Impaired Processing of 3D Motion-Defined Faces in Mild Cognitive Impairment and Healthy Aging: An fMRI Study

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Mild cognitive impairment (MCI), which shows high risk for conversion to Alzheimer’s disease (AD), is accompanied by progressive visual deteriorations that so far are poorly understood. Here, we compared dorsal and ventral visual stream functional magnetic resonance imaging (fMRI) activity among amnestic MCI, healthy elderly, and young participants during structure-from-motion (SFM) face categorization performance. Task performance varied with stimulus depth and duration levels and differences among groups were highly correlated with face-related fMRI activation patterns. Young participants showed larger activation to faces than scrambled faces (face sensitivity) in the right fusiform face area (FFA) and right occipital face area (OFA) whereas in elderly, this difference was reduced. Surprisingly, in MCI, scrambled faces elicited larger activation in right FFA/OFA than faces. The latter observation may be related to the additional finding of elevated depth sensitivity in left FFA/OFA of MCI, suggesting that an increased representation of low-level stimulus aspects may impair face perception in MCI. Discriminant function analysis using face and depth sensitivity indices in FFA/OFA classified MCI and healthy elderly with 88.2% accuracy, marking a fundamental distinction between groups. Potentially related findings include altered activation patterns in dorsal–ventral stream integration regions and attention-related networks of MCI patients. Our results highlight aberrant visual and additional potentially compensatory processes that identify dispositions of (preclinical) AD.

Keywords: face perception, functional neuroimaging, mild cognitive impairment, structure-from-motion, vision

Introduction

Mild cognitive impairment (MCI) represents a boundary cognitive stage between normal aging and dementia (Petersen et al. 1999). Among the several subtypes that have been identified, in particular amnestic MCI patients show an accelerated conversion to AD (Alzheimer’s disease) with a yearly transition rate of 10–15% (Petersen et al. 2001). Despite there being no cure or prevention for AD at present, medication for modifying or slowing down the progression of the disease is currently being developed, making biomarkers for early detection of true preclinical AD a major concern.

Apart from memory complaints, AD symptoms also include higher visual dysfunctions. Behavioral studies indicate that the most prominent visual impairments are in the domain of visuospatial function such as stereopsis (Mendez et al. 1996) and (self-) motion perception (Mapstone et al. 2003, 2006; Kavicic et al. 2011) with the latter already being present at the MCI stage. However, in AD, face- (Sauer et al. 2006) and object-recognition impairments (Cronin-Golomb et al. 1995; Mosimann et al. 2004) have also been reported. In the framework of a ventral–dorsal pathway dichotomy (Ungerleider and Mishkin 1982), these findings suggest the dorsal stream as an early and major target of neuropathological changes in the course of the disease, but also potential deficits in ventral stream processing.

These insights have been corroborated by structural neuroimaging studies, which have mainly focused on methods such as voxel-based morphometry (Pennanen et al. 2005; Bozalli et al. 2006), diffusion tensor imaging (Cherubini et al. 2010; Gold et al. 2011), and more recently also on cortical thickness measurements (Hampel et al. 2008; Li et al. 2012). Reductions in the cortical grey matter in the mediotemporal and parietal lobe (Baron et al. 2001; Pennanen et al. 2005; Singh et al. 2006) as well as in frontal regions (Baron et al. 2001; Singh et al. 2006) may all contribute to the observed visual deficits in MCI and AD. Apart from deviations in brain “structure”, alterations in brain “function” of MCI have also been addressed by numerous resting state studies (e.g. Fleisher et al. 2009). However, to our knowledge there are very few task-related functional neuroimaging studies. A notable exception are the preliminary data shown in a review article by Yamasaki et al. (2012) suggesting decreased activation in the inferior parietal lobe in response to optic flow in MCI in comparison with controls. Furthermore, Bokde et al. (2008) found that MCI patients activated both visual pathways during a location matching task while healthy controls showed selective activation of the dorsal stream. This, along with a study by Bokde et al. (2006) using functional connectivity, confirms the presence of not only dorsal but also ventral visual stream alterations in MCI brain function.

Here, we used concurrent psychophysics and functional magnetic resonance imaging (fMRI) to characterize functional alterations in both dorsal and ventral visual pathways in the normal aging and MCI brain. To that goal, we used structure-from-motion (SFM) face stimuli in which motion integration mechanisms in the dorsal stream (Andersen and Bradley 1998) form the basis for object recognition in the ventral stream. These stimuli, apart from probing dorsal–ventral cross-talk provide an additional window on temporal lobe processes related to face perception in the healthy aging and MCI. While prior psychophysical studies have shown SFM deficits to be highly correlated with MCI (Lemos et al. 2012) and AD.
Methods

