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Delayed rather than decreased BOLD response as a marker for early Alzheimer's disease

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Functional MRI (fMRI) in established Alzheimer's disease (AD) shows regionally altered blood oxygenation level dependent (BOLD) responses. Mild cognitive impairment (MCI) is thought to represent an intermediate state between health and early Alzheimer's disease.

To study this probable early dementia stage pathology, we studied in detail the BOLD response in MCI during visual encoding.

28 MCI patients, 18 AD patients, and 41 healthy elderly controls performed a face encoding task during fMRI scanning. Data were analyzed using orthogonal regressors, each representing different phases of the BOLD response (from slow to fast). Using a mixed effects model, regressor × group interactions were analyzed applying $P < 0.05$, corrected.

In occipital regions, MCI patients could be distinguished significantly better from controls and AD patients with a regressor of the early phase of the (fast) BOLD response than with the regressor of the late (slow) BOLD phase. Occipitally, the early phase BOLD response was significantly diminished in MCI patients compared to controls, and significantly increased when compared to AD. AD patients showed diminished early phase activation in widespread regions throughout the brain when compared to controls. There were no differences in the late (slow) phase of the BOLD response.

This study stresses the importance of analyzing early phase BOLD responses and not only using one model of the BOLD response in neurodegenerative diseases. The increasing delay of the BOLD response from controls to MCI to AD may be consistent with the idea that MCI is a transitional state between healthy aging and dementia. Analyzing differences in different phases of the BOLD response introduces new opportunities to understand changes in regional brain dynamics in MCI and how well this may serve as an early marker of AD pathology.

Keywords: Alzheimer's disease; Mild cognitive impairment; fMRI; BOLD; Encoding

Introduction

Alzheimer's disease (AD) is characterized by selective atrophy of medial temporal lobe (MTL) structures and various nuclei within the basal forebrain (Braak et al., 1999). Imaging research in AD aims to determine atrophy using magnetic resonance imaging (MRI), and has recently shifted towards studying brain function using functional magnetic resonance imaging (fMRI). FMRI measures neuronal activity indirectly through the blood oxygen level dependent (BOLD) hemodynamic response function (HRF). Regionally altered BOLD responses occur in established AD (Gron et al., 2002; Grossman et al., 2003; Kato et al., 2001; Lustig et al., 2003; Rombouts et al., 2000; Saykin et al., 1999; Small et al., 1999; Sperling et al., 2003). More challenging, however, is the detection of very early changes before dementia is present. FMRI may be particularly suited for this purpose because functional changes are likely to precede anatomical changes. Individuals with increased risk for developing AD due to family history and/or genetic risk show altered brain activation. FMRI studies show increased brain activation in parietal, hippocampal, and prefrontal regions (Bookheimer et al., 2000; Smith et al., 2002), but also regionally decreased activation in these individuals (Smith et al., 1999).

Mild cognitive impairment (MCI) is of special interest in functional imaging of patients before clinical dementia is overt, since MCI is thought to represent a functional continuum between healthy aging and the earliest signs of dementia (Petersen et al., 2001). Roughly half of MCI patients will convert to AD in 3–5 years time (Petersen et al., 2001). Brain activation patterns in MCI patients may therefore contain information indicative of very early AD. Structural MRI in MCI shows atrophy in the MTL (Du et al., 2001; Jack et al., 1999; Visser et al., 1999), cingulate cortex (Chetelat et al., 2002) and also more widespread pathology (Van Der Flier et al., 2002). Functional imaging in MCI with FDG PET shows decreased resting metabolism associated with cognitive decline in hippocampal regions and posterior cingulate cortex

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(Chetelat et al., 2003; DeSanti et al., 2001). The BOLD response is reduced in the MTL with a memory test, but not in the sensorimotor cortex with a motor test (Machulda et al., 2003). Others found, paradoxically, that the extent of activation of the right parahippocampal gyrus correlates with clinical impairment and that it predicts cognitive decline over 2.5 years of clinical follow-up (Dickerson et al., 2004).

