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Executive Dysfunction in Mild Cognitive Impairment is Associated with Changes in Frontal and Cingulate White Matter Tracts

Ramune Grambaite[a,b,*], Per Selnes[a,b], Ivar Reinvang[c], Dag Aarsland[b,d], Erik Hessen[a], Leif Gjerstad[e] and Tormod Fladby[a,b]
[a]*Department of Neurology, Akershus University Hospital, Lørenskog, Norway*
[b]*Faculty Division Akershus University Hospital, University of Oslo, Oslo, Norway*
[c]*Center for the Study of Human Cognition, Department of Psychology, University of Oslo, Oslo, Norway*
[d]*Centre for Age-Related Medicine, Psychiatry Clinic, Stavanger University Hospital, Stavanger, Norway*
[e]*Department of Neurology, Oslo University Hospital Rikshospitalet, Oslo, Norway*

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Abstract. Mild cognitive impairment (MCI) may affect multiple neuropsychological domains. While amnestic MCI is associated with Alzheimer's disease, patterns of brain pathology in non-amnestic subtypes have been less studied. Twenty-three patients with attention/executive MCI (a/e MCI), seen at a university-based memory clinic, and 23 normal controls, matched according to age, gender, and education, were included in this study. All subjects were assessed with a neuropsychological test battery, including tests of memory, attention and executive function, and underwent magnetic resonance imaging. Diffusion tensor imaging derived white matter (WM) tract radial and mean diffusivity (DR and MD) were assessed using Tract-Based Spatial Statistics, and cortical thickness (CTH) was assessed using FreeSurfer. This study investigated changes of WM DR/MD and CTH in subjects with a/e MCI, and associations between these changes and different a/e subfunctions. WM DR/MD underlying rostral middle frontal, medial orbitofrontal, caudal anterior cingulate, posterior cingulate, retrosplenial and entorhinal cortices was higher for the a/e MCI than the control group, but CTH was not different from controls in any of the regions. WM DR/MD underlying superior frontal, rostral middle frontal, lateral/medial orbitofrontal and retrosplenial cortices were significantly associated with inhibition/switching performance, while caudal middle frontal CTH was significantly associated with attention and divided attention in the patient group. We conclude that increased WM DR/MD in frontal and cingulate regions and cortical thinning in caudal middle frontal region are both associated with executive dysfunction in MCI.

Keywords: Alzheimer's disease, cortical thickness, diffusion tensor imaging, mild cognitive impairment, radial and mean diffusivity, white matter

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INTRODUCTION

Mild cognitive impairment (MCI) is a heterogenous condition, encompassing among others pre-dementia Alzheimer's disease (AD) [1]. When amnestic MCI is thoroughly assessed, impairment in non memory

*Correspondence to: Ramune Grambaite, Department of Neurology, Akershus University Hospital, Sykehusveien 25, NO-1478 Lørenskog, Norway. Tel.: +47 67968462; Fax: +47 67909130; E-mail: ramuneg@psykologi.uio.no.

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domains, such as attentional [2], executive [3], language [3], visuoperceptual [4], and visuospatial [5], may be detected in many MCI subjects. For pre-dementia AD, the dominating view is that attention and executive (a/e) functions become impaired as the disease progresses from an initial amnestic stage [6]. A subgroup of MCI with predominant a/e deficits (a/e MCI) and a relatively preserved memory has been identified [7–9]. Only sparse longitudinal data has been published, motivating further studies of these patients to uncover whether they can be characterized as a clinical entity with a specific pathophysiology less likely to progress to AD dementia or a separate pre-dementia AD phenotype [7, 9].

Features associated with attention deficits are distractibility and impaired ability for focused behavior. Executive deficits are associated with disturbances of the mental activity involved in planning, initiation, and regulation of behavior [10]. Operational definitions of a/e functions have not been finally established, and this renders testing in clinical practice a challenging task [11]. Executive functions control and monitor task performance and depend critically on the frontal lobes, whereas instruments for testing of executive functions contain a wide range of stimuli that tap into various brain regions. Three fronto-subcortical circuits (originating in the prefrontal cortex) have been identified as responsible for executive control functions; i.e., the dorsolateral prefrontal cortex (working memory), the lateral orbital cortex (inhibition), and the anterior cingulate cortex (response conflict) [12, 13].