Participants
Forty-five right-handed participants (15 young, 17 elderly, and 13 MCI) took part in the study. After applying experimental exclusion criteria, that is, poor or no task performance due to a lack of understanding and excessive movement during the fMRI acquisition (see details below), 12 young participants, 13 elderly participants, and 13 amnestic MCI patients were included in the analysis. Young participants were healthy graduate students from the University of Coimbra who volunteered to participate in the experiment. The elderly control group was recruited from our database of volunteers or consisted of university or hospital staff as well as their relatives with normal ophthalmological and neurological examination. To exclude cognitive impairment, healthy elderly participants underwent neuropsychological screening (Mini-Mental Status Examination [MMSE]) (Folstein et al. 1975). In the MCI patients the diagnostic investigation additionally included a standard clinical evaluation, a staging assessment, laboratory tests including Apolipoprotein E allele genotyping as well as imaging studies (computed tomography or MRI and single photon emission computed tomography) to exclude comorbidities. MCI patients were recruited from the Neurology Department of the Coimbra University Hospital where diagnosis was achieved through gold standard neurological and neuropsychological assessment following classification criteria for MCI (Petersen 2004, Albert et al. 2011). Only amnestic “single domain” MCI patients were included in this study. MCI patients were identified as follows: (1) a subjective complaint of memory decline (reported by the participant or an informant); (2) an objective memory impairment (considered when scores on a standard revised Wechsler Memory Scale (Wechsler 1987) [immediate and delayed logical memory] were >1.5 SDs below age/education adjusted norms); (3) normal general cognition suggested by normal scores in the cut-off scores (Guerreiro, Fonseca et al. 2008; Guerreiro, Silva et al. 2008); (4) Largely normal daily life activities; (5) Absence of dementia, and 6) Exclusion of comorbidities using imaging methods. Exclusion criteria were neurological/psychiatric conditions other than MCI and abnormal ophthalmological conditions. MCI and elderly control participants were matched for chronological age and education level ($P > 0.05$). Table 1 summarizes the participant demographic data.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Young participants (N = 12)</th>
<th>Elderly participants (N = 13)</th>
<th>MCI patients (N = 13)</th>
</tr>
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<tbody>
<tr>
<td><strong>Chronological age (years)</strong></td>
<td>26.1 (3.9)</td>
<td>63.6 (6.6)</td>
<td>66.5 (5.8)</td>
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<td><strong>Education level (years)</strong></td>
<td>—</td>
<td>11.2 (4.9)</td>
<td>8.0 (4.6)</td>
</tr>
<tr>
<td><strong>MMSE score</strong></td>
<td>—</td>
<td>29.5 (0.9)</td>
<td>28.9 (1.4)</td>
</tr>
<tr>
<td><strong>Gender (M:F)</strong></td>
<td>4:8</td>
<td>7:6</td>
<td>6:7</td>
</tr>
<tr>
<td><strong>APOE E4 allele carriers</strong></td>
<td>—</td>
<td>—</td>
<td>7</td>
</tr>
</tbody>
</table>

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Coimbra. All participants provided verbal and written informed consent before participating in the study. To ensure that participants had understood the task, the fMRI session was preceded by a brief training session outside the scanner. Participants lay supine in the scanner and were given earplugs and padding to maximize comfort and minimize involuntary head movements. A video recording system (RealEye 5721, Avotec Inc.) inside the scanner was used to monitor the elderly and MCI participants ensuring safety and wakefulness. At any time participants had access to a button signaling that they wished to interrupt the session.

Experimental Stimuli

The fMRI session consisted of the SFM task and subsequent localizer scans to define regions-of-interest (ROIs). The SFM stimuli and the face localizer stimuli were presented using Presentation 12.1 software (neurobehavioral systems) and the motion localizer stimuli were rendered with VR-Oculus rift sensor.
presented using MATLAB (R2009b). Stimuli were presented using an INM PC and were projected with an LCD projector (SilentVision 6011, Avotec Inc.) onto a rear-projection Fujitsu Siemens type screen (1024 x 768, refresh rate 60 Hz) located at the head of the participants. The screen was viewed at a distance of 45.5 cm with an angled mirror positioned on the head-coil and subtended 30.3° width and 23.1° height of visual angle.

**SFM Stimuli**

SFM stimuli were videos of motion-defined male faces and scrambled control faces (for details see Farivar et al. 2009; Fig. 1). Face stimuli were constructed from a laser-scanned facial surface taken from the Max-Planck Face Database. The surface was rendered with a volumetric texture map that ensures uniform texture density (as described in detail in Liu et al. 2005). Shadows and shading were removed and the face was rendered against a similarly textured random-dot background. Control versions of the face stimuli were constructed by cutting the rendered whole object videos in the horizontal plane into 10 blocks and scrambling their positions. This scrambling manipulation resulted in control stimuli that were equated on many of the visual features of the original face videos (including luminance, contrast, texture, spatial frequency, motion, and strength of curvature cues in surfaces) but showed meaningless object entities. Stimuli subtended approximately 10.6° of visual angle horizontally and 8.1° vertically.

To increase sensitivity to MCI-related deficits, the stimulus variables duration and depth were parametrically manipulated in 3 steps, resulting in an overall 2 (stimulus type) x 3 (durations) x 3 (depth levels) design. The 3 different duration conditions were approximately 980 ms, approximately 160 ms, and approximately 100 ms (Fig. 1B). In each condition, stimuli rotated from a left-to-right profile view with the extent of rotation being –22.5 to 22.5°, –4.3 to 4.3°, and –2.6 to 2.6°, respectively in long, medium, and short-duration conditions (frontal view = 0°). The global manipulation of the variable “depth” (Fig. 1C) reduced 3D information across the stimuli resulting in new stimuli with 3 different depth levels (10%, 60%, and 90%) parameterized relative to the full anterior–posterior range of the non-transformed 3D stimuli (i.e. 10% corresponding to a near-flat stimulus). The rotation speed was held constant among the different depth levels. Reducing depth caused a shift from surface curvature cues for face detection to simpler 2D (contour-related) cues. Although the analysis of gender identity was irrelevant for our study, the definition of faces by short-lived motion cues likely did not encourage the detailed luminance and color analysis of eyes, eyebrows, and mouth regions, which have been shown to be the most reliable cues for face gender discrimination in photographic stimuli (Dupuis-Roy et al. 2009).