In the field of fMRI, one often assumes that time of onset, time to peak, and full width at half maximum of the BOLD HRF is the same in different brain regions, as well as across patients and controls. This assumption may not be correct, given the evidence that aging may affect these parameters (D'Esposito et al., 2003). The coupling between neural activity and BOLD signal may be altered in the elderly in the primary motor cortex, resulting in decreased signal-to-noise ratio (D'Esposito et al., 1999). Regional differences in the HRF between motor and visual cortices were associated with age in another study. Aging had an effect on the BOLD amplitude in the visual cortex, but not in the motor cortex (Buckner et al., 2000). Furthermore, EEG studies in AD show delayed peak responses of various event-related potentials as compared to elderly control subjects (Ball et al., 1989; Olichney and Hillert, 2004; Polich and Herbst, 2000). Neurofibrillary pathology in AD follows sequential stages; hence, pathology in mild dementia has different degrees of severity across brain regions. Therefore, it is likely that perhaps between brain regions, and most likely between patients and controls, HRF parameters are not the same. In fMRI studies of early dementia, this possibility is often overlooked and the HRF is assumed to have the same parameters in different regions in disease and healthy aging.

In the present study, we applied whole-brain fMRI in 28 MCI patients with a test that challenged episodic memory with known widespread brain activation. In each brain region, the response at different time periods after stimulus presentation was compared statistically to AD and controls to understand changes in the regional BOLD response in established AD and MCI patients. Given the delayed response observed in AD patients using EEG, we hypothesized that MCI and AD patients would show an increasingly delayed BOLD response compared to control subjects. Second, we aimed to analyze whether the BOLD response was delayed rather than diminished in early dementia (that is, whether the early BOLD response shows a greater difference between the three groups than the later phase of the BOLD response).

Methods

Subject recruitment

Patients were recruited at the Alzheimer Center of the VU University Medical Center, Amsterdam, the Netherlands. MCI patients were diagnosed using criteria for amnestic MCI (Petersen et al., 2001), with mini mental state examination (MMSE) scores > 25 (Folstein et al., 1975), and clinical dementia rating (CDR) scale scores of 0.5 (Morris, 1993). Twenty-eight MCI patients were included (age 74.0 ± 7.5 years, range 54 to 84 years; MMSE 26.9 ± 1.2; 8 male, 20 female; average education 2.2 ± 0.6 on a discrete scale with 3 levels: low = 1, middle = 2, high = 3; three patients were left-handed).

AD patients were diagnosed using NINCDS-ADRDA criteria (McKhann et al., 1984), with MMSE scores > 18 and CDR < 2. These values correspond to what is known as mild AD. Eighteen AD patients were included (age 74.1 ± 8.0 years, range 55 to 83 years; MMSE 22.5 ± 2.2; 11 male, 7 female, education 1.7 ± 0.6; one patient was left-handed).

Forty-one healthy controls (age 63.1 ± 5.2 years, range 50 to 75 years; MMSE 29.0 ± 0.9; 28 male, 13 female, education 2.1 ± 0.7; two were left-handed) were also included.

The experiment was approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam. All subjects provided informed consent, patients under supervision of a lawful caregiver if necessary. Subjects were excluded if they had any significant medical, neurological, or psychiatric illness, or if they were taking medication or other substances known to influence cerebral function. In this study, only patients whose diagnosis had remained unaltered during a 6-month follow-up were included.

MR acquisition

Imaging was carried out on a 1.5-T Sonata MR scanner (Siemens, Erlangen, Germany), using a standard circularly polarized head coil with foam padding to restrict head motion. For fMRI, an echo planar imaging sequence was used (echo time = 60 ms, flip angle = 90°, matrix = 64 × 64, field of view = 192 × 192 mm), to obtain 21 transverse slices (5 mm thickness, 1 mm interslice gap). Task stimuli were projected on a screen at the head end of the scanner table via an LCD projector located outside the scanner room and viewed through a mirror on the head coil. In each hand, subjects held a response-box to react by pressing a button using their index-fingers. A T1-weighted structural MRI scan was also acquired (MPRAGE; inversion time = 300 ms, TR = 15 ms; TE = 7 ms; flip angle = 8°; 160 coronal slices, 1 × 1 × 1.5 mm voxels).

