Morphological substrate of face matching in healthy ageing and mild cognitive impairment: a combined MRI-fMRI study

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Functional MRI during face matching shows activation of the ventral visual stream, including the ventral temporal lobes and fusiform gyrus. In contrast, a location-matching task activates the dorsal visual stream, compromising parietal lobe areas. The morphological basis of the functional coupling between brain regions may be related to the distribution of neuron numbers and neuropil density, but has not yet been demonstrated in the living human brain. Regional neuron density can indirectly be assessed in vivo using structural MRI. The progression of Alzheimer's disease pathology along specific functional systems provides an in vivo lesion model to determine the interaction between reduced neuron numbers and reduced neuronal activation. In this study, we determined correlations between activation of the fusiform gyrus in fMRI during face matching and cortical grey matter density derived from structural MRI in 17 healthy elderly subjects (mean age = 67.5 years, SD = 4.5 years, 10 women) and 16 patients with amnestic mild cognitive impairment (MCI) (mean age = 69.9 years, SD = 8.0 years, 8 women), a predementia stage of Alzheimer's disease. Independently of diagnosis, stronger activation of the fusiform gyrus was correlated with larger grey matter density in the fusiform gyrus, inferior and middle temporal gyri, parahippocampal gyrus and dorsolateral prefrontal cortex. In contrast, smaller activation of the fusiform gyrus was associated with larger grey matter density in the inferior parietal lobule, post-central gyrus and dorsolateral prefrontal cortex. Compared to controls, MCI patients had more pronounced positive correlations in the ventral temporal lobes and more pronounced negative correlations in the parietal lobes. Our data suggest that fusiform activation is positively correlated with cortical grey matter density of brain areas belonging to the ventral visual stream and negatively correlated with grey matter density of brain areas belonging to the dorsal visual stream and that, these effects are more pronounced in MCI patients than in controls. These findings support the notion that the functional segregation within the visual system is based on the distribution of cortical grey matter volumes, possibly reflecting the spatial distribution of neuron density.

Keywords: Alzheimer’s disease; ageing; visual system; brain organization; MRI

Abbreviations: AD = Alzheimer’s disease; MCI = mild cognitive impairment


Introduction

Functional MRI experiments during performance of a face-matching task show activation of the primary and association visual cortex and areas within the ventral temporal lobe, including the fusiform gyrus (Clark et al., 1996). This regional activation pattern is termed the ventral visual stream and is elicited by a wide variety of object recognition tasks (Corbetta et al., 1991; Haxby et al., 1991). In contrast, during a location-matching task, healthy subjects activate areas in the parietal lobes, the so-called dorsal visual stream (Corbetta et al., 1993; Haxby et al., 1994; Ungerleider and Haxby, 1994). The functional
segregation within the visual system reflects underlying morphological features, such as synaptic density, neuron numbers and neuropil density. These features cannot directly be observed in vivo. However, structural MRI provides an in vivo surrogate measure of neuron density. Regional measures of grey matter volume account for 40–80% of variability of regional neuron density in clinical–pathological comparison studies (Nagy et al., 1996; Bobinski et al., 2000). The association between functional connectivity of neuronal systems and underlying morphological features is of particular interest in neurodegenerative disorders that progress along functional systems, such as Alzheimer’s disease (AD) (Van Hoesen and SoloDkin, 1993; Kuljis and Tikoo, 1997). Analogous to the study of experimentally induced brain lesions in animals, the system-specific neuropathology of AD can be used to determine the morphological substrate of functional connectivity within neuronal networks (Brodal, 1981). Neurofibrillary tangles and amyloid plaques, the neuropathological hallmarks of AD, occur along the ventral visual stream including the fusiform gyrus (Lewis et al., 1987; Giannakopoulos et al., 1999; Ikonomovic et al., 2005).

Additionally, primary and secondary visual areas show selective loss of pyramidal neurons maintaining long-reaching intracortical projections (Hof and Morrison, 1990). In agreement with these findings, imaging studies (Grossman et al., 2004; van Rhijn et al., 2004) suggest that the visual system is affected in AD with an involvement of the dorsal and the ventral pathway (Mendez et al., 1990; Mentis et al., 1996; Rizzo et al., 2000; Stehli Nguyen et al., 2003; Grossman et al., 2004; Done and Hajilou, 2005). Very early changes of AD which may be particularly relevant to detect the morphological substrate of functional connectivity can be observed in patients with amnestic mild cognitive impairment (MCI) representing an at risk group for AD (Wolf et al., 1998; Collie and Maruff, 2000; Larrieu et al., 2002). During face matching, patients with MCI or AD activated not only areas along the ventral, but also the dorsal visual stream (Grady et al., 1993; Horwitz et al., 1995; Bokde et al., 2006). Neuropathological changes, such as atrophy or loss of neurons, along one component of the visual system may require that these patients have to rely on additional cortical networks to maintain task performance. In agreement with this assumption, the differences in activation between AD patients and healthy controls during a task recruiting the dorsal pathway were partially explained by the degree of atrophy of the superior parietal lobule as surrogate measure of regional neuronal loss (Prvulovic et al., 2002).

