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Sensorimotor Network Rewiring in Mild Cognitive Impairment and Alzheimer's Disease

Federica Agosta,[1] Maria Assunta Rocca,[1] Elisabetta Pagani,[1] Martina Absinta,[1] Giuseppe Magnani,[2] Alessandra Marcone,[3] Monica Falautano,[2] Giancarlo Comi,[2] Maria Luisa Gorno-Tempini,[4] and Massimo Filippi[1]*

[1]*Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, Scientific Institute and University Hospital San Raffaele, Milan, Italy*
[2]*Department of Neurology, Institute of Experimental Neurology, Division of Neuroscience, Scientific Institute and University Hospital San Raffaele, Milan, Italy*
[3]*Division of Neurology, San Raffaele Turro Hospital, Milan, Italy*
[4]*Memory and Aging Center, Department of Neurology, University of California San Francisco, San Francisco*

Abstract: This study aimed at elucidating whether (a) brain areas associated with motor function show a change in functional magnetic resonance imaging (fMRI) signal in amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD), (b) such change is linear over the course of the disease, and (c) fMRI changes in aMCI and AD are driven by hippocampal atrophy, or, conversely, reflect a nonspecific neuronal network rewiring generically associated to brain tissue damage. FMRI during the performance of a simple motor task with the dominant right-hand, and structural MRI (i.e., dual-echo, 3D T1-weighted, and diffusion tensor [DT] MRI sequences) were acquired from 10 AD patients, 15 aMCI patients, and 11 healthy controls. During the simple-motor task, aMCI patients had decreased recruitment of the left (L) inferior frontal gyrus compared to controls, while they showed increased recruitment of L postcentral gyrus and head of L caudate nucleus, and decreased activation of the cingulum compared with AD patients. Effective connectivity was altered between primary sensorimotor cortices (SMC) in aMCI patients vs. controls, and between L SMC, head of L caudate nucleus, and cingulum in AD vs. aMCI patients. Altered fMRI activations and connections were correlated with the hippocampal atrophy in aMCI and with the overall GM microstructural damage in AD. Motor-associated functional cortical changes in aMCI and AD mirror fMRI changes of the cognitive network, suggesting the occurrence of a widespread brain rewiring with increasing structural damage rather than a specific response of cognitive network. *Hum Brain Mapp 31:515–525, 2010.*

Key words: Alzheimer's disease; mild cognitive impairment; functional magnetic resonance imaging; hippocampus; sensorimotor cortex; functional reorganization

*Correspondence to: Massimo Filippi, Neuroimaging Research Unit, Department of Neurology, Scientific Institute and University Hospital San Raffaele, Via Olgettina, 60, 20132 Milan, Italy.
E-mail: m.filippi@hsr.it

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INTRODUCTION

Alzheimer's disease (AD) is associated with a characteristic regional pattern of neuropathological changes as shown by the distribution of senile plaques, neurofibrillary tangles, and neuronal loss [Braak and Braak, 1991; Delacourte et al., 1999]. Amnestic mild cognitive impairment (aMCI) is generally considered a transitional stage between normal aging and clinically probable AD [Petersen et al., 2001]. MRI studies of aMCI demonstrated atrophy of the medial temporal lobe (MTL), including the hippocampus, entorhinal cortex, amygdala, and parahippocampal gyrus, which are even more pronounced in AD patients [Petersen et al., 2001].

Patients with aMCI and AD also experience functional changes of their brain cognitive networks, as revealed by several functional MRI (fMRI) studies [Sperling, 2007]. The majority of these studies focused on memory-related activations of the MTL or of regions that are functionally connected to the MTL [Celone et al., 2006; Dickerson et al., 2004, 2005; Golby et al., 2005; Hamalainen et al., 2007; Heun et al., 2007; Johnson et al., 2004, 2006; Kircher et al., 2007; Machulda et al., 2003; Pariente et al., 2005; Rombouts et al., 2000, 2005; Small et al., 1999; Sperling et al., 2003; Yetkin et al., 2006]. In patients with mild-to-moderate AD, decreased MTL activations have been found when subjects attempt to learn new information [Celone et al., 2006; Dickerson et al., 2005; Golby et al., 2005; Hamalainen et al., 2007; Machulda et al., 2003; Pariente et al., 2005; Rombouts et al., 2000; Small et al., 1999]. The pattern of functional MTL activations in aMCI seems to be more variable, ranging from decreased activations as those seen in AD [Johnson et al., 2004, 2006; Machulda et al., 2003; Small et al., 1999] to paradoxically increased activations, above the level which can be detected in healthy controls [Celone et al., 2006; Dickerson et al., 2004, 2005; Hamalainen et al., 2007; Heun et al., 2007; Kircher et al., 2007]. These findings are likely explained by the fact that aMCI subjects fall into different stages along the path between normal aging and AD. The levels of activations detected using fMRI of MTL regions during encoding strongly correlate with subjects' subsequent ability to remember the items encoded. As a consequence, it has been postulated that increased MTL activation during successful encoding in aMCI subjects with a relatively preserved performance in memory tasks may represent a compensatory response that contributes to the preservation of cognitive performance despite the accumulation of structural brain damage [Celone et al., 2006; Dickerson et al., 2004, 2005; Hamalainen et al., 2007; Heun et al., 2007; Kircher et al., 2007]. In this perspective, a nonlinear trajectory of memory-related fMRI activations over the course of prodromal AD that includes a phase of MTL hyperactivation in early stages, followed by a decreased MTL activation in later stages of aMCI and mild AD has been suggested [Celone et al., 2006]. It is not yet known, however, the nature of such functional changes: do they represent a specific disease-related phenomenon, mainly driven by MTL structural damage, or, conversely, do they reflect a nonspecific neuronal network rewiring generically associated to brain tissue loss? To address this question, we investigated the brain motor network, which is known to be relatively spared by AD pathology, and performed a structural and functional MRI study in aMCI and AD patients. Our main aim was to assess whether brain areas associated with motor function show a change in fMRI signal over the course of aMCI and AD, and if so, if such change is linear over the course of the disease. An additional aim was to investigate the relationship between motor-associated fMRI changes and structural damage to the hippocampus and the whole brain, measured by means of volumetry and diffusion tensor (DT) MRI metrics.