Memory task

A face encoding task was used to assess episodic memory (Small et al., 1999). The task was practiced extensively: the first practice was 1 day before scanning at home, the second just before scanning, the third in the MR scanner. During the first 10.5 s, subjects saw a circle indicating time left before the onset of the first condition. Two conditions alternated in a block design: face encoding and fixation. In a 42-s encoding block, 6 unfamiliar faces were presented sequentially (6 s each, followed by a 1-s delay). Subjects were instructed to remember each face and to classify gender by pressing one of two buttons (left: male, right: female; instructions below each face). Male and female faces were balanced across encoding blocks. Four encoding blocks alternated with four fixation blocks, presenting a fixation cross for 44 s. The task started with a 21-s fixation period. Responses were recorded and reaction times and gender discrimination accuracy scores were recorded. Total task duration was 6 min and 12 s. Performance accuracy was assessed immediately after encoding using a recognition task. Subjects saw 24 faces sequentially in random order, of which 12 were shown during encoding and 12 were new (presentation time 5 s, followed by a fixation cross for 3 s). Subjects were instructed to indicate whether the faces were familiar or unfamiliar by pressing one of two buttons (left: familiar; right: unfamiliar; instructions appearing below the face). Recognition scores were rated between 0 (chance) and 1 (no errors).

MR data analysis

The brain response was only analyzed for the encoding task, not for the recognition task. FMRI analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.1, part of FSL (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl). Pre-statistical processing consisted of motion correction (Jenkinson et al., 2002), non-brain removal (Smith, 2002b), spatial smoothing using a Gaussian kernel of FWHM 6 mm, mean-based intensity normalization of all volumes by the same factor, and high-pass temporal filtering (Gaussian-weighted LSF straight line fitting, with sigma = 60.0 s). Time-series statistical analysis was done with local autocorrelation correction (Woolrich et al., 2001). Based on pilot data showing earlier responses than modeled by the default HRF, data were modeled in an event-related fashion with 7 different gamma HRFs:

$$G(x;\alpha,\beta) = \frac{x^{\alpha-1}e^{-\frac{x}{\beta}}}{\Gamma(\alpha)\beta^{\alpha}}, \qquad \text{with } \alpha = \frac{\mu^2}{\sigma^2},\ \beta = \frac{\sigma^2}{\mu} \text{ and}$$

$$\Gamma(\alpha) = \int_0^{\infty} t^{\alpha-1}e^{-t}dt.$$

In the equation, μ is the delay and varied between 6 and 0 s (explained below), σ was equal to 3, which is the default value in FEAT. The seven regressors in the analysis were these HRFs convolved with the on/off stimulus pattern. The first HRF reached maximal amplitude after 6 s (μ = 6, default gamma HRF). The second HRF peaked after 5 s. The second regressor was orthogonalized with respect to the first. Hence, this second regressor modeled earlier or later (depending on the parameter estimate corresponding to this regressor being positive or negative) responses with any overlap with the first regressor removed. The next 5 regressors were added in the same manner (stimulus convolved with gamma HRFs with maximal amplitudes at 4, 3, 2, 1, and 0 s), all orthogonalized to the previous ones (Fig. 1). This gave seven images of parameter estimates representing signal explained by each of the regressors, as well as the seven corresponding variance images. FMRI images were registered to the individual's structural scan, which was registered to standard space images (Jenkinson and Smith, 2001; Jenkinson et al., 2002). These transformations were applied to images of parameter estimates and variances to put them in standard space.

Higher-level (group level) analysis was carried out using mixed effects analysis (Woolrich et al., 2004). In the first analysis, the group averages were calculated for each of the seven parameter estimates. Second, both differences between groups for each parameter estimate as well as group × parameter estimate interactions were analyzed with a repeated measures model with age and gender as covariates across groups. Z (Gaussianized T/F) statistic images were thresholded using clusters determined by $Z > 3.1$ and a corrected cluster significance threshold of $P = 0.05$ (Forman et al., 1995; Friston et al., 1994; Worsley et al., 1992). For the differences and interactions, the analysis was limited to regions that showed activation for any regressor in any group, allowing less stringent cluster corrections.