**Localizer Stimuli**

Localizer stimuli used to define ROIs for object and face perception were static grayscale images of faces, places (landscapes, skylines), objects (tools, cars, chairs), and scrambled versions of objects (9.5 by 9.5°). Stimuli were presented on a dark background centered at fixation (fixation cross with radius 0.15° in middle of display). MT localized stimuli (12.6 by 12.6°) were textures that were either static or coherently moving, consisting of arrays of 600 white dots (0.3° diameter) on a dark background. Dots coherently moved in 1 of 4 possible directions (right, left, up, and down) at a constant speed (5°/s).

**Experimental Design and Behavioral Tasks**

**SFM Runs and Task**

The SFM experiment was divided into 4 separate sequential runs lasting approximately 6 min each. We employed a slow event-related design comprising 18 conditions (stimulus type [intact, scrambled] x duration [short, medium, and long] x depth level [high, intermediate, and low]) that were presented randomly within a run. There were 8 trials per condition in total. Participants of all 3 groups performed an SFM face detection task in which they indicated by a button press whether the stimulus shown belonged to the face- or the scrambled face category (2 alternative forced choice). A single trial consisted of an SFM stimulus presentation followed by a long variable interstimulus fixation (baseline) interval (on average 9.6 s) during which responses were given. Prior to the present fMRI experiment, all elderly and MCI patients performed a similar psychophysical task to calibrate the paradigm used here (in preparation).

**Localizer Runs and Task**

During the face localizer scans, participants viewed blocks of stimuli from a given class (faces, places, objects, and scrambled images), divided into 2 runs. Each run consisted of 12 blocks lasting 20 s (20 images, 800 ms duration each, and 200 ms interstimulus intervals), separated by 10 s fixation baseline intervals. In each block, participants performed a 1-back task to keep stable attention levels. Three repetitions per block were employed. To localize area MT, a single 4.18 min run was acquired in which 30 s-blocks (6 stimuli, 4.5 s duration each, 200 ms interstimulus intervals) of coherently moving texture patterns alternated with 30 s-blocks of the same static pattern. Between blocks there were 10 s periods of fixation. Participants were instructed to watch passively but attentively.

**Data Analysis**

**Behavioral Data**

For the statistical analysis of the behavioral data a d’ performance measure was computed for face detection in the 9 conditions (3 durations x 3 depth levels) in each participant ([d’ = Z(hit rate)—Z(false alarm rate)]. Performance data were entered into repeated-measures general linear models (GLMs) with within-subject factors stimulus type, depth, duration, and between-subject factor group. Where applicable, P values were corrected for nonphericity using the Greenhouse-Geisser or Huynh-Feldt correction.

**fMRI Data**

**Preprocessing.** The data were preprocessed and analyzed using Brainvoyager QX 2.3 (Brain Innovation). Slice-scan-time correction, head-motion-correction, as well as temporal high-pass filtering were applied and subsequently anatomical and functional data were spatially normalized to the Talairach coordinate system (Talairach and Tournoux 1988). The sinc interpolation option was used to transform each brain into the size of the standard Talairach brain using manually specified reference points. Within-run movement exceeding more than 3 mm led to the exclusion of a run for further analysis. In addition, spatial smoothing (8 mm) of individual datasets was applied only for the group analysis.

**ROI Analyses**

ROIs were defined for each participant individually by face and motion localizer scans. The ROIs responding preferentially to faces (FFA, OFA, STS) were defined by the contrast faces > objects, places, and scrambled images (P<10^-4, uncorrected) and were restricted to a maximum cluster size of 125 voxels, to achieve optimal statistical face sensitivity (Fox et al. 2009). Motion-sensitive area MT was identified by the contrast motion > no
motion ($P<0.005$, Bonferroni corrected). The statistical thresholds used are based on conventional definitions. Talairach coordinates of the localized ROIs were consistent with previous studies (see Table 2).

To examine fMRI responses in the face-selective ROIs and in MT, z-scored beta weights were extracted for each condition from unsmoothed files of each participant. Subsequently, beta weights were subjected to a separate repeated-measures analysis of variance (ANOVA) for each ROI. We performed 2 different analyses: First, to gain insight into face perception from SFM in our 3 participant groups, we pooled across depth levels (but not durations) and compared ROI activations for intact and scrambled SFM face conditions. Therefore, we computed repeated-measures ANOVAs for each duration using stimulus type (scrambled vs. intact) as within-subject factor and participant group (3 levels) as between-subject factor. Second, to understand the overall effect of the depth manipulation on the fMRI response we pooled data from intact and scrambled SFM face stimuli in the face-selective regions FFA, OFA, and STS as well as in area MT and computed separate GLMs per participant group. Within-subject factors were depth level and duration. The magnitude of the depth effect was estimated using the partial $\eta^2$ index, quantifying the percentage of overall variance explained by the depth factor alone after factoring out effects of other variables.

**Linear Discriminant Analysis.** Based on the effects revealed in the ROI analysis of right and left FFA/OFA, a linear discriminant function was used to test whether group membership (MCI vs. healthy elderly controls) could be predicted from a linear combination of face and depth-sensitivity scores. As face-sensitivity index we used the difference between beta values of faces and scrambled faces in the medium duration condition of right FFA and OFA. The depth-sensitivity index was determined by the slope computed from the beta values associated with the 3 depth levels in left FFA and left OFA.