METHODS

Patients

From the Outpatient Dementia Clinics of our Institution, we recruited 15 right-handed subjects with aMCI and 12 right-handed subjects with probable AD, according to the MCI criteria [Petersen et al., 1999, 2001] and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRA) criteria [McKhann et al., 1984]. Eleven cognitively preserved healthy right-handed subjects served as controls. Handedness was established according to the 10-item version of the Edinburgh Handedness Inventory Scale [Oldfield, 1971]. Inclusion/exclusion criteria were: no major systemic, psychiatric, and other neurological illnesses, including cerebrovascular disorders; no clinical sensorimotor involvement (including gait disorders) or praxis deficit of the right-dominant upper limb. Patients who failed at the fine motor control assessment included in our bedside neurological evaluation (i.e., finger tapping and praxis to imitation test) and/or scored two standard deviations below the mean maximum finger tapping rate [MFTR] of healthy controls during the functional assessment (see below) were excluded. They should also be able to provide informed consent, as judged by an experienced neurologist with a decennial experience in assessing demented patients. All subjects underwent the Mini Mental State Examination (MMSE) [Folstein et al., 1975] and the Clinical Dementia Rating scale [Morris, 1993]. Local Ethical Committee approval and written informed consent from all subjects were obtained.

Functional Assessment

All subjects were tested before fMRI acquisition and only those who were able to perform the simple motor task at a 1-Hz frequency, for the entire duration of the task, without additional movements (i.e., mirror movements) were included. Motor functional assessment was performed using the MFTR [Herndon, 1997] observed for two 30-s trial periods. The mean frequency to the nearest 0.5 Hz was considered.

Experimental Design

A block design (ABAB), where eight periods of activation were alternated with eight periods of rest (with no break between blocks), was used. Each period of activation or rest included five measurements (block duration = 14 s). The subjects were scanned while performing a simple motor task consisting of repetitive flexion-extension of the last four fingers of the right hand. The task (i.e., both activation and rest periods) was paced by a metronome at a 1-Hz frequency; change from active to rest period was indicated by a vocal command. Subjects were trained before fMRI, instructed to keep their eyes closed during fMRI, and monitored visually during scanning by an operator inside the scanner room to ensure accurate task performance and to assess for additional movements. Two AD were excluded from the study for their inability to perform the task correctly. The task was performed equally well (in terms of movements performance and rate, and without additional movements) by all the remaining subjects.

fMRI Acquisition

On a 1.5 Tesla scanner (Vision, Siemens, Erlangen, Germany), fMRI was acquired using a T2*-weighted single-shot echo-planar imaging (EPI) sequence (echo-time [TE] = 60 ms, interscan interval = 2.8 s, flip angle = 90°, matrix size = 64 × 64 mm^2; 24 axial slices, thickness = 5 mm). Shimming was performed for the entire brain using an auto-shim routine.

Structural MRI Acquisition

The following additional sequences were obtained: dual-echo (DE) turbo spin echo (repetition time [TR]/TE = 3,300/16–98 ms, echo train length = 5; 24 contiguous axial slices, thickness = 5 mm; matrix = 256 × 256, field of view [FOV] = 250 × 250 mm^2); pulsed gradient SE (PGSE) EP (inter-echo spacing = 0.8, TE = 123 ms, 10 axial slices, thickness = 5 mm; matrix = 128 × 128; FOV = 250 × 250 mm^2, eight non-collinear directions, duration and maximum amplitude of the diffusion gradients = 25 ms and 21 m Tm^{-1}, maximum b factor in each direction = 1,044 s mm^{-2}); and sagittal 3D T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE) (TR/TE = 11.4/4.4 ms, flip angle = 15°, matrix size = 256 × 256, FOV = 256 × 256 mm^2, voxel size = 1 × 1 × 1 mm^3, slab thickness = 160 mm).

Structural MRI Postprocessing

White matter hyperintensities (WMHs) were identified on DE scans and lesion load measured [Rovaris et al., 1997]. Normalized volumes of the whole brain (NBV), global grey matter (GM), cortical GM, and white matter (WM) were measured using the MP-RAGE images and the SIENAx (Structural Imaging Evaluation of Normalized Atrophy) software [Smith et al., 2002]. Hippocampal volume was calculated from the MP-RAGE images using FIRST [Patenaude, 2007] within the FSL library (http://www.fmrib.ox.ac.uk/fsl/first/index.html). From diffusion-weighted images, the diffusion tensor (DT) was estimated using linear regression, and mean diffusivity (MD) and fractional anisotropy (FA) maps calculated [Pierpaoli et al., 1996]. After the erosion of the first-line outer voxels from the GM and WM maps, MD histograms of the GM and normal-appearing WM (NAWM) and FA histograms of the NAWM were produced as previously described [Ceccarelli et al., 2007].

fMRI Analysis

fMRI data were analyzed using SPM2. Functional EPI scans were realigned to the first image to correct for subject motion, spatially normalized into the standard space (EPI template), and smoothed using an 8-mm 3D-Gaussian filter. Changes in blood oxygenation level dependent (BOLD) contrast associated with the performance of the motor task were assessed on a pixel-by-pixel basis, using the General Linear Model [Friston et al., 1995] and the theory of Gaussian fields [Worsley and Friston, 1995]. Motion parameters from the realignment were included as regressors of noninterest at the first level analysis. Specific effects were tested by applying appropriate linear contrasts. Significant hemodynamic changes for each contrast were assessed using t statistical parametric maps (SPMt).

Statistical Analysis

An analysis of covariance (ANCOVA), adjusted for age, was used to compare clinical and structural MRI variables between groups. On the basis of available degrees of freedom and clinical relevance, the following two comparisons were decided a priori: aMCI patients vs. healthy controls, and AD vs. aMCI patients.

The intragroup fMRI activations and between-group comparisons were investigated using SPM2 and a random-effect analysis, with a one-sample t test or ANCOVA, as appropriate, including age, sex, MFTR, and NBV as nuisance covariates. Two statistical analyses were carried out. First, we performed a whole-brain analysis, in which we accepted a conservative level of significance of $P < 0.05$ (family wise error [FWE]) corrected for multiple comparisons. Then, the significance threshold for fMRI comparisons was set at $P < 0.001$, uncorrected for multiple comparisons. Since this less stringent threshold might have led to false positive results, only those areas that passed a small volume correction (SVC) for multiple comparisons (10-mm radius, and cut-off value for significance at $P < 0.05$) are reported. To assess the correlations of fMRI changes with clinical and structural MRI measures, the corresponding metrics were entered into the SPM design matrix, using basic models and linear regression analysis ($P < 0.001$, uncorrected).