Analysis of behavioral data

For each group, separate performance scores were calculated. Age and gender were compared between groups using univariate ANOVA and a Chi-square test, respectively. A univariate analysis of variance was performed using SPSS 9.0, with performance score as dependent variables, 'group' as fixed factor and 'age' and 'gender' as covariates. If a significant effect of a covariate was

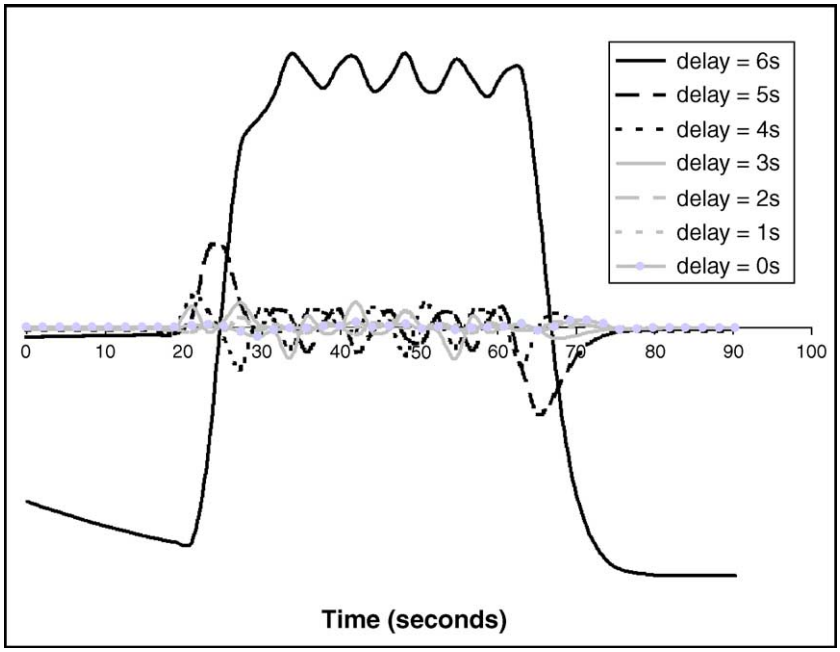

Fig. 1. Regressors used in the data analysis. The 7 regressors as they are included in the model for first-level data analysis. The model is shown for one activation block of 6 face presentations. Data were modeled in an event-related fashion with 7 different gamma hemodynamic response functions (HRFs). These were convolved with the on/off stimulus pattern. The first HRF reached maximal amplitude after 6 s (default gamma HRF). The second HRF peaked after 5 s. The second regressor was orthogonalized with respect to the first. Hence, this second regressor modeled earlier or later (depending on the parameter estimate being positive or negative) responses with any overlap with the first regressor removed. The next 5 regressors were added in the same manner (stimulus convolved with gamma HRFs with maximal amplitudes at 4, 3, 2, 1, and 0 s), all orthogonalized to the previous ones.

found, the model was adjusted to contain the relevant covariate as a fixed factor in a subsequent analysis of the group effect.

Results

Controls were significantly younger than AD [$F(1,57) = 39.82$, $P = 0.0004$], and MCI patients [$F(1,65) = 51.41$, $P = 0.001$], but MCI and AD did not differ in age [$F(1,44) = 0.072$, $P = 0.79$]. Gender ratio was different between controls and MCI patients (Chi-square = 9.0, $df = 1$, $P = 0.003$) and between MCI and AD patients (Chi-square = 4.0, $df = 1$, $P = 0.04$), but not between controls and AD (Chi-square = 0.29, $df = 1$, $P = 0.59$). Both gender and age were included as covariates of no interest in the fMRI analysis (see below).

All subjects were presented with faces during fMRI scanning and had to indicate the gender of each face using a button box. Mean accuracy scores for gender discrimination were 0.96 (SD 0.02) in controls, 0.96 (SD 0.02) in MCI, and 0.87 (SD 0.03) in AD. AD accuracy scores differed significantly from controls [$F(1,57) = 14.7$, $P = 0.0003$] and MCI patients [$F(1,44) = 5.27$, $P = 0.027$]. Mean reaction times were 1.13 s (SD 0.08 s) in controls, 1.39 s (SD 0.08 s) in MCI, and 1.50 s (SD 0.10 s) in AD patients. AD patients had significantly slower reaction times than controls [$F(1,57) = 10.0$, $df = 1$, $P = 0.003$]. Other pair-wise comparisons were not significant. The brain activation results of this encoding task are described below.

