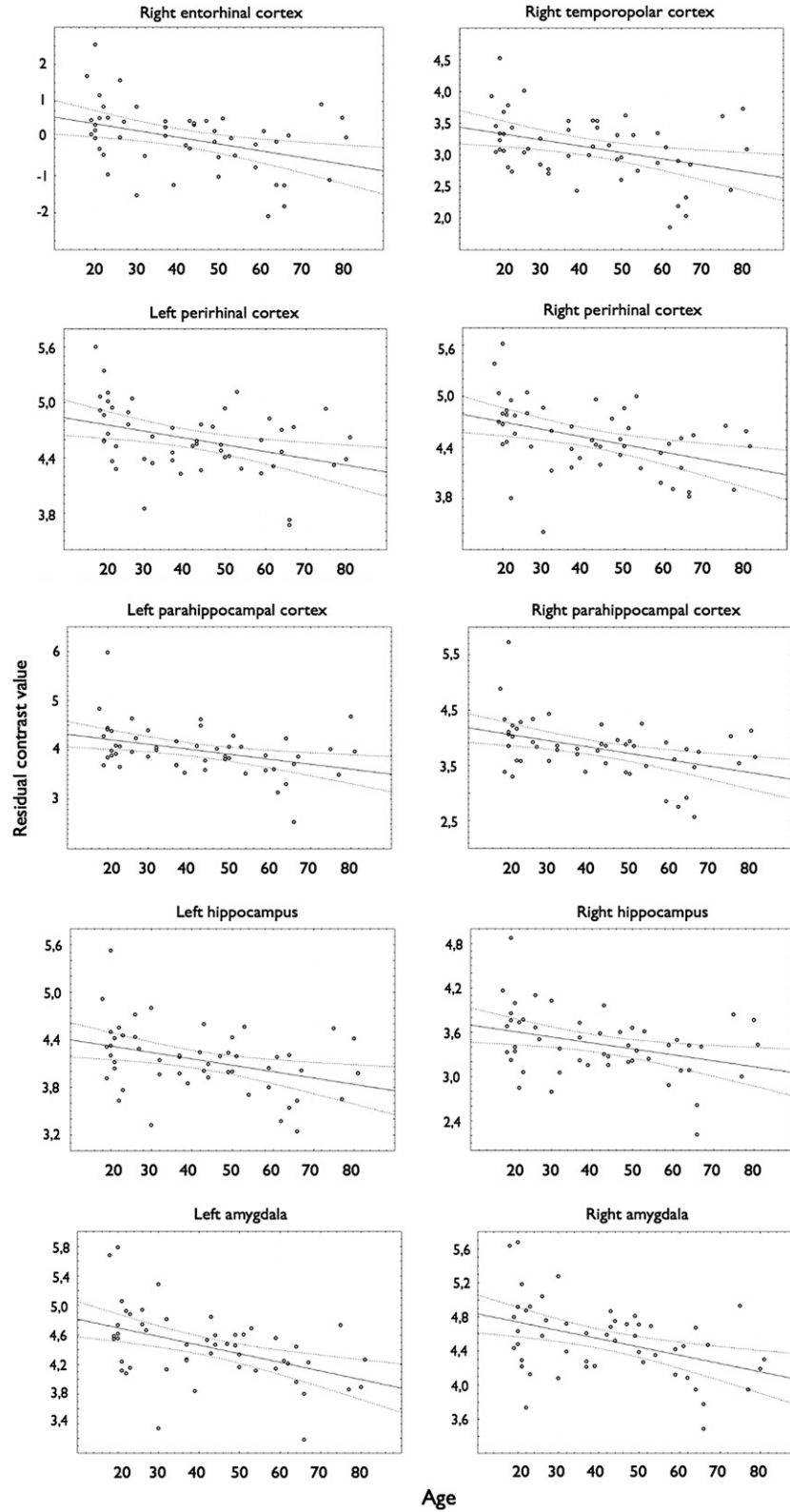


Fig. 6. Age-related changes in contrast value during recognition. Dots indicate individual residual contrast values after correction for the effects of gender and perfusion. The solid line shows linear regression line of the mean, and the dotted line demonstrates the 95% confidence interval.