MCI patients can be discriminated from controls through neuropsychological assessment of a/e functions [14] and neuroimaging assessments; i.e., measurement of cortical thickness (CTH), which is a reliable indicator of cortical atrophy, and diffusion tensor imaging (DTI) which can be used for analysis of white matter (WM) integrity (i.e., structural integrity of the axonal bundles beneath the cortex) [15]. Neuropathological studies have shown that axonal pathology is strongly associated with cognitive impairment [16], and experimental studies also suggest that axonal integrity is extremely sensitive to factors promoting neurodegeneration [17]. MCI patients may have cortical thinning (low CTH) and increased WM diffusivity in frontal and temporal regions [15]. While neuropathology in patients with amnestic MCI typically involves medial temporal lobe structures [18], PIB-PET shows amyloid deposition in frontal lobes [19]. Some studies have reported an association between prefrontal cortical changes and a/e impairment in MCI [7, 11, 20], and in patients with isolated executive impairment neurofibrillary degeneration has been proposed to occur earlier in cingulate regions than in the frontal lobe [21]. MCI patients may have WM changes in both anterior [22] and posterior [23] cingulate regions. The anterior cingulate region is regarded to belong to a network responsible for executive control function and the posterior cingulate to a memory network [24].

Previously, we have found that DTI WM radial (DR) and mean (MD) diffusivity (but not fractional anisotropy) underlying the entorhinal cortex were higher in an amnestic MCI group than in an MCI group with less advanced cognitive impairment and that these changes explained unique variance in memory that could not be explained by secondary effects of cortical thinning [25]. To our knowledge DTI has not been used to characterize executive networks in a/e MCI. The aims of this study were to describe a/e MCI patients with respect to changes in CTH and WM DR/MD, and to identify measures of a/e functions associated with these changes. Two hypotheses were tested: 1) WM DR/MD is higher in the frontal and cingulate regions in the a/e MCI than the control group and group differences are more pronounced for WM DR/MD than for CTH. 2) Changes in a/e subfunctions are associated with changes in frontal and cingulate regions in the a/e MCI group.

MATERIALS AND METHODS

Eligibility and subject selection criteria

The project was approved by the South-Eastern Norway committee for medical research ethics. Participants' consent was obtained according to the Declaration of Helsinki.

Eligibility for study inclusion was assessed for subjects who were admitted to a university-based memory clinic in the period January 2007-January 2010 because of subjective cognitive complaints of at least six months duration. Inclusion criteria were absence of dementia; i.e., preserved general intellectual function and very mild or no problems with activities of daily living, and Global Deterioration Scale [26, 27] (GDS) score 2 and 3 as determined from a clinical interview and screening tests. The screening tests and GDS classification procedure are described elsewhere [28]. All patients underwent a neurological examination, and symptoms or signs of neurological disorders other than MCI led to exclusion. Other exclusion criteria included psychiatric disease, cancer, drug abuse, solvent exposure or anoxic brain damage. a/e MCI was further

defined on the basis of neuropsychological tests, as described in the next section. Spouses of participating patients were included as controls. They had no subjective cognitive impairment, and a GDS score of 1 was confirmed in a clinical interview [27]. Control subjects were selected manually to match the a/e MCI group as closely as possible with respect to age, gender, and education. In total, 23 a/e MCI and 23 control subjects were included.

Neuropsychological assessment

Neuropsychological examinations were performed within three months of the MRI scan date. All tests were administered in Norwegian language. For assessment of *general cognitive ability*, Vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence (WASI) [29] and Matrix reasoning subtest from Wechsler Adult Intelligence Scale - Third Edition (WAIS-III) [30] were used. The *memory* tests included Logical Memory Subtest from the Wechsler Memory Scale – Revised (WMS-R) [31], the Rey Auditory Verbal Learning Test (RAVLT) [32] and visual reproduction from the Rey Complex Figure Test (RCFT) [33]. Boston Naming Test (BNT) [34] was used to assess *language* function and RCFT copy trial was used to assess *visuospatial* function.