Five minutes after the encoding phase, all subjects were presented old and new faces to determine encoding success. Mean accuracy scores (0 is chance level, 1 means no errors) during face recognition after the encoding task were 0.71 (SD 0.054) in controls, 0.36 (SD 0.051) in MCI, and 0.15 (SD 0.061) in AD patients. Accuracy scores in each patient group differed significantly from the other two groups [$F(2,84) = 76.1$, $P < 0.0001$]. Mean reaction times were 1.72 s (SD 0.12 s) in controls, 2.41 s (SD 0.11 s) in MCI, and 2.23 s (SD 0.14 s) in AD patients. These were different between controls and MCI [$F(1,67) = 55.4$, $P = 0.0003$], controls and AD [$F(1,57) = 15.6$, $P = 0.0002$], but not between MCI and AD patients [$F(1,44) = 1.87$, $P = 0.18$].

FMRI data

All group pairs showed significant interactions with regressor 1 (with maximal amplitude after a delay of 6 s) and regressor 2 (orthogonal to regressor 1 with a peak after 5 s). Parameter estimate (regressor 1, regressor 2) × group (MCI, controls) interactions were significant occipitally in the lingual gyrus (cluster $P = 0.004$) (Fig. 2). Parameter estimate (regressor 1, regressor 2) × group (AD, controls) interactions were present in occipital regions including cuneus, lingual gyrus, and fusiform gyrus (cluster $P = 2 \times 10^{-28}$) (Fig. 2). Other clusters showing this interaction were caudate nucleus, putamen and thalamus (one cluster, $P = 3 \times 10^{-13}$), medial ($P = 0.00003$), inferior ($P = 0.003$), middle ($P = 0.002$) and superior frontal gyrus ($P = 0.01$), postcentral gyrus ($P = 0.003$), anterior cingulate gyrus ($P = 0.009$) and inferior temporal gyrus ($P = 0.03$). Also, the interaction parameter estimate (regressor 1, regressor 2) × group (MCI, AD) was significant in the lingual gyrus (cluster $P = 0.01$) and cuneus ($P = 0.04$) (Fig. 2). Other interactions involving other regressors were not significant.

Further exploration of these interactions revealed that activation corresponding to regressor 1 was found in the occipital regions, fusiform and lingual gyrus, thalamus, frontal cortex, parietal cortex, anterior cingulate, hippocampus, putamen, and caudate nucleus (Fig. 3). All activated regions displayed an early response in controls, corresponding to a positive parameter estimate of regressor 2, shown in Fig. 3.