**Whole Brain Analysis.** Random effects (RFx) whole brain analysis was used to investigate between group activation differences. As in the behavioral data analysis, comparisons were restricted to the investigation of effects due to healthy aging (young vs. healthy elderly) and the specific impairments in MCI compared with age-matched controls (healthy elderly vs. MCI). Statistical maps were projected onto an "average brain" that was computed by averaging cortices from all participants. First, to identify regions that show differences between groups during SFM perception (overall task performance), we computed difference maps for all SFM conditions pooled. Second, to answer the question whether there are group differences in brain regions that are recruited to "successfully" perform the SFM task, we also computed group difference maps for the contrast correct–incorrect trials. Resulting difference maps were first thresholded at $P<0.02$, uncorrected for multiple comparisons and were then submitted to cluster-level statistical threshold estimation based on Monte Carlo simulations with 1000 iterations. The minimum cluster size that survived the thresholding was then used as cluster-size threshold of the source statistical map corresponding to a multiple comparison correction of $P=0.05$ at the cluster level.

### Table 2

<table>
<thead>
<tr>
<th>Region</th>
<th>$N$</th>
<th>Talairach coordinates</th>
<th>Cluster size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Total (young, elderly, MCI)</td>
<td></td>
<td>$x$</td>
<td>$y$</td>
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<tr>
<td>rFFA</td>
<td>35</td>
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<td>−39</td>
</tr>
<tr>
<td>lFFA</td>
<td>35</td>
<td>(11, 12, 12)</td>
<td>−40</td>
</tr>
<tr>
<td>rOFA</td>
<td>35</td>
<td>(11, 11, 11)</td>
<td>−39</td>
</tr>
<tr>
<td>lOFA</td>
<td>35</td>
<td>(8, 9, 9)</td>
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</tr>
<tr>
<td>rSTS</td>
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<td>(19, 9, 10)</td>
<td>49</td>
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<tr>
<td>lSTS</td>
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<td>(9, 9, 9)</td>
<td>−51</td>
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<tr>
<td>rMT</td>
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<td>43</td>
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<tr>
<td>lMT</td>
<td>32</td>
<td>(12, 10, 10)</td>
<td>−45</td>
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</table>

### Results

**Behavioral Results**

A $d'$ performance measure was entered into 2 separate repeated measures ANOVAs with within-subject factors depth, duration, and between-subject factor group. The first ANOVA compared face detection performance in healthy young and healthy elderly (i.e. effects of healthy aging, Fig. 2A). This analysis revealed significant main effects of depth ($F_{2,46} = 17.987$, $P=0.001$), duration ($F_{2,46} = 92.971$, $P=0.001$), and group ($F_{1,23} = 4.560$, $P=0.044$) as well as a significant 3-way interaction between the factors depth, duration, and group ($F_{1,92} = 2.766$, $P=0.032$). Posthoc tests per duration indicated improved performance at higher depth levels in the medium- and long-duration conditions ($F_{2,46} = 3.921$, $P=0.027$ and $F_{2,46} = 24.419$, $P=0.001$, respectively), but not in the short-duration condition ($P>0.5$). A significant effect of the between-subject factor group was only found in the medium-duration condition ($F_{1,92} = 5.025$, $P=0.035$), indicating better performance in the young compared with the elderly group.

The second ANOVA, comparing elderly and MCI participants (i.e. effect of pathological aging, Fig. 2B), revealed a

![Figure 2](image-url). Psychophysics: SFM task performance in the young, elderly, and MCI. Bars indicate SFM task performance ($d'$ performance measure) for the 3 durations and 3 depth levels. (A) Analysis including the young and elderly participants revealed that depth influenced task performance significantly in the medium- and long-duration conditions but not in the short durations. Performance between groups differed significantly in the medium duration condition for which young participants outperformed the elderly. (B) Investigating differences in SFM task performance between elderly and MCI participants revealed that depth influenced performance only in the longest duration condition while it had no effect in the medium- and short-duration conditions. Interestingly, differences in performance between healthy elderly and MCI participants were again only significant in the medium duration condition.
significant main effect of depth ($F_{2,48} = 4.206, P = 0.021$), duration ($F_{2,48} = 69.971, P < 0.001$), and group ($F_{1,24} = 4.493, P = 0.045$) as well as an interaction between depth and duration ($F_{2,96} = 8.980, P < 0.001$). Posthoc analyses per duration showed a significant main effect of depth only for the longest duration ($F_{2,48} = 27.276, P < 0.001$). Interestingly, also healthy elderly and MCI participants only showed statistically different performance in the medium-duration stimuli ($F_{1,24} = 4.481, P = 0.045$). These results suggest that the medium-duration condition is best suited for discriminating between participant groups.

**fMRI: ROI Analysis**

Face-selective clusters were located in bilateral middle fusiform gyr (FFA), bilateral inferior occipital gyr (OFA), and bilateral superior temporal sulci (STS). Motion-selective area MT was localized in bilateral medial temporal sulci (Table 2).

**Differential Activation Patterns to SFM Faces in Aging and MCI**

Here we intended to study differences in SFM face perception among groups in areas FFA, OFA, STS, and MT. A repeated-measures GLM with the within-subject factors stimulus type (intact vs. scrambled face) and between-subject factor group (young, elderly, and MCI) was performed after pooling across the 3 depth conditions. Since differences in task performance between participant groups were found to be critically dependent on stimulus duration (Fig. 2B), we here computed separate a priori planned ANOVAS for each duration condition. As the most interesting and consistent effects (behaviorally and in the ROI analysis) were found in the medium duration, Fig. 3 shows only the results of this condition. For comparison and completeness results for both left and right ROIs are depicted.