In the present study, we used fMRI and structural MRI to investigate in vivo structural features that underlie the functional segregation within the visual system. We selected the visual system, because of its well-described functional organization. We determined the correlation of the BOLD response in the fusiform gyrus during face matching with cortical grey matter density in MCI patients and healthy elderly subjects using voxel-based morphometry. Resting state fMRI and PET studies suggest that neuronal activity is positively correlated within neuronal systems (Fukuda et al., 2001; Fox et al., 2005). Therefore, we hypothesized that the extent of fusiform activation would be positively correlated with grey matter density not only within the fusiform gyrus, but also along the entire ventral pathway. This hypothesis implies a higher positive covariance of regional volumes (as surrogate measure of neuron and neuropil density) between regions belonging to the same functional system than between regions belonging to different functional systems. We expected that these effects would be more pronounced in the MCI patients than in the controls if AD-pathology was present in the visual system. AD pathology stronger affecting the ventral visual stream would lead to lower activation of the fusiform gyrus. Correlations between the degree of functional integrity (measured through fusiform activation) and neuronal density (measured through volume of cortical grey matter) would be stronger if functional integrity and neuronal density would be influenced in the same direction through the effect of AD pathology.

**Material and Methods**

**Subjects**

Sixteen subjects with amnestic MCI and 17 healthy comparison subjects underwent structural and functional MRI examinations. The mean ages of the MCI and comparison groups were similar: 69.9 years (SD = 8.0) and 67.5 years (SD = 4.5) (two-tailed t-test: t_{13} = 1.1, P = 0.28). Gender distributions were similar: 8 women and 8 men in the MCI group and 10 women and 7 men in the control group (Pearson chi-square test: \chi^2 = 0.26, df = 1, P = 0.61).

MCI subjects fulfilled the Mayo criteria of amnestic MCI (i.e. subjective memory complaints, delayed verbal recall at least 1.5 SD below the respective age norm, normal general cognitive function and normal activities of daily living) (Petersen et al., 1999, 2001). Severity of cognitive impairment was assessed with the ‘Mini Mental State Examination’ (MMSE) (Folstein et al., 1975). The MMSE scores of the MCI and comparison groups were significantly different: 27.9 (SD = 1.6, ranging between 25 and 30) and 29.1 (SD = 1.1, ranging between 26 and 30) (two-tailed t-test: t_{32} = -2.6, P = 0.014).

Controls did not have cognitive complaints and scored within 1 SD from the age-adjusted mean in all subtests of the CERAD cognitive battery (Morris et al., 1989). There were statistically significant differences between both groups in the mean scores of the word list memory, word list recall, word list recognition and verbal fluency subtests (P < 0.05, uncorrected for multiple comparisons), but not of the naming and constructional praxis subtests of the CERAD battery (Table 1). The performance of the MCI group in the verbal fluency subtest was lower than the performance in the control group, but within the normal range. There was no statistically significant difference in the level of education between the HC and MCI groups: 12.8 (2.0) and 12.5 (2.8) years (unpaired t-test, P = 0.2).
Morphological basis of visual processing

Brain (2007), 130, 1745–1758 1747

Table I  Demographic and neuropsychological characteristics of the HC and MCI groups

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>7M/10F</td>
<td>8M/8F</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>67.5 (4.5)</td>
<td>69.9 (8.0)</td>
</tr>
<tr>
<td>Age (median, min–max)</td>
<td>68 (62–75)</td>
<td>73 (56–80)</td>
</tr>
<tr>
<td>Education</td>
<td>12.5 (2.9)</td>
<td>12.5 (2.8)</td>
</tr>
<tr>
<td>MMSE [30]</td>
<td>291 (1.1)</td>
<td>279 (1.6)**</td>
</tr>
<tr>
<td>Word list memory [30]</td>
<td>23.6 (3.0)</td>
<td>15.9 (3.5)**</td>
</tr>
<tr>
<td>Word list recall [10]</td>
<td>8.1 (1.8)</td>
<td>3.8 (2.0)**</td>
</tr>
<tr>
<td>Word list recognition [10]</td>
<td>9.9 (0.2)</td>
<td>8.4 (1.6)**</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>22.9 (6.3)</td>
<td>16.8 (4.2)**</td>
</tr>
<tr>
<td>Modified Boston Naming Test [15]</td>
<td>14.5 (0.7)</td>
<td>14.1 (1.7)</td>
</tr>
<tr>
<td>Constructional Praxis [11]</td>
<td>10.4 (0.9)</td>
<td>10.5 (0.8)</td>
</tr>
</tbody>
</table>

Note: Values in square brackets [ ] indicate maximum possible score for each specified test except verbal fluency for which a maximum score does not exist. Values are mean (standard deviation).

*Statistically significant difference at the $P<0.05$ level.

Statistically significant difference at the $P<0.001$ level.

Statistically significant difference at the $P<0.0001$ level.