TABLE I. Main demographic and clinical characteristics of healthy controls, patients with amnestic mild cognitive impairment (aMCI), and patients with Alzheimer's disease (AD)

	Healthy controls	aMCI patients	AD patients	*P**
Number of subjects	11	15	10	–
Men/Women	4/6	5/10	2/8	n.s.
Mean age (range) [years]	65.6 (54–77)	66.8 (41–79)	69.1 (52–84)	n.s.
Median disease duration (range) [years]	–	2.8 (0.5–5.0)	2.9 (1.0–5.0)	n.s.
Median MMSE (range)	28 (27–30)	27 (23–28)	17 (12–25)	<0.001**
Median CDR (range)	0.0 (0.0–0.0)	0.5 (0.5–0.5)	1.0 (1.0–2.0)	<0.001**
Mean maximum finger tapping frequency for 30-s trial (range)	1.6 (1.4–1.9)	1.6 (1.2–1.9)	1.5 (1.1–1.8)	n.s.

Abbreviations: aMCI = amnestic mild cognitive impairment; AD = Alzheimer's disease; MMSE = Mini Mental State Examination; CDR = Clinical Dementia Rating scale.
*Analysis of covariance (ANCOVA) between groups. See text for further details.
**Adjusted for age.

RESULTS

Demographic and Clinical Findings

Table I shows demographic and clinical characteristics of the three groups.

WMHs, Volumes, and Diffusivity Changes

Table II reports structural MRI metrics for each group. One or more WMHs were seen on the DE scans from four controls (36%), eight aMCI (53%), and all AD patients. A-MCI had significantly increased GM MD ($P = 0.03$), and decreased NAWM FA ($P = 0.04$) and hippocampal volumes (right [R]: $P = 0.01$; L: $P = 0.05$) vs. controls. AD had significantly decreased NBV ($P = 0.03$) vs. aMCI.

Movement-Associated fMRI Activations

In Figure 1, the activated areas in the three groups of subjects are shown ($P < 0.001$). Compared with controls, aMCI patients showed a decreased recruitment of the L IFG (SPM coordinates: −60, 8, 16, t value 3.58, Brodman area [BA] 44; $P < 0.05$, SVC) (see Fig. 2). Compared with AD patients, patients with aMCI showed an increased recruitment of the L postcentral gyrus (SPM coordinates: −54, −22, 34, t value 4.90, BA 2; $P < 0.05$, SVC) and the head of the L caudate nucleus (SPM coordinates: −20, −10, 24, t value 4.60; $P < 0.05$, SVC) (see Fig. 3). Conversely, AD patients had an increased recruitment of the cingulum compared with aMCI patients (SPM coordinates: 2, −26, 48, t value 3.81, BA 23; $P < 0.05$, SVC) (see Fig. 3). The whole-brain analysis with significance threshold at $P < 0.05$ did not demonstrate between-group fMRI changes.

Post-Hoc Analysis: Effective Connectivity of Brain Regions Activated During the Experimental Task

To evaluate the functional relationship between brain regions activated during the experimental task in controls

TABLE II. Structural MRI findings from healthy controls, patients with amnestic mild cognitive impairment (aMCI), and patients with Alzheimer's disease (AD)

	Healthy controls	aMCI patients	AD patients	*P**
WMHs load (SD) [ml]	3.52 (3.07)	6.16 (11.02)	4.64 (4.06)	n.s.
NBV (SD) [ml]	1,438 (91)	1,416 (99)	1,335 (54)	0.03
Normalized GM volume (SD) [ml]	747 (50)	699 (88)	656 (82)	0.05
Normalized cortical GM volume (SD) [ml]	571 (45)	530 (75)	483 (62)	0.02
Normalized WM volume (SD) [ml]	691 (59)	716 (56)	679 (84)	n.s.
R hippocampus volume (SD) [ml]	5.1 (0.03)	4.4 (0.04)	4.1 (0.07)	0.001
L hippocampus volume (SD) [ml]	5.1 (0.05)	4.5 (0.05)	4.2 (0.07)	0.01
GM average MD (SD) [$\times 10^{-3}$ mm^2 s^{-1}]	1.06 (0.09)	1.14 (0.12)	1.20 (0.11)	0.01
NAWM average MD (SD) [$\times 10^{-3}$ mm^2 s^{-1}]	0.83 (0.04)	0.87 (0.06)	0.91 (0.08)	0.03
NAWM average FA (SD)	0.30 (0.02)	0.28 (0.03)	0.26 (0.03)	0.02

Abbreviations: aMCI = amnestic mild cognitive impairment; AD = Alzheimer's disease; WMHs = white matter hyperintensities; SD = standard deviation; NBV = normalized brain volume; GM = grey matter; WM = white matter; R = right; L = left; MD = mean diffusivity; NAWM = normal-appearing white matter; FA = fractional anisotropy.
*Analysis of covariance (ANCOVA) between groups adjusted for age. See text for further details.