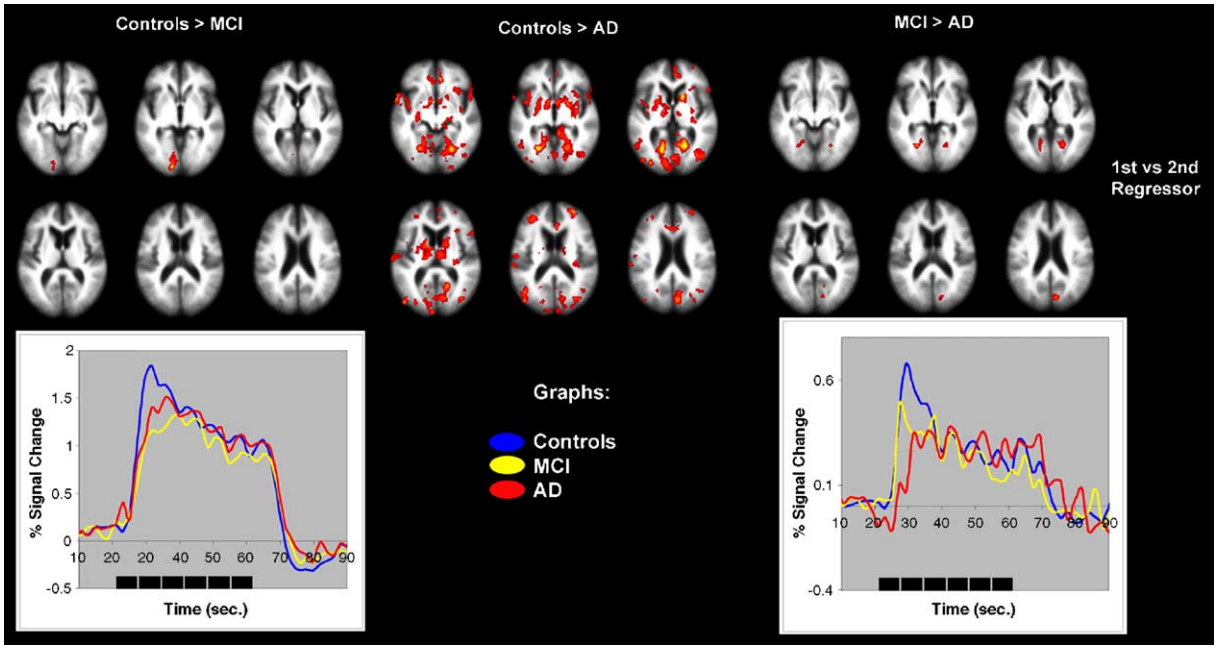

Fig. 2. Regions showing a significant group × parameter estimate (regressor 1, regressor 2) interaction. *Z* scores are color coded from 3.1 (red) to 6.6 (yellow). The graphs on the left and right illustrate the mean BOLD signals in each group separately. The plotted signal underwent motion correction and spatial and temporal filtering, and was averaged over the significant voxels in the image above the graph and over the four activation blocks. The black rectangles represent the six occurrences of 6 s each of face display.