Medical comorbidity in the patients and controls was excluded on the basis of medical history, physical and neurological examination, psychiatric evaluation, chest X-ray, ECG, EEG, brain MRI and laboratory tests (complete blood count, sedimentation rate, electrolytes, glucose, blood urea nitrogen, creatinine, liver-associated enzymes, cholesterol, HDL, triglycerides, antinuclear antibodies, rheumatoid factor, VDRL, HIV, vitamin B12, folate, thyroid function tests and urine analysis). MCI and control subjects were excluded also on factors based on MRI criteria such as pacemaker or recent metallic implants. A single control subject and two MCI patients were excluded because of metallic implants. All subjects had normal vision or corrected by use of MR-compatible eyeglasses to normal vision. All subjects gave written informed consent to participate in the study after the study was explained to them. The study was performed in accordance with the Declaration of Helsinki and the Ethics Committee of the Medical Faculty of Ludwig-Maximilian University approved the study.

Stimulus and task

The object-matching task consisted of two black and white images of faces presented simultaneously and participants were asked to decide on each trial if a pair of faces were identical or not. If they were, the subject would respond by pressing a button in the right hand. No response was required if the faces were dissimilar. If the subject could not decide, he or she would not respond. Each trial in the task had two squares in which two identical or dissimilar faces were located. The faces were grey scale stimuli where only the face was visible. Each trial was 2.8 s long with an interval of 0.318 s between pairs of faces. There were eight trials per block and three blocks of the task in each scan. At the beginning of each block, there was a 7.2 s task instruction. The frequent instructions were to minimize the risk of confusion on part of the participants as to which task was to be performed. The subjects viewed a paper version of the tasks before entering the scanner room. The different conditions were counter-balanced across subjects. The faces were from the Max Planck Institute for Biological Cybernetics database (Blanz et al., 2000).

In the control task, the subject had to press the button every time an abstract image appeared. There were four blocks of the control task with the same length as the face-matching task. The parameters for the presentation of the images were identical to the face-matching task.

During the task, performance was monitored and the percentage correct and reaction times were measured. The correct response rate was 87.8% (11.3) for the MCI and 91.4% (7.6) for control group. The average response time was 1.5 (0.3) s in the MCI group and 1.6 (0.4) s in the control group. There was no statistically significant difference between groups in either the correct response rate or response time (unpaired t-test, $P=0.2$ level).

Scanning

MRI examinations were performed on a 1.5 T Siemens Magnetom Vision MRI scanner (Siemens, Erlangen, Germany). The fMRI sequence was an interleaved T2* weighted echoplanar sequence with 28 axial slices (4 mm slice thickness and slice gap = 1 mm, repetition time (TR) = 3.6 s, echo time (TE) = 60 ms, flip angle = 90°, field of view = 240 mm, matrix = 64 × 64) and 69 frames acquired per scan. For anatomical reference in each subject, a T1 weighted sequence with 28 slices was acquired in the same orientation as the EPI sequence (TR = 620 ms, TE = 12 ms, flip angle = 90°, FOV = 240 mm, matrix = 224 × 256, Rect. FOV = 7/8, effective thickness = 1.25 mm). For morphometric analysis, a high resolution T1-weighted 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) structural image was performed (TR = 11.4 ms, TE = 4.4 ms, flip angle = 8°, FOV = 270 mm, matrix = 224 × 256, Rect. FOV = 7/8, effective thickness = 1.25 mm), subsequently named 3D sequence. For the visual presentation of the stimuli during the fMRI experiment a commercial available video beamer was used. Stimuli were projected on a translucent screen at the subject’s feet. Lying in the scanner, subjects viewed the screen with a head coil compatible mirror system (eye-to-mirror distance 15 cm, mirror-to-screen distance 3.0 m, screen-to-beamer distance 1.6 m). The imaging session lasted about 30 min with the fMRI run 248 s long.

Data analysis

FMRI

The data were analysed off line on a computer with an Intel Pentium III CPU (San Jose, California, USA) running Linux (Red Hat version 7.0, Red Hat Inc, Rayleigh, North Carolina, USA) using AFNI (Cox, 1996) (available at afni.nimh.nih.gov/afni/) and FSL (FMRI Software Library—available at www.fmrib.ox.ac.uk/fsl).

Initially, the first four volumes of each scan were deleted to remove the initial T1 magnetic transients in the data. The remaining data were corrected for the timing differences between each slice using Fourier interpolation. Then the data were corrected for motion effects (6-parameter rigid body) with the reference volume in the centre of the run.