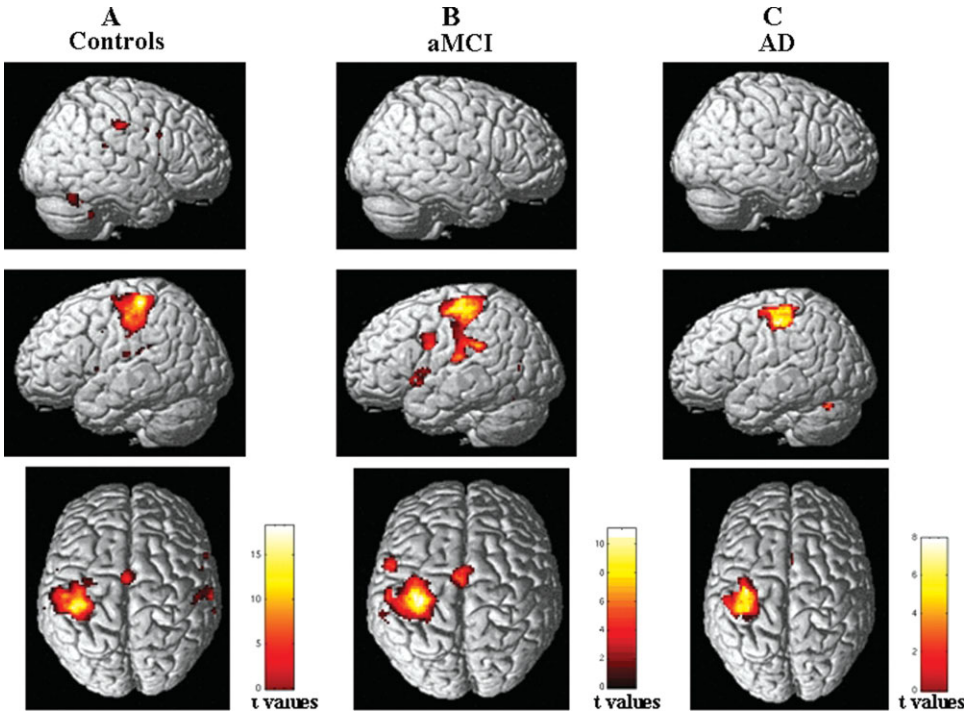

Figure 1.

Cortical activations on a rendered brain from healthy controls (**A**), patients with amnestic mild cognitive impairment (aMCI) (**B**), and patients with Alzheimer's disease (AD) (**C**) during the performance of a simple motor task with the right hand (within-group analysis; one-sample *t* test). Activated foci are shown with a significance threshold set at $P < 0.001$, uncorrected for multiple comparisons (color-coded *t* values). See text for further details.

and patients, effective connectivity (EC) was evaluated using a dynamic causal model (DCM) approach [Friston et al., 2003]. Thus, the model consisted of six areas, five (L primary sensorimotor cortex [SMC], supplementary motor area, L IFG, head of the L caudate nucleus, and cingulum) resulting from the previous analysis and one (R primary SMC) included due to its role in simple movement execution [Reddy et al., 2002; Rocca et al., 2002]. Time series,

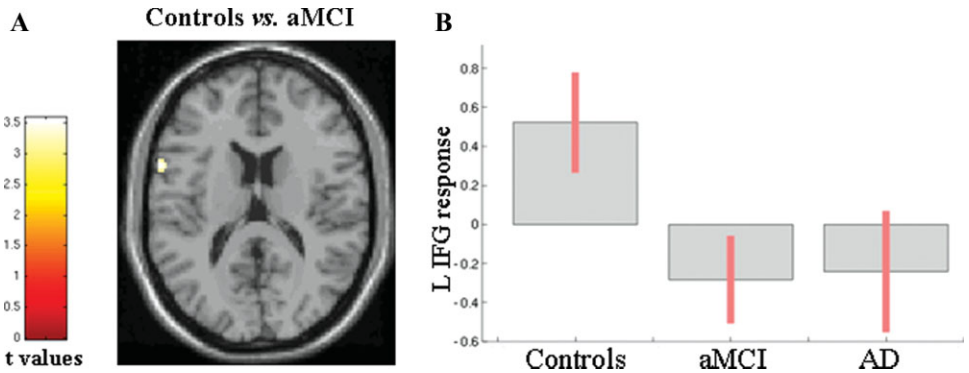

Figure 2.

Comparison between healthy controls and patients with amnestic mild cognitive impairment (aMCI) during the performance of a simple motor task with the right hand (random effect analysis, ANOVA, $P < 0.05$, after small volume correction). Compared with patients with aMCI, healthy controls showed an increased recruitment of the left inferior frontal gyrus (IFG) (**A**). The activation is shown on a high-resolution T1-weighted image in the standard SPM space. In **B**, signal plots detected in the three groups of subjects of the study (healthy controls, aMCI and Alzheimer's disease [AD] patients) in the previous region are shown.