**FFA.** In right FFA, the short- and long-duration conditions did not reveal any significant stimulus type or group effects ($P > 0.05$), but the medium-duration condition (Fig. 3A, left column) showed differential patterns of category specificity in the 3 groups (interaction group × stimulus type: $F_{2,32} = 6.734, P = 0.004$). Main effects of stimulus type and group were not significant ($P > 0.05$). Posthoc tests per group revealed a significant SFM face-sensitive effect in the young group ($F_{1,10} = 5.797, P = 0.037$), shown by significantly higher activation for faces compared with scrambled control faces. The elderly group showed no evidence for SFM face sensitivity in this region ($F_{1,11} = 0.555, P = 0.472$). Interestingly, in the MCI patients, the data pattern reversed compared with the young group, showing significantly higher activation for scrambled faces than for intact faces ($F_{1,11} = 7.320, P = 0.02$).

Analysis in left FFA (Fig. 3B, left column for data in medium duration condition) revealed neither a significant main effect of stimulus type nor significant interactions between stimulus type and group in any of the durations ($P > 0.05$). A significant effect of the between-subject factor group was found in the short ($F_{2,32} = 3.528, P = 0.041$) and medium-duration conditions ($F_{2,32} = 5.560, P = 0.008$; Fig. 3B, left column). Posthoc testing suggested decreasing activation in the healthy elderly and MCI compared with the young group, but after Bonferroni correction only reduced activity in MCI relative to young proved significant ($P = 0.004$ and $P = 0.042$, for the short- and medium-duration conditions, respectively).

**OFA.** Similar to right FFA, also right OFA revealed an absence of significant effects in the short- and the long-duration conditions ($P > 0.05$), while in the medium-duration condition (Fig. 3A, right column) face-related activation differed significantly between the groups (interaction stimulus type × group: $F_{2,30} = 5.361, P = 0.011$). Main effects of stimulus type and group did not reach significance ($P > 0.05$). Testing for a main effect of stimulus type separately in each group revealed significantly greater activity for faces than for scrambled controls in the young group ($F_{1,10} = 6.983, P = 0.025$), a lack of face sensitivity in the elderly group ($F_{1,10} = 0.072, P = 0.793$), and smaller activity for faces than scrambled faces in the MCI group ($F_{1,10} = 6.918, P = 0.025$).

Left OFA showed no significant main effects or interactions in the medium and long durations, although the medium-duration condition (Fig. 3B, right column) showed a trend towards a data pattern similar to the one observed in right FFA and right OFA (interaction stimulus type × group: $F_{2,23} = 2.600, P = 0.096$). The short duration showed a significant interaction between stimulus type and group ($F_{2,23} = 6.454, P = 0.006$), which was due to activation for faces being smaller than for scrambled faces in the elderly ($F_{1,8} = 6.093, P = 0.039$) while the other groups showed no stimulus specificity.

**STS.** ROI analysis in STS revealed no face-sensitive effects, no group effects, and no significant interactions ($P > 0.05$), indicating that this region did not contribute significantly to face-sensitive SFM processing in the present task in any of the groups (but see also whole-brain analysis results).

**MT.** We found significant effects of stimulus type (larger activation to scrambled faces compared with faces) in the short-duration conditions for left MT ($F_{1,29} = 4.318, P = 0.047$) and right MT ($F_{1,29} = 9.646, P = 0.004$) but not for the other durations ($P > 0.5$). There were no group effects and no significant interactions ($P > 0.05$).

In sum, healthy aging was characterized by the disappearance of face-sensitive responses in both right FFA and right OFA. In MCI, right FFA, and OFA showed an extreme decline of face-sensitive responses witnessed by “greater” activation for scrambled than for intact faces, suggesting an increased sensitivity to low-to-intermediate level stimulus features at the detriment of sensitivity for the higher-level features that define a face. These fMRI findings are specific to the medium stimulus duration, and therefore likely to be related to differences in task performance among the participant groups at that duration (Fig. 2).

**Increased Sensitivity to Depth from SFM Perception in MCI Patients**

To test the idea of increased/abnormal susceptibility to stimulus features in MCI as an explanation for the reduced category specificity in the previous analysis, we compared sensitivity to stimulus depth among the 3 groups. For this analysis, face and scrambled face conditions were pooled and depth (high, medium, and low) and duration (short, medium, and long) were included as within-subject factors in the analysis. Separate ANOVAs that had been planned a priori were computed...
for each group (young, elderly, and MCI). Since we aimed to test depth-sensitivity, we additionally computed partial $\eta^2$ values, which quantify the percentage of overall variance explained by the depth factor alone (effect size) after factoring out effects of duration (see Materials and Methods; Fig. 4).

**FFA**

In the right FFA, none of the groups showed a significant main effect of depth ($P > 0.05$; partial $\eta^2$ young = 0.054, partial $\eta^2$ elderly = 0.060, partial $\eta^2$ MCI = 0.10; effect sizes $\eta^2$ shown in Fig. 4A). There were significant main effects of duration in all groups ($P < 0.05$), but no significant interactions between depth and duration in any of the groups ($P > 0.05$). On the other hand, analysis in left FFA revealed a surprisingly strong sensitivity to stimulus depth, which was present only in the MCI group ($F_{2,22} = 10.182, P = 0.001$, partial $\eta^2 = 0.481$) but not in the young and elderly control groups ($P > 0.05$, partial $\eta^2$ young = 0.190, partial $\eta^2$ elderly = 0.066; Fig. 4B). Duration had a significant effect in all 3 groups ($P < 0.05$) while none of the interactions reached significance ($P > 0.05$).