Each run for each subject was analysed using a fixed effects general linear model as implemented in FSL. Each model comprised regressors for the task of interest and the instructions together with their respective time derivatives, as well as motion during the run. The task and instruction models were square...
wave-forms (on-off). The regressors for the task of interest and instructions were convolved with a standard double gamma hemodynamic response function. The data were smoothed (Gaussian filter at full width at half maximum = 8 × 8 × 8 mm³) and high pass filtered with a cutoff at (1/100) Hz. The statistical results were normalized to the Montreal Neurological Institute/International Consortium for Brain Mapping 152 standard (MNI/ICBM), as contained within the FSL software package. The location of the activation in the brain was done with reference to the Talairach and Tournoux template (Talairach and Tournoux, 1988). To convert the MNI/ICBM coordinates to the Talairach and Tournoux coordinates, we utilized a non-linear transformation developed by M. Brett for transforming coordinate location between both stereotaxic spaces (see online at http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

The definitions for the region of interest (ROI) of the left and right fusiform gyrus were based on the labels of the Talairach Daemon database (http://ric.uthscsa.edu/projects/talairachdaemon.html) as contained within the AFNI software package. To convert the ROIs in the Talairach and Tournoux space to the MNI/ICBM space, we utilized a transformation developed by M. Brett for transforming coordinate location between both stereotaxic spaces. The percent increase in the signal (face matching compared to control task) were derived for the object-matching task and the control task affected the activation level that the different number of scans obtained for the object each voxel in the ROI and averaged to obtain the individual (face matching compared to control task) were derived for both stereotaxic spaces. To test this hypothesis, we subsequently investigated the correlations between fusiform activation and grey matter volume between MCI patients and controls? We tested the interaction effect in both directions, i.e. effect of fusiform activation on grey matter volume greater for controls or greater for MCI. One has to note that an interaction effect favouring controls can reflect a stronger positive correlation in controls or a stronger negative correlation in MCI patients. In the same way, an interaction effect in favour of MCI patients can represent a stronger positive correlation in MCI patients or a stronger negative correlation in controls. We hypothesized that due to system-specific neurodegeneration in MCI the interaction effect would reflect stronger positive correlations along ventral and stronger negative correlations along alternative pathways in MCI patients compared to controls. In order to test this hypothesis, we subsequently investigated the correlations between fusiform activation and grey matter volume within each group.

**Statistical analysis**

For statistical analysis, we employed the general linear model on a voxel basis with activation in the fusiform gyrus as independent regressor, and diagnosis as between subjects factor and fusiform activation by diagnosis as interaction term. We assessed two separate models, one for left and one for right hemispheric fusiform activation. We determined two effects: (i) the main effect of fusiform activation controlling for diagnosis and interaction effects and (ii) the interaction effect of diagnosis by activation controlling for diagnosis and the overall effect of fusiform activation. The interaction term addresses the following question: is there a difference in the correlation between fusiform activation and grey matter volume between MCI patients and controls? We tested the interaction effect in both directions, i.e. effect of fusiform activation on grey matter volume greater for controls or greater for MCI. One has to note that an interaction effect favouring controls can reflect a stronger positive correlation in controls or a stronger negative correlation in MCI patients. In the same way, an interaction effect in favour of MCI patients can represent a stronger positive correlation in MCI patients or a stronger negative correlation in controls. We hypothesized that due to system-specific neurodegeneration in MCI the interaction effect would reflect stronger positive correlations along ventral and stronger negative correlations along alternative pathways in MCI patients compared to controls. In order to test this hypothesis, we subsequently investigated the correlations between fusiform activation and grey matter volume within each group.

Prior to regression analysis, structural scans were proportionally scaled to the global mean and thresholded at 40% of global intensity to reduce the influence of any remaining non-brain tissue. Proportional scaling to the global mean allows detection of voxels with a relatively accelerated loss or a relative preservation of grey matter (i.e. more or less than the global loss). We considered significant effects in the negative and positive direction. Results were thresholded at a P level <0.001, uncorrected for multiple comparisons, and an extent threshold of 50 contiguous voxels was applied. We derived voxel intensities at peak locations of significant main effects to determine Pearson’s product moment correlations between fusiform activation and grey matter density within each diagnostic group (MCI and controls).
Results
Correlation between activation and grey matter controlling for diagnosis
When we assessed the main effect of the 2-way ANOVA model, i.e. correlation between fusiform activation and cortical grey matter controlling for diagnosis and the interaction of diagnosis by activation, cluster of relatively larger grey matter density associated with stronger activation of the left fusiform gyrus during face recognition were located in the left hemisphere within the temporal lobe in the fusiform gyrus and the inferior and middle temporal gyrus and the limbic system in the parahippocampal gyrus and uncus. In the right hemisphere, peak correlations were located within the limbic system in the parahippocampal gyrus and the frontal lobe in the middle frontal gyrus. (Table 2, Fig. 1). The opposite contrast, i.e. larger grey matter density associated with smaller activation of the left fusiform gyrus during face recognition, showed clusters located in the right hemisphere, within the parietal lobe in the inferior parietal lobule and the post-central gyrus and the frontal lobe in the inferior frontal gyrus (Table 2, Fig. 1). There were no significant clusters in the left hemisphere. We determined correlations between fusiform activation and cortical grey matter volume at the peak coordinates separately within each diagnostic group. Within the MCI patients correlations were significant for all clusters, within the controls the positive contrast showed significant correlations for temporal and fusiform clusters, the negative contrast for parietal and frontal clusters (Table 2 and Fig. 2).