lack of correlation also argues against the possibility that the age-related reduction in MTL specialization constitutes an adaptive mechanism that effectively compensates for the reduced processing capacities in MTL circuits. However, it remains a challenge to demonstrate a link between changes in MTL activity and memory in healthy aging. For example, Daselaar et al. (2003) found reduced activation in the left anterior MTL with successful recognition only in older adults with reduced memory performance as opposed to young healthy adults. Older adults with memory impairments demonstrated a general activation increase in the brain when comparing correctly rejected items. Of note, these changes were not present in older adults without memory impairments.

At first glance, the results seem to suggest that the age effect on task-related specialization in MTL regions were more pronounced during recognition than encoding. However, design-related differences in the 2 stages may in part explain this apparent difference in sensitivity to age effects. During encoding, the visual stimuli were identical showing individual objects positioned within the grid. Without the foregoing instructions, subjects would be unable to determine whether the task was to focus on objects or positions. In contrast, different visual stimuli were presented in the recognition stage. In the object recognition task, single objects (3 novel and 3 repeated) presented serially during the recognition phase in the middle of the grid. In the position recognition task, orange squares (3 novel and 3 trial-unique from the encoding stage) were presented serially within the  $3 \times 3$  grid. Because the visual stimuli during recognition were structurally different between the object and position task, age related changes in visual processing of object or spatial information might have contributed to the age-related shifts in MTL activity during recognition. This concern does not apply to age-related activity shifts during encoding because the visual stimuli were identical.

Even if age-dependent changes in visual processing might account at least to some extent for the age-related differences in MTL activity in the recognition phase, our finding is still relevant to the question how aging impacts on the relative specialization of the MTL areas to recognize object-related and spatial memory features. By definition, it is difficult to dissociate MTL activity related to the processing of the target stimuli from recognition processes during memory retrieval. Depending on whether recognition is directed toward object identity or spatial position, retrieval-related processes will introduce a processing bias in the visual processing stream that favors the relevant features of the target stimuli presented in the recognition phase, even if the target stimuli would be completely identical. Therefore, we think that the observed age-related change in MTL activity during the recognition phase is tightly coupled to memory retrieval and might be caused by an age effect on retrieval-related activity of object-related or spatial infor-

mation or on visual processing of the stimulus feature on which the memory judgment is based.

In some MTL regions, the degree of content differentiation correlated with the subjects' pattern of recognition accuracy. In left and right temporopolar cortex and right amygdala, during the preparation period, a relative increase in BOLD signal during object relative to position memory conditions was associated with better object recognition. This finding may relate to a change in the view of amygdala function suggesting a role in noting the salience of present and expected events (see, for example, Murray, 2007; Pessoa et al., 2002; Vuilleumier, 2005). Similarly, the temporopolar cortex has been proposed to play a role in the processing of salient events (see, e.g., Asari et al., 2008), in conjunction with the amygdala (Höistad and Barbas, 2008). Our results imply a role for the amygdala and temporopolar cortex during preparatory stages in object encoding, though we observed no evidence for an effect of aging on these functions.

Conversely, in left parahippocampus, the higher the activity level during position (relative to object) recognition the more accurately participants performed the position memory task. This is consistent with a general role for the parahippocampal region in spatial memory processing (Düzel et al., 2003; Ekstrom and Bookheimer, 2007; Ramsøy et al., 2009; Sommer et al., 2005), and consistent with previous research linking spatial recognition success and the parahippocampal region (Ekstrom and Bookheimer, 2007; Kircher et al., 2008; see also Wais, 2008). Together, our results suggest that, across the life span, patterns of content modulation of activity within distinct MTL regions are linked to variability in encoding and retrieval success for this content.