The procedure for selection of patients with a/e MCI was based on selected test results and included two measures of *attention*, i.e., scores from the Trail Making Test A (TMT-A) [35] and the Digit Symbol-Coding subtest of the WAIS-III [30], and five measures of *executive* subfunctions: divided attention (TMT-B [35]), working memory (Letter-Number Sequencing subtest [30]), verbal fluency (COWAT-FAS [the Controlled Oral Word Association Test] [35]), response inhibition (CWIT [Color-Word Interference Test from Delis-Kaplan Executive Function System] [36] condition 3) and response inhibition/switching (CWIT condition 4). *Time to complete* was the variable of interest for TMT and CWIT, and *number correct* was the variable of interest for the remaining attention/executive tests. To be classified as a/e MCI, a patient had to be impaired, i.e., to score $\geq$1.3 standard deviations (SD) below the mean for the normative sample (based on norms for the tests), on at least two of seven measures of a/e functions. The proportions of a/e MCI patients with impairment on each a/e measure were: 70% (Digit Symbol-Coding subtest), 52% (TMT-A), 30% (TMT-B), 48% (Letter-Number Sequencing subtest), 43% (COWAT), 43% (CWIT condition 3) and 35% (CWIT condition 4). None of the patients satisfied the criteria for amnestic MCI as defined in our previous study [25]. Patients who were impaired on other non-memory domains, in addition to a/e impairment, were not excluded. There were 11 patients (48%) with isolated a/e deficits; 39% of a/e MCI patients had visuospatial deficit (RCFT copy trial), 9% were impaired on language test (BNT) and 1 patient (4%) had both visuospatial and language deficit. The same neuropsychological measures, except for the Digit Symbol-Coding subtest, RCFT, Logical Memory subtest and measures of general cognitive ability, were available for controls.

MRI/DTI acquisition and regions of interest

All MRI scans were obtained from a Siemens Espree 1.5 T. Sequences were: one 3D MP-RAGE, T1-weighted sequence (TR/TE/TI/FA = 2400/3.65/1000/8°, matrix = 240 × 192), 160 sagittal slices, thickness = 1.2 mm, in-plane resolution of 1 mm × 1.2 mm. The pulse sequences for DTI were: $b = 750$; 12 directions repeated 5 times; 5 b0-values per slice, TR = 6100 ms, TE = 117 ms, number of slices: 30, slice thickness: 3 mm (gap 1.9 mm), in-plane resolution: 1.2 × 1.2 mm2, bandwidth: 840 Hz/pixel.

Regional CTH and WM DR/MD values were extracted from the following ROIs and the WM immediately underlying them (with a 5 mm limit) (all illustrated in Figs. 2 and 3): superior frontal, rostral middle frontal, caudal middle frontal, lateral orbitofrontal, medial orbitofrontal, rostral anterior cingulate (AC), caudal AC, posterior cingulate, retrosplenial (isthmus cingulate) and entorhinal cortices [37], averaged across hemispheres. The retrosplenial/posterior cingulate and entorhinal ROIs were included, as these regions are affected in early AD [24, 38] and the frontal and AC regions were included because of expected correlations with executive function [12].

MRI segmentations and analyses

Morphometric and DTI data were processed by one physician (P.S.). Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite version 4.5.0 (http://surfer.nmr.mgh.harvard.edu/). This includes segmentation of the subcortical WM and deep gray matter volumetric structures [39] and parcellation of the cortical surface [40] according to a parcellation scheme [41]. This labels cortical sulci and gyri, and thickness values are calculated in the ROIs.

DTI data were processed using FSL version 4.1 [42]. Initially, an affine registration was done for each DTI volume to the low-b ($b = 0$) image using FLIRT [43]. Motion between scans and residual eddy-currents were corrected for, before FA and eigenvalue maps were created. DR was defined as the mean of the second and third eigenvalues ($[\lambda_2 + \lambda_3]/2$). MD was defined as the mean of three eigenvalues ($[\lambda_1 + \lambda_2 + \lambda_3]/3$). FA images were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using BET [44]. Further processing of FA, DR and MD data was carried out using TBSS (Tract-Based Spatial Statistics) version 1.2 [45], part of FSL. All subjects' FA data were aligned into a common space using the nonlinear registration tool FNIRT [46] which uses a b-spline representation of the registration warp field [47]. Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to all subjects in the group. Each subject's aligned FA data were projected onto this skeleton. DR/MD data were extracted from each subject according to the skeletonized FA map.