The positive contrast for larger activation of the right fusiform gyrus during face recognition showed cluster of larger grey matter density in the left hemisphere within the temporal lobe in the inferior temporal and the fusiform gyrus, and the frontal lobe in the middle frontal gyrus. In the right hemisphere, peak correlations were located within the temporal lobe in the inferior temporal gyrus (Table 3, Fig. 3). The opposite contrast, i.e. larger grey matter density associated with smaller activation of the right fusiform gyrus during face recognition, showed clusters located in left hemisphere within the cerebellum and the parietal lobe in the inferior parietal lobule. In the right hemisphere, peak correlations were located within the cerebellum (Table 3, Fig. 3). When we determined correlations between fusiform activation and cortical grey matter volume within each diagnostic group, MCI patients showed significant correlations for all clusters, the controls showed significant positive correlations for temporal and fusiform clusters and significant negative correlations for parietal and cerebellar clusters (Table 3 and Fig. 4).

When the correlations in the MCI and control groups were controlled for age, the results remained essentially unchanged (data not shown).

Table 2 Voxelwise correlations with left fusiform activation controlling for diagnosis and interaction effects

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>BA</th>
<th>Coordinates (mm)</th>
<th>$T_{29}$</th>
<th>$r_{MCI}$</th>
<th>$r_{Con}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$x$</td>
<td>$y$</td>
<td>$z$</td>
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<td>Positive correlations</td>
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<td></td>
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<tr>
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<td>20</td>
<td>-43</td>
<td>0</td>
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<td>Uncus</td>
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<tr>
<td>Middle temporal gyrus</td>
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<td>4.14</td>
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<tr>
<td>Middle frontal gyrus</td>
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<td>28</td>
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</tr>
</tbody>
</table>

Note: The height threshold was set at $P < 0.001$, uncorrected for multiple comparisons. The cluster extension, representing the number of contiguous voxels passing the height threshold was set at >50. Coordinates in bold delineate a cluster and the peak T-value (29 degrees of freedom) within the cluster. Subsequent non-bold coordinates identify further peaks within the same cluster that meet the significance level. Brain regions are indicated by Talairach and Tournoux coordinates, $x$, $y$ and $z$ (Talairach and Tournoux, 1988): $x =$ the medial to lateral distance relative to midline (positive = right hemisphere); $y =$ the anterior to posterior distance relative to the anterior commissure (positive = anterior); $z =$ superior to inferior distance relative to the anterior commissure—inferior commissure line (positive = superior). $r_{MCI}/r_{Con} =$ Pearson’s product moment correlation between fusiform activation and grey matter density at the peak coordinate within the MCI and the control groups, respectively. The level of significance for two-sided testing with 16 (MCI) or 17 (controls) degrees of freedom is indicated with *($P < 0.05$) and **($P < 0.01$). n.s.: not significant; R/L = right/left; BA = Brodmann area.
Interaction effect of diagnosis by fusiform activation on grey matter volume

When we assessed the interaction effect of diagnosis by left fusiform activation [i.e. between groups (MCI versus controls) differences in the correlations of fusiform activation with grey matter volume], patients with MCI had stronger positive correlations between left fusiform gyrus activation and grey matter density within the left temporal lobe in the inferior and middle temporal gyrus and the right frontal lobe in the middle frontal gyrus.

Fig. 1 Correlations with left fusiform activation during face recognition controlling for diagnosis and interaction effects. Positive (red) and negative (green) correlations between left fusiform activation and grey matter in MCI patients and controls, cluster extension set at >50 contiguous voxels passing the significance threshold of $P < 0.001$. Colour coded SPM(T) map projected on the normalized rendered brain surface from the MRI scan of a normal subject.
An additional peak was found in the right cerebellum (Table 4 and Fig. 5). MCI patients had stronger negative correlations between left fusiform activation and grey matter density within the right parietal lobe and the left frontal lobe in the middle frontal gyrus (Table 4 and Fig. 5).

The interaction effect of diagnosis by right fusiform activation revealed stronger positive correlations in MCI between right fusiform activation and grey matter density in the right superior temporal gyrus (Table 5). There were no stronger negative correlations in MCI patients compared to controls with right fusiform activation.

Figures 6 and 7 illustrate that the interaction effects indeed reflect stronger positive and negative correlations in MCI patients compared to controls. There were no stronger negative or positive correlations in controls.

**Discussion**

We investigated correlations between activation in the fusiform gyrus during face matching in fMRI and cortical grey matter density both in MCI and healthy elderly subjects. A previous study had investigated to what extent the degree of regional atrophy accounts for differences in activation between AD patients and controls (Prvulovic et al., 2002). In the present study, we chose the opposite approach: we determined to what extent activation in the fusiform gyrus, a key area of face matching, correlates with regional cortical grey matter. This approach was based on the assumption that the segregation between functional systems in the brain is based on the regional distribution of some morphological feature, such as neuronal density, that can be assessed *in vivo* using structural MRI (Nagy et al., 1996; Bobinski et al., 2000). This implies that correlations between volumes of different cortical areas are higher if they belong to the same than if they belong to different regions.