**OFA**

In the right OFA (Fig. 4C), only the young group showed a significant depth effect ($F_{2,20} = 5.689, P = 0.011$, partial $\eta^2 = 0.362$) in the absence of any depth effects in the elderly and MCI ($P > 0.05$, partial $\eta^2 = 0.085$, and partial $\eta^2 = 0.083$, respectively). Duration was significant in all 3 groups ($P < 0.05$) but did not interact with depth in any of the groups ($P > 0.05$). In the left OFA (Fig. 4D), similar to left FFA (Fig. 4B), there was neither a significant depth effect ($P > 0.05$, partial $\eta^2 = 0.290$) in the young group, nor in the elderly group ($P > 0.05$, partial $\eta^2 = 0.114$), but there was a strong depth effect in the MCI group ($F_{2,16} = 6.859, P = 0.007$, partial $\eta^2 = 0.462$). In all groups the factor duration had a significant main effect ($P < 0.05$) but did not interact significantly with depth ($P > 0.05$).

**STS**

In right and left STS, there were no significant main effects of depth ($P > 0.05$; Fig. 4E,F) while the factor duration was significant in all groups ($P < 0.05$). However, in the right STS of the MCI, the factors depth and duration interacted ($F_{4,26} = 2.910, P = 0.035$) indicating a sensitivity to depth only in the short ($F_{2,18} = 6.279, P = 0.009$, partial $\eta^2 = 0.411$) and long-duration conditions ($F_{2,18} = 4.209, P = 0.032$, partial $\eta^2 = 0.319$) but not in the medium duration ($P > 0.05$, partial $\eta^2 = 0.033$). This indicates abnormalities in depth processing of SFM stimuli also in STS of the MCI group.

**MT**

Area MT in all 3 groups revealed a strong sensitivity to stimulus depth in the right hemisphere (young: $F_{2,22} = 6.669, P = 0.005$, partial $\eta^2 = 0.377$; elderly: $F_{2,18} = 7.522, P = 0.004$, partial $\eta^2 = 0.455$; MCI: $F_{2,18} = 10.846, P = 0.001$, partial $\eta^2 = 0.547$; Fig. 4G) as well as in the left hemisphere (young: $F_{2,22} = 4.895, P = 0.017$, partial $\eta^2 = 0.308$; elderly: $F_{2,18} = 10.283, P = 0.001$, partial $\eta^2 = 0.533$; MCI: $F_{2,18} = 7.684, P = 0.004$, partial $\eta^2 = 0.461$; Fig. 4H). Stimulus duration was significant in all 3 groups ($P < 0.05$) and did not interact with depth. These results suggest intact mechanisms for extracting depth from motion in area MT in all 3 participant groups.

**Figure 3.** Face sensitivity in areas FFA and OFA. (A) A ROI analysis in face-sensitive areas FFA and OFA in the right hemisphere showed significant differences in face sensitivity between the 3 participant groups in the medium duration condition. While right FFA and right OFA were selective to SFM faces in the young group, in the elderly group activation between faces and scrambled faces did not differ. Interestingly, the MCI patients showed higher sensitivity to scrambled control faces. (B) Analysis of FFA and OFA in the left hemisphere revealed no significant category specific effects in any of the groups, however, a trend towards the data pattern found in the right FFA and OFA was also observed in left OFA. Bar graphs indicate standardized beta values of the face and scrambled face conditions (depth levels are pooled) in the medium-duration condition. Error bars indicate significant differences between conditions at the 0.05 level. For illustration, individually localized FFA and OFA are shown on a reconstructed inflated cortical surface of 1 representative participant.
towards higher depth sensitivity in the MCI patients compared with the control groups. (C and D) A similar lateralization pattern was also observed in area OFA. ROI analysis in the left OFA showed high depth sensitivity in the MCI but not in the young and elderly. Instead, the young were sensitive to depth in the right OFA. (E and F) In both left and right STS no overall depth sensitivity was found, however, bar graphs indicate a trend towards higher depth sensitivity in the MCI patients compared with the control groups. (G and H) All 3 groups exhibited a large depth sensitivity in bilateral MT. Bar graphs indicate the effect size (partial $\eta^2$) of the depth variable for all 3 groups pooled over duration and stimulus type. Asterisks indicate significant main effects of depth at the 0.05 level.

In sum, we found a high sensitivity to depth in the left FFA and left OFA of MCI patients that was absent in the young and healthy elderly participants. These results suggest that the decreased sensitivity for faces in right FFA and OFA might be in part related to increased sensitivity in the left hemisphere to lower-level aspects of SFM stimuli.

**Classifying MCI and Elderly Control Groups Based on Depth and Face Sensitivity**

To assess the diagnostic utility of the effects revealed in the above reported ROI analysis, we tested whether group membership (MCI vs. healthy elderly controls) could be predicted from face and depth-sensitivity scores (based on beta values, see Materials and Methods) from FFA and OFA using a linear discriminant function (for a similar application of linear discriminant analysis [LDA] see Ihssen et al. 2011). Thus, each participant was scored on both the face and depth index leading to scatter plots for the healthy elderly and the MCI characterized along 2 dimensions. Figure 5 depicts results for FFA (Fig. 5A), OFA (Fig. 5B), and combined data from FFA/OFA (Fig. 5C). The discriminant function is based on a linear combination of the 2 predictor variables that best separates the groups. Results for FFA showed larger standardized canonical discriminant function coefficients for the depth (0.886) than for the face index (0.628) indicating that the depth index had greater discriminating ability. The function classified MCI and elderly controls with 83.3% accuracy (Wilks’ $\lambda = 0.543$, $\chi^2 = 12.816$, df = 2, $P = 0.002$). In OFA, the face index had slightly higher discriminating ability than the depth index (standardized canonical discriminant function coefficients 0.731 and 0.693, respectively) while the model predicted group membership with 70.6% accuracy (Wilks’ $\lambda = 0.647$, $\chi^2 = 6.104$, df = 2, $P = 0.047$). A linear discriminant function including all 4 predictors, that is, depth and face indices from both FFA and OFA yielded the highest accuracy (Wilks’ $\lambda = 0.343$, $\chi^2 = 13.910$, df = 4, $P = 0.008$, 88.2% of cases correctly classified). Taken together, these findings indicate that in the present study, MCI patients and healthy elderly participants could be classified with high accuracy based on face- and depth-sensitivity indices in face sensitive regions FFA and OFA.