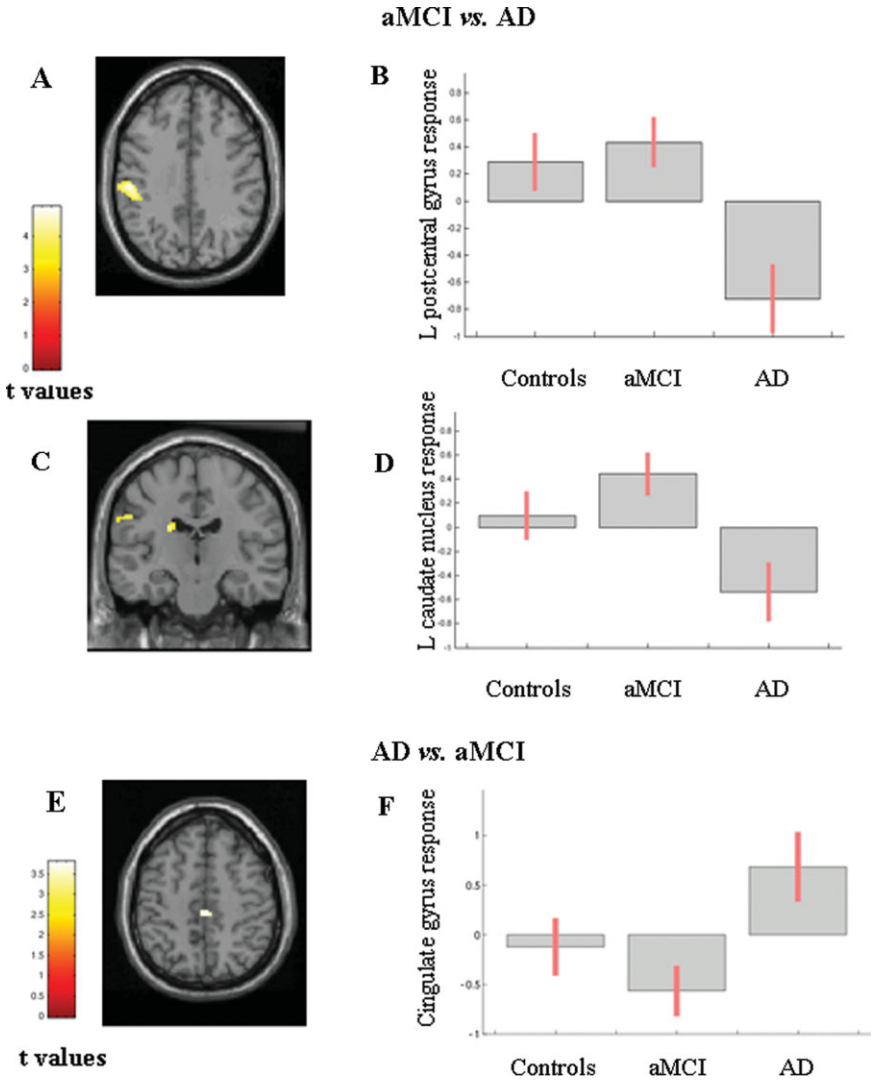

Figure 3.
Comparison between patients with amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD) during the performance of a simple motor task with the right hand (random effect analysis, ANOVA, $P < 0.05$, after small volume correction). Compared with AD, aMCI patients had an increased recruitment of the left postcentral gyrus (**A**) and the head of the left caudate nucleus (**C**). Compared with aMCI, AD patients had an increased recruitment of the cingulum (**E**). Foci of activations are shown on a high-resolution T1-weighted image in the standard SPM space. In **B**, **D**, and **F**, signal plots detected in the three groups of subjects of the study (healthy controls, aMCI and AD patients) in the previous regions are shown.

which were adjusted for the effect of interest, were extracted from a spherical volume (5-mm radius) centered at the most significant voxel within an a priori defined cluster in the SPMf maps (i.e., SPM maps thresholded using an F-contrast) in each subject. Volumes of interest were extracted from the clusters with the highest peak of activations in each region. We assumed that the effect of the task entered the network via the activation cluster of the L primary SMC. Our model comprised bidirectional connectivity between all regions extracted. The intrinsic connectivity strength coefficients were estimated using a Bayesian approach [Friston et al., 2003]. Between-group comparisons were assessed using an ANCOVA model, adjusted for subject's age. Table III and Figure 4 shows the results of the comparisons of path coefficient strengths in controls vs. aMCI and aMCI vs. AD. Only connections significantly different in at least one between-group comparison are reported. Compared to controls, aMCI had a reduced effective connectivity between R and L primary SMC ($P = 0.04$). Compared to aMCI, AD had reduced effective connectivity between: (a) L primary SMC and head of the L caudate and vice versa ($P = 0.04$); and (b) head of the L caudate and cingulum ($P = 0.03$). Compared with aMCI patients, they also showed increased effective connectivity between cingulum and L primary SMC ($P = 0.03$).

Correlations Between fMRI, Clinical, and Structural MRI Findings

In the entire group of patients, significant correlations were found between: (a) reduced connectivity between L primary SMC and head of the L caudate vs. hippocampal volume ($r = 0.50$, $P = 0.01$); (b) increased connectivity between cingulum and L primary SMC vs. disease

TABLE III. Significant paths coefficients (mean values) between brain regions of healthy controls, patients with amnestic mild cognitive impairment (aMCI), and patients with Alzheimer's disease (AD)

	Connection strength		
	Healthy controls	aMCI patients	AD patients
R primary SMC—L primary SMC	0.09	0.009*	0.05
L primary SMC—Head of L caudate nucleus	−0.06	−0.09	−0.2**
Head of L caudate nucleus—L primary SMC	−0.02	−0.03	−0.09**
Head of L caudate nucleus—Cingulum	−0.04	−0.009	−0.06**
Cingulum—L primary SMC	−0.004	0.01	0.09**

Abbreviations: L = left, R = right, SMC = sensorimotor cortex, aMCI = amnestic mild cognitive impairment; AD = Alzheimer's disease.
Only connections significantly different in at least one between-group comparison have been reported. Note that positive values have to be interpreted as direct coupling of activity between the two areas, while negative values have to be interpreted as an inverse coupling of activity.
*Significantly different between healthy controls and aMCI patients ($P < 0.05$).
**Significantly different between aMCI and AD patients ($P < 0.05$).

duration ($r = -0.41$, $P = 0.05$); (c) reduced connectivity between L primary SMC and head of the L caudate vs. increased connectivity between cingulum and L primary SMC ($r = -0.48$, $P = 0.02$). In aMCI, disease duration was correlated with the L postcentral gyrus activation ($r = -0.92$, $P < 0.05$), and hippocampal volume with the head of the L caudate activation ($r = -0.93$, $P < 0.001$). In AD, increased connectivity between cingulum and L primary SMC was correlated with GM average MD ($r = 0.71$, $P = 0.03$); and increased connectivity between cingulum and L primary SMC with the decreased connectivity between head of the L caudate and cingulum ($r = -0.93$, $P < 0.001$).

DISCUSSION

Several studies of the cognitive brain network in patients with aMCI and AD have demonstrated convincingly the presence of functional cortical changes which have been supposed to contribute, at least in the initial phase of the disease, to limit the clinical consequences of irreversible tissue damage. Compared to cognitively healthy older subjects, patients with AD have decreased cortical activations in the hippocampus and related structures within the MTL during the encoding of new memories [Celone et al., 2006; Dickerson et al., 2005; Golby et al., 2005; Hamalainen et al., 2007; Machulda et al., 2003; Pariente et al., 2005; Rombouts et al., 2000; Small et al., 1999]. fMRI studies of subjects at risk for AD, by virtue of their genetics or evidence of MCI, have yielded variable results; however, some of these studies suggest that there may be a phase of paradoxically increased activation early in the course of prodromal AD [Celone et al., 2006; Dickerson et al., 2004, 2005; Hamalainen et al., 2007; Heun et al., 2007; Kircher et al., 2007]. In this study, we assessed the sensorimotor network of these patients, with the ultimate aim to improve our understanding of the nature of the fMRI changes seen in the different stages of the disease.