**Table 3** Voxelwise correlations with right fusiform activation controlling for diagnosis and interaction effects

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>BA</th>
<th>Coordinates (mm)</th>
<th>$T_{29}$</th>
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<th>$r_{Con}$</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td>$x$</td>
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<td>−42</td>
<td>−40</td>
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Note: The height threshold was set at $P<0.001$, uncorrected for multiple comparisons. The cluster extension, representing the number of contiguous voxels passing the height threshold was set at $>50$. Coordinates in bold delineate a cluster and the peak $T$-value (14 degrees of freedom) within the cluster. Subsequent non-bold coordinates identify further peaks within the same cluster that meet the significance level. Brain regions are indicated by Talairach and Tournoux coordinates, $x$, $y$ and $z$ (Talairach and Tournoux, 1988): $x =$ the medial to lateral distance relative to midline (positive = right hemisphere); $y =$ the anterior to posterior distance relative to the anterior commissure (positive = anterior); $z =$ superior to inferior distance relative to the anterior commissure − posterior commissure line (positive = superior). $r_{MCI}/r_{Con} =$ Pearson’s product moment correlation between fusiform activation and grey matter density at the peak coordinate within the MCI and the control groups, respectively. The level of significance for two-sided testing with 16 (MCI) or 17 (controls) degrees of freedom is indicated with *($P<0.05$) and **($P<0.01$). n.s.: not significant; R/L = right/left; BA = Brodmann area.
neuroanatomical systems. AD-type pathology within the cerebral neocortex has primarily been found in a regularly clustered organization affecting neuronal populations that maintain long-reaching cortico-cortical projections, suggesting that AD lesions develop along specific neuron-anatomical pathways (Armstrong et al., 2001). We expected that the spread of AD-type pathology along specific neuroanatomical systems in MCI patients

Fig. 3 Correlations with right fusiform activation during face recognition controlling for diagnosis and interaction effects. Positive (red) and negative (green) correlations between left fusiform activation and grey matter in MCI patients and controls, cluster extension set at >50 contiguous voxels passing the significance threshold of $P < 0.001$. Colour-coded SPM(T) map projected on the normalized rendered brain surface from the MRI scan of a normal subject.
would help to reveal the structural segregation of neuronal networks.

Those temporal lobe areas that were positively correlated with activation of fusiform gyrus in MCI and controls were located along the ventral visual stream, implicated in object recognition (Corbetta et al., 1991; Haxby et al., 1991). Within the temporal lobe, we found correlations mainly between fusiform activation and inferior temporal gyrus, much less with superior temporal sulcus areas. In monkeys, neurons responding to faces have been found both in dorsal superior temporal sulcus (TPO) and in anterior and medial inferior temporal gyrus (TEa and TEM) (Baylis et al., 1987). It has been suggested that TPO areas are more responsive to facial expression, whereas TE areas are more responsive to facial identity (Hasselmo et al., 1989). This division is supported by fMRI data in monkeys and humans (Tsao et al., 2003). The inferior temporal visual area (TE) is considered to be the final stage of the ventral visual processing pathway and to be critical for short-term retention of visual object features. The stimulus in our experiment were black and white images of faces without emotional expression demanding working memory for discrimination without carrying much emotional valence. Consistently, fusiform activation was mainly correlated with inferior and middle temporal gyrus activation within the temporal lobe in an fMRI experiment using this paradigm (Bokde et al., 2006). Additionally, a PET study found primary activation of inferior temporal lobe with a visual discrimination task (Nakamura et al., 2000). In contrast, emotional faces have been shown to elicit activation within the superior temporal sulcus (Kawashima et al., 1998). The predominant involvement of the inferior temporal gyrus in our study underscores the specificity of the findings for the visual subsystem involved.

Additionally, positive correlations were found in the parahippocampal gyrus, implicated in object recognition (Murray et al., 2000), identification of houses (Reinholz and Pollmann, in press) and scene processing (Epstein et al., 2005), and in the dorsolateral prefrontal cortex, implicated in executive function and working memory (Petrides, 2005).

**Figure 4** Correlation between right fusiform activation and fusiform grey matter volume. Scatter plot of left fusiform activation versus grey matter density in the left fusiform gyrus (x/y/z coordinates = −56/−10/−25) for MCI patients (blue circles) and controls (green circles).