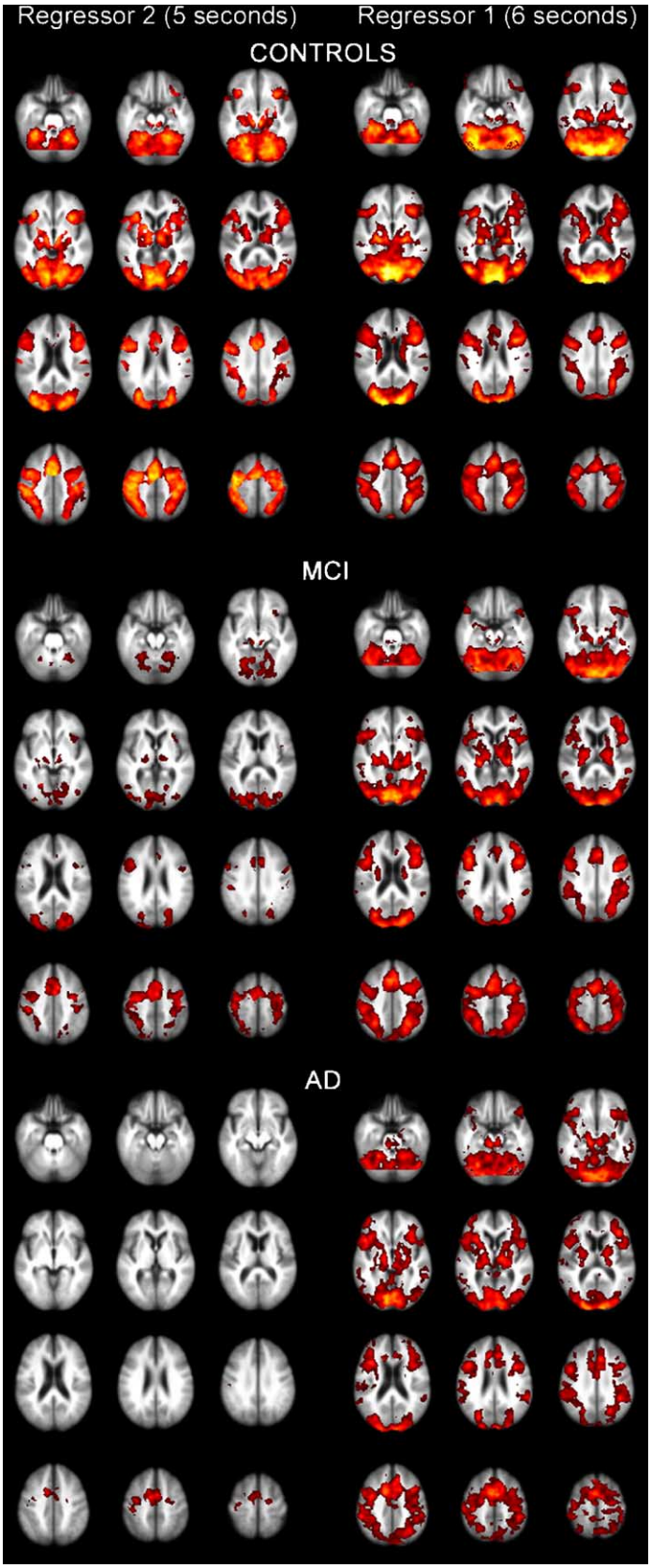

Fig. 3. Average activation in controls, MCI, and AD patients. Z statistics for regressors 1 and 2 (with 6 and 5 s delay) that are significantly different from 0 in each group ($P < 0.05$, corrected). Z scores are color coded from 3.1 (red) to 12 (yellow). The underlying structural image is the average image of all controls and patients; left in image is left in the brain. MCI patients (middle) show fewer regions with an early response than controls (top). This is further diminished in AD (bottom), where most of the early response is restricted to the anterior cingulate cortex.

MCI patients had activation corresponding to the first regressor in the same regions as controls (Fig. 3). A large part of this network which included visual regions, anterior cingulate cortex, hippocampus, thalamus, and parietal cortex also showed a significant *early* response (Fig. 3), significantly explained by a positive parameter estimate of the second regressor.

AD patients showed a comparable activation pattern, yet with lower Z scores (Fig. 3). On the other hand, the early response was expressed to a much smaller extent in AD as compared to MCI, indicating a delay in the hemodynamic response in many regions in AD.

In all regions of interactions, the interaction effects were caused by significant group differences for regressor 2. The parameter estimates of regressor 1 did *not* show a difference between any group at the applied threshold determined by $Z > 3.1$ and a corrected cluster significance threshold of $P = 0.05$ (see Methods). Hence, regressor × group interactions shown in Fig. 2 represent regions of greater signal difference between groups for regressor 2, which were in itself significant, as compared to the group difference of regressor 1, which were not significant.

Neither age nor gender was significantly associated with brain activation, not within groups or across groups at the applied threshold determined by $Z > 3.1$ and a corrected cluster significance threshold of $P = 0.05$.

The group analysis described above was repeated in regions with any significant group difference, but now with one extra covariate representing reaction times of gender decisions. Correction for multiple comparisons in this post hoc analysis was based on the imaging data in these regions only (Forman et al., 1995; Friston et al., 1994; Worsley et al., 1992). This was done to see whether the observed group differences were perhaps associated with reaction time, given the significantly slower reaction times of AD patients when making gender decisions. We found in none of these regions brain activation significantly associated with reaction times and all significant differences between groups remained significant. Additionally, we also analyzed whether there was a correlation between brain response delay and task performance on the recognition task across groups. This analysis did not show a significant correlation either ($Z > 3.1$, corrected cluster significance threshold of $P = 0.05$, limited to regions with group differences).

Within the MCI group, we also analyzed whether response delay or recognition memory were associated with BOLD delay. There were no significant correlations.

Discussion

In occipital regions, MCI patients could be distinguished significantly better from controls and AD patients with a regressor of the early phase of the BOLD response than with the regressor of the late BOLD phase. Occipitally, the early phase BOLD response was significantly diminished in MCI patients compared to controls, and significantly increased when compared to AD. AD patients showed diminished early phase activation in widespread regions throughout the brain when compared to controls. This decreased early phase BOLD was not significantly associated with reaction times.