The main finding of this study is that, in aMCI and AD without motor clinical impairment, fMRI changes occur also in the motor system, resembling those described for the cognitive network. We indeed found an increased activation of several regions of the sensorimotor network in

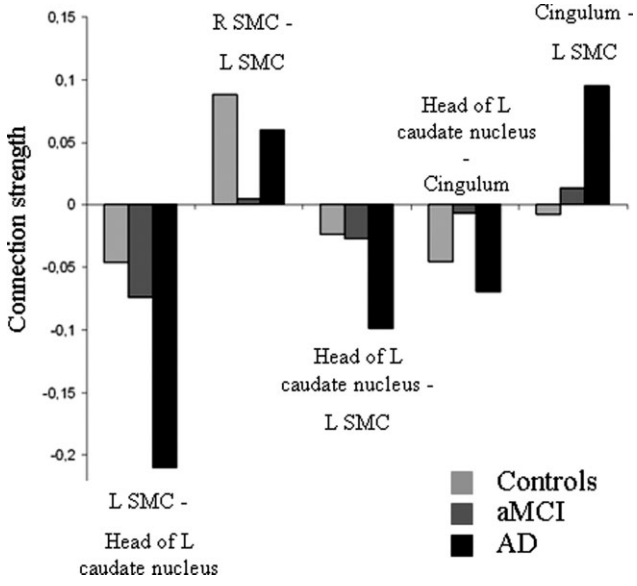

Figure 4.
Results of the between-group analysis of connectivity: histograms of path coefficients (mean values) which were significantly different at the between-group comparisons are shown in light grey for healthy controls, dark grey for amnestic mild cognitive impairment (aMCI) patients, and black for Alzheimer's disease (AD) patients.

aMCI compared to AD and, albeit more weakly, to healthy controls, including the postcentral gyrus and the caudate nucleus (as shown in Fig. 3). These two latter regions showed to be hypoactive in AD, who, conversely, had an increased activation of the cingulum, a structure which is supposed to have a central role in attention, motor modulation and response selection [Corbetta et al., 1991]. The increased activation of the postcentral gyrus in aMCI is not surprising. It is well-known that the parietal cortex, which has extensive connections with regions of the frontal lobes, where it sends rich sensory information for movement control, is involved in the elaboration of somatosensory inputs and in movement preparation and planning [Rizzolatti et al., 1997]. Motor-related increased activations of the postcentral gyrus have also been demonstrated with normal aging [Smith et al., 1999]. In addition, studies in patients with neurological diseases, including stroke [Pineiro et al., 2001] and multiple sclerosis [Reddy et al., 2000], described a posterior shift of the center of activation of the primary SMC toward the postcentral gyrus. The abnormal postcentral gyrus activation can therefore be interpreted as reflecting an enhanced somatosensory response in diseased patients relative to the normal control subjects.

To the best of our knowledge, the only fMRI study which investigated the movement-associated cortical changes in clinically demented patients showed a preservation of the characteristics of the hemodynamic response of the sensorimotor regions of demented vs. nondemented elderly [Buckner et al., 2000]. As a consequence, we do not believe that between-group differences in the hemodynamic response are likely to have influenced our results. More recently, Machulda et al. [2003] used a passive palm-brushing task to compare activations of the hand region between healthy controls, MCI and AD and found no between-group differences in the activity of this area. However, differences in fMRI task and methods of analysis, as well as in the clinical characteristics of the cohorts of patients studied, may contribute to explain these discrepant results. Therefore, our results suggest that some of the areas of the sensorimotor network, in particular the SMC and the head of the caudate, show a nonlinear trajectory of activation characterized by an initial phase of hyperactivation in aMCI, followed by a phase of hypoactivation in AD patients, similarly to what has been described when investigating memory-related task for MTL activation in these patients.

To elucidate the mechanisms for the fMRI changes observed, we assessed the effective connectivity of the brain regions shown to be differently activated between groups and the R SMC. The post-hoc analysis showed abnormalities of the brain connections in both aMCI and AD patients. In aMCI, we showed a reduced functional interaction between the contralateral and ipsilateral primary SMC. In addition, in AD compared with aMCI patients, we found a more widespread alteration of brain connections, which included an abnormal interaction between the L SMC and the head of the L caudate nucleus, between the head of the L caudate nucleus and the cingulum, and between the cingulum and the L SMC. This latter change is of particular interest, since previous studies of memory-related and resting state networks convincingly showed an impairment of deactivation of several areas that are part of the so-called default mode network (DMN) [Raichle et al., 2001], including the cingulum, in both MCI [Rombouts et al., 2005; Sorg et al., 2007] and AD [Celone et al., 2006; Greicius et al., 2004]. Similarly to the behavior described for MTL activation during memory tasks, such an impairment of deactivations has been supposed to follow a nonlinear trajectory from aMCI to AD [Rombouts et al., 2005], and this might contribute to explain the increased activation of the cingulum we found in AD in comparison to aMCI. It should be noted that deactivation of the cingulum, as part of the DMN, is thought to represent a normal way for efficient reallocation of neurocognitive resources during externally directed, attention-demanding, goal-oriented tasks [Raichle et al., 2001]. Nevertheless, it should be kept in mind that there is an intrinsic limitation related to the DCM, because such an analysis necessarily assesses the connectivity of brain regions activated consistently during the experimental task in both controls and patients [Friston et al., 2003]. As a consequence, interpretation of DCM findings only pertains to those regions and connections that are selected in the model. However, additional regions may influence the performance of a motor network during the simple motor task, such as those located in anterior frontal lobe. Hence, it remains possible that the altered connectivity reported here is mediated through polysynaptic circuits not included in the model.

Based on these considerations, it is tempting to speculate that fMRI changes observed in aMCI and AD during performance of active tasks might reflect a more general impairment of brain network function, which might be characterized by an initial phase of over-activation of areas selectively devoted to the performance of the investigated task, observed in aMCI, and by the exhaustion of the functional properties of these areas later on in AD. In this latter stage of the disease, the increased recruitment of areas with a higher-order function in the performance of the investigated task may reflect progressively impaired deactivation mechanisms.

In an attempt to define the possible pathological substrates of sensorimotor network dysfunction in aMCI and AD, we also evaluated the correlation between the observed fMRI changes and structural MRI measures of tissue damage. In line with previous studies, whole brain volume [Falini et al., 2005; Karas et al., 2004] as well as DT MRI metrics of NAWM and GM damage [Bozzali et al., 2002; Medina et al., 2006] showed a progressive worsening from aMCI to AD, even if only a few of the a priori comparisons reached statistical significance in this relatively small cohort. In concert, the results from global measurements support the notion that aMCI is a transitional phase

which lies halfway between AD and healthy subjects. Since several pathological [Braak and Braak, 1991] and imaging [Bozzali et al., 2006; Chetelat et al., 2002; Karas et al., 2004] studies have supported the theory of a hierarchical distribution of AD pathology, characterized by an initial involvement of the MTL and the subsequent spreading to cortical association areas [Braak and Braak, 1991], we also quantified the volume of the hippocampus in the different groups of subjects. Consistent with previous studies [Bozzali et al., 2006; Karas et al., 2004], this analysis demonstrated reduction of the hippocampal volume bilaterally in aMCI compared with controls. Interestingly, as previously reported [Chetelat et al., 2002], there was no significant reduction of hippocampal volume in AD patients compared to those with aMCI. The limited progression of hippocampal pathology in the transition to AD [Braak and Braak, 1991] is likely to play a role for this lack of additional volume loss in AD.