**fMRI: Whole Brain Analysis**

**Between-Group Comparisons: Overall-Activation Differences**

Comparing overall activation between the young and the healthy elderly group during the SFM face detection task pooled over all conditions revealed more activity in the elderly compared with the young in a bilateral superior parietal network, in bilateral inferior temporal and parahippocampal gyri, and in predominantly right-lateralized frontal regions. Conversely, the elderly showed significantly less activation than the young in a small patch in the posterior cingulate cortex ($P < 0.05$, corrected).

The overall activation comparison between healthy elderly and MCI group revealed stronger activation in the MCI than in healthy elderly in the right putamen and right pallidum as well as in an area in the right superior temporal lobe ($P < 0.05$, corrected; Fig. 6A). There were no areas that showed less activation in the MCI than in the elderly.

**Between-Group Comparisons: Regions Involved in Correct Task Performance**

Differences in the network involved in correct task performance between young and elderly control participants were found in the right superior temporal pole, which was more active in the elderly compared with the young participants. On the other hand, elderly showed less activation than the young in bilateral inferior parietal regions as well as in confined bilateral inferior occipital regions presumably corresponding to OFA ($P < 0.05$, corrected).

Activation associated with correct task performance (correct > incorrect trials) also differed significantly between elderly control participants and the MCI patients. The MCI group displayed more activation in bilateral medial parietal/cingulate cortex, the left anterior and medial temporal cortex, the left parahippocampal cortex, and a predominantly right-lateralized fronto-parietal network including a region in the left insular cortex and inferior parietal cortex, relative to the elderly control group ($P < 0.05$, corrected; Fig. 6B). There were no areas that were less activated in the MCI compared with the elderly for this contrast.
Figure 5. Face- and depth-sensitivity indices discriminate between MCI patient and elderly control group. A LDA indicated that face- and depth-sensitivity patterns in FFA and OFA were highly predictive of group membership. Scatterplots indicate face indices in right FFA/OFA plotted against depth indices in left FFA/OFA for each participant in the healthy control and MCI group. (A) Using face and depth indices in FFA, the distributions for the healthy elderly and the MCI could be separated correctly in 83.3% of the cases. (B) In OFA the model classified between healthy elderly and MCI with 70.6% accuracy. (C) A combination of depth and face indices from all 4 ROIs (right FFA/OFA and left FFA/OFA) as predictors yielded a prediction accuracy of 88.2%.

Discussion

In the present study, we aimed to detect early alterations in visual brain function in amnestic MCI, a condition associated with likely conversion to AD. To that goal, we used SFM stimuli enabling us to study both dorsal and ventral stream visual functions using concurrent behavioral and fMRI measurements.

Our findings indicate a decline in the ability to extract face information from short-lived motion cues in healthy aging and particularly in MCI, witnessed by behavioral measures and fMRI activation in temporal lobe areas. Young participants showed selective fMRI activation to SFM faces compared with scrambled control stimuli in right FFA/OFA and low sensitivity to stimulus depth modulations in the left FFA/OFA. In healthy elderly participants this face-sensitive processing in the right FFA/OFA was greatly reduced while an essentially normal low sensitivity to local features in the left hemisphere was retained. Intriguingly, in the MCI we found higher fMRI responses to scrambled than to intact faces in right FFA/OFA associated with a large sensitivity for low-level stimulus features (depth) in left FFA/OFA. This reversed sensitivity pattern in FFA and OFA marks a fundamental distinction between healthy aging and MCI participants that is closely associated with their task performance.

Additional findings included overall stronger activation in MCI than in healthy elderly in the right putamen, right pallidum, and an area in the right superior temporal lobe, as well as increased activation in a broad network of areas during correct as opposed to incorrect performance. Our findings on healthy and pathological aging in MCI will be first placed in the context of hemispheric asymmetries in normal face perception, after which contributions of impairments in dorsal-ventral integration and attention to MCI will be discussed.

Hemispheric Asymmetries in Face Perception in Normal and MCI Participants

FFA, OFA, and STS constitute the core regions of the face- processing system in healthy adults (Kanwisher and Yovel 2006). Area FFA has also been shown to be selectively activated in response to SFM faces (Kriegeskorte et al. 2003). Here we confirm this finding for right FFA and additionally report SFM face sensitivity in right OFA. However, no face-sensitive effects were found in equivalent regions in the left hemisphere. This lateralization of face-sensitive effects is in line with behavioral data indicating stronger face-sensitive effects in the right hemisphere and generally larger right-lateralized face sensitivity in FFA (for a review see [Cabeza and Nyberg 2000]). These findings relate to a more general lateral asymmetry that has been observed in visual processing, having inspired notions of analytic versus configural processing (Bradshaw and Nettleton 1981), or processing high versus low spatial frequencies (Ivry and Robertson 1998; Flevaris and Robertson 2011) in left and right hemispheres, respectively. A more recent model proposes that the left hemisphere focuses on isolating features as well as associative relationships between features while the right hemisphere is sensitive to holistic stimulus aspects and conjoining features (Dien 2009). In the context of the present study this would imply that the left FFA/OFA extracts face-related features from spatial and depth cues in the SFM stimuli while the right FFA/OFA is involved in assembling visual features for more holistic processing which in turn would lead to a greater face-sensitive fMRI response.