The results stress the importance of analyzing onset-time and time to peak of the BOLD signal in neurodegenerative diseases. We applied a model with different orthogonalized regressors, each specifying increasingly fast HRFs. A more common way to model the presence of earlier or later responses is to include the temporal derivative of the hemodynamic response function. Would a single standard hemodynamic response function have been used in the modeling of the data, neglecting possible early or late responses, we would have found no significant differences in BOLD signal between patients and controls. Excellent examples of empirical estimations of BOLD responses in regions of interest have been described previously (for example, Cohen and DuBois, 1999; Handwerker et al., 2004). These methods, when implemented voxelwise, or based on regions of interest, would also allow a statistical comparison between groups for different parameters (time to peak, time to onset, full width at half maximum). Future work may apply these methods to study parameter differences in dementia.

In the fMRI literature, little attention has been given to the effects of changes in the cerebrovascular system on the BOLD response. One study found evidence for decreased signal-to-noise ratio in the BOLD response in the motor cortex in healthy elderly (D'Esposito et al., 1999). Although neural activity was not directly assessed in that study, it was assumed not to be associated with age in that region, and it was concluded that the change in signal was due to altered neurovascular coupling. Others have shown intact BOLD responses in the motor cortex in aging and dementia, while the visual cortex showed a decreased signal (Buckner et al., 2000). This may be evidence for a *regional difference* in the alteration of neurovascular coupling with age and dementia. An alternative explanation would be a regional modulation of neuronal activity. The data presented in the current study may be consistent with both possible explanations. The diminished activity of neurotransmitters such as acetylcholine in AD, or the possible up-regulation of acetylcholine in MCI (Dekosky et al., 2002), may alter neurovascular coupling. The non-uniform cholinergic cortical innervations might cause regional variability in the modifications of neurovascular coupling. On the other hand, neuronal responses are also decreased and slower in AD as has been observed with evoked electrical responses (Ball et al., 1989; Olichney and Hillert, 2004; Polich and Herbst, 2000). Our data most likely reflect a combination of these two processes.

The decreased early phase BOLD response in MCI is restricted to the occipital cortex, whereas in AD this altered BOLD response is present in more widespread regions. This pattern may be consistent with the idea that MCI is a transitional state between healthy aging and dementia. The observed pattern of brain activation changes in MCI suggests that, in a context of visual encoding, the first and most significant changes in AD occur in the occipital cortex. This may appear as a remarkable finding since neurofibrillary pathology in AD has been postulated to follow a different sequence: from entorhinal cortex to hippocampus and MTL, then to temporoparietal regions, and in late stages of AD, most of the neocortex is affected (Smith, 2002a). However, pathologic damage and measures of metabolism, flow, and BOLD may not have the same association in each brain region. For example, it has been shown that pathologic damage in AD can be strongly associated with metabolic deficits in certain brain regions, while this association is lost in the temporal lobes (Mega et al., 1999). Second, if our method is sensitive to regional changes in neurovascular coupling or possibly to vascular pathology, we may not necessarily be sensitive to detecting alterations in regions known to have early neurofibrillary pathology. Third, the fMRI task we applied has

strongest activation (hence, highest signal-to-noise ratio) in the occipital cortex. Clearly, this increases the sensitivity in these regions to detect changes in the BOLD signal.

Although the early phase BOLD signal may have regionally different specific sensitivity to very early pathologic changes in the course of dementia (Fig. 2), it can not be concluded from our data that regional delays we found are specific to (early) AD. This would require these analyses to be applied to data of other neurodegenerative diseases as well.

It must be noted that the presence of a delayed occipital BOLD signal in MCI patients does not necessarily imply that this is an early marker of AD. Probably half of MCI patients will convert to AD in 3–5 years time (Petersen et al., 2001). Only clinical follow-up of the MCI group will show whether decreased early phase BOLD signal in MCI is associated with increased likelihood of conversion to AD. Current analysis, without clinical follow-up, showed that there were no correlations between task performance and early phase BOLD signal in the MCI group. However, task performance on the face encoding task probably is not a good predictor for AD conversion likelihood.

In conclusion, the described methods and results introduce new opportunities to understand changes in regional brain dynamics in MCI as a model for early AD, how they change during the disease course, and how well they may serve as an early marker of AD pathology in MCI. Furthermore, the described approach may be of value for functional neuroimaging studies examining the effects of neural change in general, such as clinical studies of aging, disease progression, and pharmacological intervention.

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