**Table 4** Voxelwise interaction effect of diagnosis by left fusiform activation

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>BA</th>
<th>Coordinates (mm)</th>
<th>$T_{29}$</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>$x$</td>
<td>$y$</td>
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<tr>
<td><strong>Positive effects</strong></td>
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<tr>
<td>Inferior temporal gyrus</td>
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<td>Middle temporal gyrus</td>
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<td>−75</td>
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<td>−61</td>
<td>−26</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
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<td>−32</td>
</tr>
<tr>
<td>Medial frontal gyrus</td>
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<td>50</td>
</tr>
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<td>Cerebellum</td>
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<td>29</td>
<td>−42</td>
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**Note:** The height threshold was set at $P < 0.001$, uncorrected for multiple comparisons. The cluster extension, representing the number of contiguous voxels passing the height threshold was set at $> 50$. Coordinates in bold delineate a cluster and the peak $T$-value (29 degrees of freedom) within the cluster. Subsequent non-bold coordinates identify further peaks within the same cluster that meet the significance level. Brain regions are indicated by Talairach and Tournoux coordinates, x, y and z (Talairach and Tournoux, 1988): x = the medio-lateral distance relative to midline (positive = right hemisphere); y = the anterior to posterior distance relative to the anterior commissure (positive = anterior); z = superior to inferior distance relative to the anterior commissure–posterior commissure line (positive = superior). R/L = right/left; BA = Brodmann area.
Those parietal lobe areas that were negatively correlated with fusiform activation in MCI patients and controls were distributed within the dorsal visual pathway (Corbetta et al., 1993; Haxby et al., 1994; Ungerleider and Haxby, 1994). Additionally, areas in the dorsolateral prefrontal cortex were negatively correlated with fusiform activation. The dorsolateral prefrontal cortex is the main area of integration of visual information between the
ventral and the dorsal visual pathways (Ungerleider et al., 1998). The distribution of positive and negative correlations within the prefrontal cortex agrees with the observation that prefrontal cortex is divided into ventrally located object and dorsally located spatial domains (Wilson et al., 1993; Ungerleider et al., 1998). Negative correlations were found within cerebellar grey matter. The cerebellum plays an important role in controlling of motor function and eye movements, but functional imaging studies suggest that the cerebellum is also involved in a range of cognitive functions, including object recognition (Ioannides and Fenwick, 2005) and visual attention (Barrett et al., 2003).

The question remains on the substrate of the dissociation of grey matter volumes between the ventral and dorsal visual pathways. The extent of fusiform activation was positively correlated with grey matter density along the ventral visual stream. This correlation may represent an underlying morphological feature, such as neuronal density, for functional connectivity within the ventral visual stream. This interpretation agrees with findings from resting state fMRI examining the correlation matrix of low frequency fluctuations, where highly correlated fluctuations were found within specific neuroanatomical systems such as the somatomotor, visual, auditory and language-related systems.

### Table 5 Voxelwise interaction effect of diagnosis by right fusiform activation

<table>
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<tr>
<th>Region</th>
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<th>BA</th>
<th>Coordinates (mm)</th>
<th>$T_{29}$</th>
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<td>Superior temporal gyrus</td>
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<td>29/13/−35</td>
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Note: The height threshold was set at $P < 0.001$, uncorrected for multiple comparisons. The cluster extension, representing the number of contiguous voxels passing the height threshold was set at >50. Coordinates in bold delineate a cluster and the peak $T$-value (29 degrees of freedom) within the cluster. Brain regions are indicated by Talairach and Tournoux coordinates, $x$, $y$, and $z$ (Talairach and Tournoux, 1988): $x = \text{the medial to lateral distance relative to midline (positive = right hemisphere)}$; $y = \text{the anterior to posterior distance relative to the anterior commissure (positive = anterior)}$; $z = \text{superior to inferior distance relative to the anterior commissure – posterior commissure line (positive = superior)}$. $R/L = \text{right/left}; BA = \text{Brodmann area}$.  

**Fig. 6** Interaction effect of fusiform activation by diagnosis on grey matter density (inferior temporal gyrus). Scatter plot of left fusiform activation versus grey matter density in the left inferior temporal gyrus ($x/y/z$ coordinates = $−63/−10/−16$) for MCI patients (blue circles) and controls (green circles). $R^2$ is 0.62 in the MCI and 0.06 in the control group, indicating a stronger positive correlation in MCI compared to controls (significant interaction effect of diagnosis by fusiform activation at univariate $P < 0.001$).