The pattern of age-related change in MTL specialization may vary depending on the experimental features of the memory task. Our memory task evoked less position-related activity than object-related activity throughout the MTL in young subjects; whereas other studies have suggested greater activity in some MTL regions during spatial than object processing (Buffalo et al., 2006; Mitchell et al., 2000; Pihlajamäki et al., 2003, 2004, 2005). Our spatial memory task was relatively simple, perhaps evoking only low-level spatial memory processing in the MTL. This may explain why in young individuals, although our position encoding task evoked stronger activation in the dorsal visual and ventral parietal regions than did the object encoding task, such effects were not observed in any component of the MTL region (Ramsøy et al., 2009). The use of more complex spatial stimuli (e.g., images of scenes) might have led to stronger activation in regions such as the parahippocampal cortex and the hippocampus and thus may have resulted in a different pattern of MTL specialization (Burgess et al., 2002; Epstein et al., 1999; Pihlajamäki et al., 2005).

It is also possible that the object and position encoding tasks differed with respect to how much they taxed the



encoding machinery. The objects presented represented members of a virtually limitless set of possibilities, while the positions to be encoded represented a small set of possibilities. Objects were thus “low frequency” stimuli, while positions were “high frequency” stimuli. Low frequency stimuli are known to be more difficult to process at study phase, although they may be more easily recognized at the test phase (Diana and Reder, 2006; Glanzer and Adams, 1985; Ostergaard, 1998).

Our analysis of the preparation and rehearsal stages did not reveal any significant effects of age. At lower statistical thresholds, the right temporopolar cortex and right parahippocampal cortex showed age-related effects for the preparation and rehearsal stages, respectively. Other studies (Mencl et al., 2000; Vandenbroucke et al., 2004) have demonstrated age-related reduced activations in the MTL during working memory. We wish to emphasize that due to the short duration of the preparation stage the present paradigm may have limited sensitivity to age-related changes in content specialization during preparation and rehearsal.

It should be noted that the present analysis was not performed by comparing object and position processing to a baseline, but as direct comparisons of object and position processing epochs (e.g., object encoding vs. position epochs). We are aware of the discussions in the literature concerning the use of baseline (for example Shulman et al., 2007; and in particular Morcom and Fletcher, 2007). From this discussion, one can identify at least 2 traditions: 1 tradition favoring the use of a baseline, and a second tradition favoring direct comparisons of 2 (or more) conditions that differ only on 1 (or at most a few) critical parameters. We employed the latter approach without introducing a functional “baseline.” This means that the present study cannot estimate the overall level of mediotemporal activation during object or position encoding per se, or the underlying nature of the age-related changes in these processes. If MTL activation is lower overall in older subjects, then the relative differences between activity levels in the 2 task conditions (i.e., the contrast values) may reflect these baseline differences to some degree. The present study does not allow us to address these questions, and further studies that include appropriate baseline estimates may provide insights into the nature of the changes we report here. Future extensions may include data analyses focusing on those voxels in the ROIs that show peak activation rather than estimating the mean activation across the entire ROI. Alternatively, one might adopt a pattern analysis approach and test whether a classifier trained on task-related mediotemporal activation patterns would be able to reliably discriminate between young and old individuals.

We employed ASL to capture and correct for age-related changes in regional brain perfusion (Restom et al., 2007). Our ASL measurements failed to reveal systematic age related perfusion changes in MTL. This is surprising, as other studies have demonstrated age-related changes in per-

fusion (Biagi et al., 2007; Parkes et al., 2004; Restom et al., 2007), although such changes have rarely been reported in the MTL region. Because MTL perfusion estimates derived from ASL have a low signal-to-noise ratio, our measurements cannot exclude minor perfusion changes in MTL. Further research into age-related perfusion changes in the MTL region and methods for optimizing CBF assessment in this region are needed.

### Disclosure statement

All authors disclose no conflicts of interest.

The study was approved by the local ethics committee (KF 01–131/03).

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### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2011.09.032.

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