While the loss of SFM face sensitivity in right FFA/OFA of the elderly control participants is likely due to “differen
tiation”, a phenomenon referring to less distinct neural activation in the elderly (Carp et al. 2011; Grady et al. 1994; Lee et al. 2011), the fMRI activation patterns in the MCI suggest a fundamental change in the different hemispheric mechanisms for face perception. The stronger activation to scrambled faces compared with faces in the medium-duration condition (most performance discriminative) indicates that holistic processing of faces in right FFA/OFA is impaired, presumably contributing to the observed decline in psychophysical task performance. The mechanism underlying this impairment of integrative function may be an over-representation of lower-level stimulus features, which is suggested both by the preference for scrambled compared with intact faces in right FFA/OFA and additionally by the increased sensitivity to stimulus depth in left FFA/OFA. Thus, the absence of the “normal” selectivity pattern in MCI suggests that instead of a holistic approach other, less efficient perceptual strategies are used. While the alterations in left and right FFA/OFA might reflect independent parallel processes, one might also speculate that they are functionally dependent. In terms of the different
Impaired Dorsal–Ventral Cross-Talk during Face Perception in MCI

Psychophysical studies have indicated specific deficits in SFM perception in AD (Rizzo 2000; Kim and Park 2010) and more recently also in MCI (Lemos et al. 2012). Despite reports of impairments at motion perception tasks in AD (Kavcic et al. 2011) as well as alterations in fMRI activation patterns related to motion processing (Thiyagsh et al. 2009), the present study showed normal patterns of fMRI activation in MT of the 2 elderly groups. Hence, the observed SFM impairments in our study are unlikely to primarily reflect motion processing deficits. Instead, since the integration of information from dorsal and ventral visual streams is crucial in SFM perception, we suggest that the mechanisms of dorsal–ventral integration might be impaired in MCI. The superior temporal cortex has long been hypothesized to play a major role in dorsal–ventral interaction. From monkey anatomical studies it is known that the STS/STG receives inputs from both streams (Seltzer and Pandya 1978; Morel and Bullier 1990) and has direct anatomical connections to the putamen, caudate nucleus, and the pulvinar (Veterian and Pandya 1998). Significantly, we found an overall hyperactivation during SFM perception in the MCI in the superior temporal cortex as well as the right putamen and right pallidum. Hyperactivation in the putamen of the MCI may result from microstructural damage in the right caudate (Cherubini et al. 2010), a structure that together with the putamen forms the dorsal striatum. These findings hence suggest overactivations in MCI that may underlie suboptimal integrative processing in dorsal/ventral conjunction regions, and may be related to the impaired temporal lobe face perception mechanisms in this group. It is conceivable that deficient integration causes an overemphasis of low-level stimulus aspects to the detriment of more global integrative processes in the face-processing network.

Contributions of Attention to SFM Face Perception in MCI

Face processing mechanisms are heavily influenced by attention processes. Object specificity in several visual areas including the FFA (Murray and Wojcikulik 2004; Reddy and Kanwisher 2007) has been shown to increase when the object category is attended. In AD, selective attention is known to be affected early in the course of the disease (Baddeley et al.
Therefore, in the present study an attentional bias towards predominantly local stimulus features at the detriment of configural processing in right FFA/OFA might underlie the observed pattern of results in MCI. However, results from our whole brain analysis provide strong support for an alternative interpretation, suggesting that attention may have been allocated more strongly in MCI to compensate for an automatic emphasis on lower-level features in SFM face processing in the temporal lobe. This interpretation is confirmed by increased activation in MCI during correct task performance in the medial parietal/cingulate cortex, a fronto-parietal network including the insula, and inferior parietal regions. Several frontal and parietal regions have been shown to be involved in attention (Corbetta and Shulman 2002) and the insula and the medial cingulate cortex are known to play a role in environmental monitoring and response selection (Taylor et al. 2009). In a highly relevant study, Grady et al. (2003) proposed that AD patients compared with controls recruit additional unique neural networks that may indicate compensatory mechanisms for gray matter losses. Hence, also in the present study the hyperactivations in regions involved in attention and executive control may be a mechanism to maintain adequate performance levels in the setting of early brain pathology.

Our study design, focusing on performance-related changes instead of resting-state alterations, adds to previous fMRI studies by using a relevant cognitive task (perception of motion-defined face stimuli) probing both temporal and parietal mechanisms in healthy aging and MCI. Our principal finding is an overemphasis of low-level at the cost of global processing during SFM face perception in MCI, which was evident in aberrant patterns of activation in FFA/OFA. Furthermore, MCI was characterized by alterations in dorsal-ventral integrative regions and attention-related networks. Although previous studies have emphasized visual dorsal stream dysfunction in MCI, we found activity patterns of visual ventral stream areas FFA/OFA to be a highly accurate biomarker for MCI. With early diagnosis, pharmacological or cognitive therapies may be one way to halt or slow down progression of the disease (e.g. Bokde et al. 2009). Since in mild stages of the disease a high degree of cortical plasticity might still be preserved, timely application of perceptual, and other skill learning paradigms (e.g. Kim and Park 2010) as well as decoded fMRI neurofeedback (Shibata et al. 2011) may be other particularly promising approaches for reversing/sparing visual and other functions in MCI and preclinical AD.

### References


### Notes

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