**Fig. 7** Interaction effect of fusiform activation by diagnosis on grey matter density (inferior parietal lobule). Scatter plot of left fusiform activation versus grey matter density in the right inferior parietal lobule ($x/y/z$ coordinates = $46/−47/42$) for MCI patients (blue circles) and controls (green circles). $R^2$ is 0.75 in the MCI and 0.02 in the control group, indicating a stronger negative correlation in MCI compared to controls (significant interaction effect of diagnosis by fusiform activation at univariate $P < 0.001$).
The significant negative correlations between fusiform activation and grey matter volume along dorsal visual areas cannot finally be resolved. One possible explanation, however, can be based on the observation that those subjects with lower fusiform activation still had preserved face-matching accuracy. Therefore, they would rely on alternative activation pathways to maintain task performance. Such an alternative recruitment has been shown associated with AD, MCI and ApoE genotype in a range of fMRI studies (Becker et al., 1996; Bookheimer et al., 2000; Prvulovic et al., 2005). Even healthy control subjects show variation in the extent of ventral and dorsal activation with face-matching with some subjects showing strictly ventral and some ventral plus some dorsal activation, probably independently of pathological factors such as neurodegeneration (Brodtmann et al., 2003). The inverse correlation between fusiform gyrus activation and cortical grey matter volume along areas belonging to the dorsal visual system may represent the morphological basis on which subjects are able to recruit alternative pathways. One can speculate that this inverse correlation represents a feature of brain organization that makes a subject more likely to recruit dorsal pathway areas with face matching, be it a habitual feature in a healthy subject (representing normal variation in brain organization) or a result of brain pathology (differentially involving ventral and dorsal visual areas). The neuronal basis of such alternative recruitments or variability in recruitment pattern (strictly ventral versus ventral plus dorsal) may be the distribution of neuronal densities across neuronal networks. This assumption would account for our observation of more ventral correlations with higher and more dorsal correlations with lower fusiform activation, but needs further testing in independent experiments.

When we assessed the effect of diagnosis by activation, we found that MCI patients had stronger positive correlations between fusiform activation and grey matter density along the ventral visual stream, including the ventral prefrontal cortex, and stronger negative correlations in parietal lobe areas belonging to the dorsal visual stream. Amnestic MCI patients are thought to represent a predementia stage of AD (Wolf et al., 1998; Collie and Maruff, 2000; Larrieu et al., 2002) and have been shown to exhibit neuropathological changes of the AD-type (Troncoso et al., 1996; Price and Morris, 1999). Based on the notion that AD-type pathology progresses within functional systems (Buckner, 2004), we expected that neuronal density would be reduced along the entire ventral visual stream in those MCI patients that showed less activation in the fusiform gyrus during face matching. As expected, the correlation between fusiform gyrus activation and regional grey matter density was not restricted to the fusiform gyrus, but involved the entire ventral stream, and was more pronounced in the MCI patients than in the controls. However, not only the positive but also the negative correlations between fusiform activation and cortical grey matter along the dorsal visual stream were more pronounced in MCI patients than in controls. Since accuracy of face matching was preserved in the MCI patients one has to assume some compensatory mechanism of brain activation. Indeed, whereas healthy controls showed predominant ventral activation during face matching, MCI patients showed additional activation in dorsal visual areas (Bokde et al., 2006). The stronger negative correlations in MCI relative to controls suggest that those MCI patients that showed less fusiform activation had better preserved grey matter along the dorsal visual stream. The relative involvement or preservation of grey matter density within the visual pathways would determine to which extent the dorsal stream can be employed to maintain task performance. It has to be considered, however, to what extent MCI can serve as a model of predementia AD pathology. After more than 4 years about 80% of amnestic MCI patients converted to AD, 20% converted to normal in the Cardiovascular Health Study Cognition Study (Lopez et al., 2007). In the Vienna Trans-Danube Aging Study, a community-based study, about 50% of subjects with amnestic MCI converted to AD after 2.5 years of follow-up (Fischer et al., 2007). Thus, amnestic MCI clearly is a risk stage of AD, but there will always remain a subgroup of subjects that will convert to some other form of dementia or even to normal. Therefore, we will have to follow our MCI patients for several years to determine whether all subjects were in predementia stages of AD. Alternatively, one would have to study patients with manifest dementia. When studying AD patients, however, fMRI data become affected by movement artefacts and systematic decline in task performance with increasing dementia severity.

One might argue that part of the correlations in the healthy controls and the MCI subjects is accounted for by an age effect if age-related changes in brain structure progress along functional systems (Esposito et al., 1999). However, the dissociation between ventral and dorsal visual areas remained unchanged when the correlations were controlled for age. There is one methodological source of false positive findings when using voxel-based morphometry. This technique is based on the analysis of local variations in grey matter concentration after global shape differences between individual scans have been removed (Ashburner and Friston, 2000). Therefore, the analysis is sensitive to local misregistrations independently of differences in local grey matter concentration (Bookstein, 2001). We tried to minimize the potential influence of local misregistrations by using a group-specific template for normalization. We also applied a modified voxel-based morphomety technique that has recently been proposed to attenuate some of these effects (Ashburner and Friston, 2001; Good et al., 2001). Following this protocol, the normalization to standard stereotactic space was driven by grey matter only, thereby reducing the influence...
of non-grey matter tissue on the registration (Ashburner and Friston, 2001; Good et al., 2001).

In summary, analysis of the correlation between fusiform activation and cortical grey matter density identified two distinct sets of brain regions in MCI patients and healthy elderly subjects corresponding to the location of the ventral and the dorsal visual stream and including the prefrontal cortex. This correlation may represent the effect of systemspecific AD type pathology in MCI or even a primary morphological feature underlying the functional differentiation within the visual system, possibly linked to the distribution profile of neuronal density. Our data further suggest that the interpretation of activation pattern in fMRI should take into account the degree of cortical atrophy not only at the peak of activation but along the entire functional system underlying the task under study.

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