The analysis of correlation also supports the notion that damage to the hippocampus might drive the fMRI changes in the sensorimotor cortices in the early stage of the disease. In aMCI, a strong correlation was found between increased activation of the head of the L caudate and hippocampal volume loss. It is worth noting that in these patients a strong inverse correlation was also found between disease duration and relative activation of the L postcentral gyrus, suggesting that an overactivation of selected areas of the sensorimotor network might be one of the mechanisms with a potential adaptive role early in the course of the disease. On the other hand, in AD patients no correlation was found between regional damage in the hippocampus and fMRI metrics. Conversely, measures of abnormal effective connectivity were significantly correlated with overall GM damage. There are two possible, albeit not mutually exclusive, explanations for such finding. First, there was less hippocampal volume loss to correlate with brain activation in AD patients. This possibility is, however, unlikely given the fact that we found similar hippocampal volume in the two diseased patient groups. Second, in the more advanced stages of the disease, overall rather than regional GM damage may contribute to the progressive failure of mechanisms of brain reorganization.

Previous studies showed the functional correlates of AD pathology within the MTL and the DMN. Our study not only provides additional support for the hypothesis of a nonlinear trajectory of fMRI activations over the course of AD, but it also sheds light into the nature of such abnormalities: while in the early phase of the disease the increased recruitment of the cortex seems to be driven by the loss of hippocampal volume, in patients with overt dementia it is likely the consequence of nonspecific neuronal network rewiring, generically associated to brain tissue damage. Further studies, possibly in larger cohorts of MCI patients, are now warranted to elucidate whether these phenomena represent a compensatory process (i.e., increased neuronal recruitment) in the setting of early pathology, associated biochemical alterations (i.e., upregulation of choline acetyltransferase activity), or a direct result of the pathophysiological process of AD (i.e., aberrant axonal sprouting).

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REFERENCES

Bozzali M, Falini A, Franceschi M, Cercignani M, Zuffi M, Scotti G, Comi G, Filippi M (2002): White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. J Neurol Neurosurg Psychiatry 72:742–746.

Bozzali M, Filippi M, Magnani G, Cercignani M, Franceschi M, Schiatti E, Castiglioni S, Mossini R, Falautano M, Scotti G, Comi G, Falini A (2006): The contribution of voxel-based morphometry in staging patients with mild cognitive impairment. Neurology 67:453–460.

Braak H, Braak E (1991): Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82:239–259.

Buckner RL, Snyder AZ, Sanders AL, Raichle ME, Morris JC (2000): Functional brain imaging of young, nondemented, and demented older adults. J Cogn Neurosci 12 (Suppl 2):24–34.

Ceccarelli A, Rocca MA, Falini A, Tortorella P, Pagani E, Rodegher M, Comi G, Scotti G, Filippi M (2007): Normal-appearing white and grey matter damage in MS. A volumetric and diffusion tensor MRI study at 3.0 Tesla. J Neurol 254:513–518.

Celone KA, Calhoun VD, Dickerson BC, Atri A, Chua EF, Miller SL, DePeau K, Rentz DM, Selkoe DJ, Blacker D, Albert MS, Sperling RA (2006): Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: An independent component analysis. J Neurosci 26:10222–10231.

Chetelat G, Desgranges B, De La Sayette V, Viader F, Eustache F, Baron JC (2002): Mapping gray matter loss with voxel-based morphometry in mild cognitive impairment. Neuroreport 13: 1939–1943.

Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE (1991): Selective and divided attention during visual discriminations of shape, color, and speed: Functional anatomy by positron emission tomography. J Neurosci 11:2383–2402.

Delacourte A, David JP, Sergeant N, Buee L, Wattez A, Vermersch P, Ghozali F, Fallet-Bianco C, Pasquier F, Lebert F, Petit H, Di Menza C (1999): The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 52: 1158–1165.

Dickerson BC, Salat DH, Bates JF, Atiya M, Killiany RJ, Greve DN, Dale AM, Stern CE, Blacker D, Albert MS, Sperling RA (2004): Medial temporal lobe function and structure in mild cognitive impairment. Ann Neurol 56:27–35.

Dickerson BC, Salat DH, Greve DN, Chua EF, Rand-Giovannetti E, Rentz DM, Bertram L, Mullin K, Tanzi RE, Blacker D, Albert MS, Sperling RA (2005): Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. Neurology 65:404–411.

Falini A, Bozzali M, Magnani G, Pero G, Gambini A, Benedetti B, Mossini R, Franceschi M, Comi G, Scotti G, Filippi M (2005): A whole brain MR spectroscopy study from patients with Alzheimer's disease and mild cognitive impairment. NeuroImage 26: 1159–1163.

Folstein MF, Folstein SE, McHugh PR (1975): "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198.

Friston KJ, Holmes AP, Poline JB, Grasby PJ, Williams SC, Frackowiak RS, Turner R (1995): Analysis of fMRI time-series revisited. NeuroImage 2:45–53.

Friston KJ, Harrison L, Penny W (2003): Dynamic causal modelling. NeuroImage 19:1273–1302.

Golby A, Silverberg G, Race E, Gabrieli S, O'shea J, Knierim K, Stebbins G, Gabrieli J (2005): Memory encoding in Alzheimer's disease: An fMRI study of explicit and implicit memory. Brain 128:773–787.

Greicius MD, Srivastava G, Reiss AL, Menon V (2004): Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. Proc Natl Acad Sci USA 101:4637–4642.

Hamalainen A, Pihlajamaki M, Tanila H, Hanninen T, Niskanen E, Tervo S, Karjalainen PA, Vanninen RL, Soininen H (2007): Increased fMRI responses during encoding in mild cognitive impairment. Neurobiol Aging 28:1889–1903.

Herndon RM (1997): Handbook of Neurologic Rating Scales. New York: Demos Vermande.

Heun R, Freymann K, Erb M, Leube DT, Jessen F, Kircher TT, Grodd W (2007): Mild cognitive impairment (MCI) and actual retrieval performance affect cerebral activation in the elderly. Neurobiol Aging 28:404–413.

Johnson SC, Baxter LC, Susskind-Wilder L, Connor DJ, Sabbagh MN, Caselli RJ (2004): Hippocampal adaptation to face repetition in healthy elderly and mild cognitive impairment. Neuropsychologia 42:980–989.

Johnson SC, Schmitz TW, Moritz CH, Meyerand ME, Rowley HA, Alexander AL, Hansen KW, Gleason CE, Carlsson CM, Ries ML, Asthana S, Chen K, Reiman EM, Alexander GE (2006): Activation of brain regions vulnerable to Alzheimer's disease: The effect of mild cognitive impairment. Neurobiol Aging 27: 1604–1612.

Karas GB, Scheltens P, Rombouts SA, Visser PJ, van Schijndel RA, Fox NC, Barkhof F (2004): Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. NeuroImage 23:708–716.

Kircher TT, Weis S, Freymann K, Erb M, Jessen F, Grodd W, Heun R, Leube DT (2007): Hippocampal activation in patients with mild cognitive impairment is necessary for successful memory encoding. J Neurol Neurosurg Psychiatry 78:812–818.

Machulda MM, Ward HA, Borowski B, Gunter JL, Cha RH, O'Brien PC, Petersen RC, Boeve BF, Knopman D, Tang-Wai DF, Ivnik RG, Smith GE, Tangalos EG, Jack CR Jr (2003): Comparison of memory fMRI response among normal, MCI, and Alzheimer's patients. Neurology 61:500–506.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984): Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34:939–944.

Medina D, DeToledo-Morrell L, Urresta F, Gabrieli JD, Moseley M, Fleischman D, Bennett DA, Leurgans S, Turner DA, Stebbins GT (2006): White matter changes in mild cognitive impairment and AD: A diffusion tensor imaging study. Neurobiol Aging 27:663–672.

Morris JC (1993): The clinical dementia rating (CDR): Current version and scoring rules. Neurology 43:2412–2414.

Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9:97–113.

Pariente J, Cole S, Henson R, Clare L, Kennedy A, Rossor M, Cipoloti L, Puel M, Demonet JF, Chollet F, Frackowiak RS (2005): Alzheimer's patients engage an alternative network during a memory task. Ann Neurol 58:870–879.

Patenaude B, Smith S, Kennedy D, Jenkinson M (2007): FIRST—FMRIB's integrated registration and segmentation tool. In: Thirteen Annual Meeting of the Orgainzation for Human Brain Mapping.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999): Mild cognitive impairment: Clinical characterization and outcome. Arch Neurol 56:303–308.

Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B (2001): Current concepts in mild cognitive impairment. Arch Neurol 58:1985–1992.

Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G (1996): Diffusion tensor MR imaging of the human brain. Radiology 201:637–648.

Pineiro R, Pendlebury S, Johansen-Berg H, Matthews PM (2001): Functional MRI detects posterior shifts in primary sensorimotor cortex activation after stroke: Evidence of local adaptive reorganization? Stroke 32:1134–1139.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001): A default mode of brain function. Proc Natl Acad Sci USA 98:676–682.

Reddy H, Narayanan S, Arnoutelis R, Jenkinson M, Antel J, Matthews PM, Arnold DL (2000): Evidence for adaptive functional changes in the cerebral cortex with axonal injury from multiple sclerosis. Brain 123:2314–2320.

Reddy H, Narayanan S, Woolrich M, Mitsumori T, Lapierre Y, Arnold DL, Matthews PM (2002): Functional brain reorganization for hand movement in patients with multiple sclerosis: Defining distinct effects of injury and disability. Brain 125: 2646–2657.

Rizzolatti G, Fogassi L, Gallese V (1997): Parietal cortex: From sight to action. Curr Opin Neurobiol 7:562–567.

Rocca MA, Falini A, Colombo B, Scotti G, Comi G, Filippi M (2002): Adaptive functional changes in the cerebral cortex of patients with nondisabling multiple sclerosis correlate with the extent of brain structural damage. Ann Neurol 51:330–339.

Rombouts SA, Barkhof F, Veltman DJ, Machielsen WC, Witter MP, Bierlaagh MA, Lazeron RH, Valk J, Scheltens P (2000): Functional MR imaging in Alzheimer's disease during memory encoding. AJNR Am J Neuroradiol 21:1869–1875.

Rombouts SA, Goekoop R, Stam CJ, Barkhof F, Scheltens P (2005): Delayed rather than decreased BOLD response as a marker for early Alzheimer's disease. NeuroImage 26:1078–1085.

Rovaris M, Filippi M, Calori G, Rodegher M, Campi A, Colombo B, Comi G (1997): Intra-observer reproducibility in measuring new putative MR markers of demyelination and axonal loss in multiple sclerosis: A comparison with conventional T2-weighted images. J Neurol 244:266–270.

Small SA, Perera GM, DeLaPaz R, Mayeux R, Stern Y (1999): Differential regional dysfunction of the hippocampal formation among elderly with memory decline and Alzheimer's disease. Ann Neurol 45:466–472.

Smith CD, Umberger GH, Manning EL, Slevin JT, Wekstein DR, Schmitt FA, Markesbery WR, Zhang Z, Gerhardt GA, Kryscio RJ, Gash DM (1999): Critical decline in fine motor hand movements in human aging. Neurology 53:1458–1461.

Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, De Stefano N (2002): Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. NeuroImage 17:479–489.

Sorg C, Riedl V, Muhlau M, Calhoun VD, Eichele T, Laer L, Drzezga A, Forstl H, Kurz A, Zimmer C, Wohlschläger AM (2007): Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proc Natl Acad Sci USA 104:18760–18765.

Sperling R (2007): Functional MRI studies of associative encoding in normal aging, mild cognitive impairment, and Alzheimer's disease. Ann N Y Acad Sci 1097:146–155.

Sperling RA, Bates JF, Chua EF, Cocchiarella AJ, Rentz DM, Rosen BR, Schacter DL, Albert MS (2003): fMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. J Neurol Neurosurg Psychiatry 74:44–50.

Worsley KJ, Friston KJ (1995): Analysis of fMRI time-series revisited—Again. NeuroImage 2:173–181.

Yetkin FZ, Rosenberg RN, Weiner MF, Purdy PD, Cullum CM (2006): FMRI of working memory in patients with mild cognitive impairment and probable Alzheimer's disease. Eur Radiol 16:193–206.