The FreeSurfer parcellation algorithm was employed to assess predilection sites for WM tract changes. WM ROIs based on the FreeSurfer WM parcellations were then extracted for DR/MD: The FSL FMRIB58_FA template (to which every subjects FA volume initially was registered) was coregistered to the standard space T1 volume MNI152, which subsequently went through the FreeSurfer processing stream to create a volume with WM parcellations. By applying the registration between the FA template and the MNI152 volume to the volume with the WM parcellations, the resulting volume could be used to extract the skeletonized DR/MD data from each WM ROI [48].

Statistical analysis

Randomise (part of FSL) was used to estimate whole-brain voxelwise differences between the two groups of subjects. Multiple comparisons were corrected for using threshold-free cluster enhancement. The Statistical Package for Social Sciences (SPSS 16.0) was used for the remaining statistical analyses. The Chi-Square test and the Student's t-test were used for comparison of demographic and neuropsychological data; the latter was also used for analysis of group differences with regard to WM DR/MD and CTH. Raw scores of the imaging and neuropsychological variables were regressed on age and sex, and the standardized residuals were used in all analyses, except for the comparison of neuropsychological data (provided in Table1). Pearson's correlation method was used to test for associations between imaging and a/e variables. For each ROI, Bonferroni correction was used to adjust for multiple testing; p-values were corrected for the number of a/e variables. The term "significant", used in this article, refer to p values < 0.05.

Table 1
Demographic and neuropsychological data by group

	a/e MCI $n = 23$	*Controls* $n = 23$	*P*
Age (SD), y	61.3 (7.5)	63.2 (8.0)	0.416
Education (SD), y	12.3 (2.6)	12.1 (2.5)	0.777
Male, n (%)	13 (57%)	11 (49%)	0.768
Right handedness, n (%)	23 (100%)	23 (100%)	1.00
APOE ε4, n carriers (%)	10 (43%)	-	
GDS, n 1/2/3	−/6/17	23/-/-	
MMSE (SD)	28.0 (1.4)	29.4 (0.6)	<0.001
Matrix reasoning (SD)	16.2 (5.9)	-	
Vocabulary (SD)	58.0 (12.7)	-	
Digit Symbol-Coding (SD)	40.0 (13.0)	-	
TMT-A (SD)	55.5 (23.3)	39.1 (12.6)	0.005
TMT-B (SD)	142.7 (98.3)	87.3 (30.3)	0.016
Letter-Number Sequencing (SD)	6.6 (2.1)	9.2 (1.9)	<0.001
COWAT-FAS (SD)	31.3 (11.4)	42.0 (11.0)	0.002
CWIT 3 (SD)	84.4 (33.64)	62.3 (12.1)	0.005
CWIT 4 (SD)	98.9 (38.6)	65.0 (19.5)	0.001
RAVLT, short-term memory (SD)	8.2 (2.9)	8.9 (2.4)	0.354
RAVLT, long-term memory (SD)	7.8 (3.1)	8.5 (2.6)	0.387

Abbreviations: APOE, Apolipoprotein E; GDS, Global Deterioration Scale; MMSE, Mini-Mental State Examination; COWAT-FAS, the Controlled Oral Word Association Test; CWIT 3 and 4, Color-Word Interference Test, conditions 3 and 4; RAVLT, the Rey Auditory Verbal Learning Test.
Raw scores are presented for all tests. The comparison of gender and handedness between groups was made with a chi-square test (Pearson Chi-square test p value is shown). The Student's t-test was used to compare the groups for the remaining variables.

RESULTS

Table 1 shows demographic and neuropsychological data for the a/e MCI and control groups.

The groups did not differ with respect to age, gender, handedness, length of education and memory (RAVLT), but they did differ (significantly) for MMSE and all a/e measures.

Group differences for white matter and cortical thickness

Figure 1 presents the preselected (and color-coded) WM ROIs superimposed on DR data from the

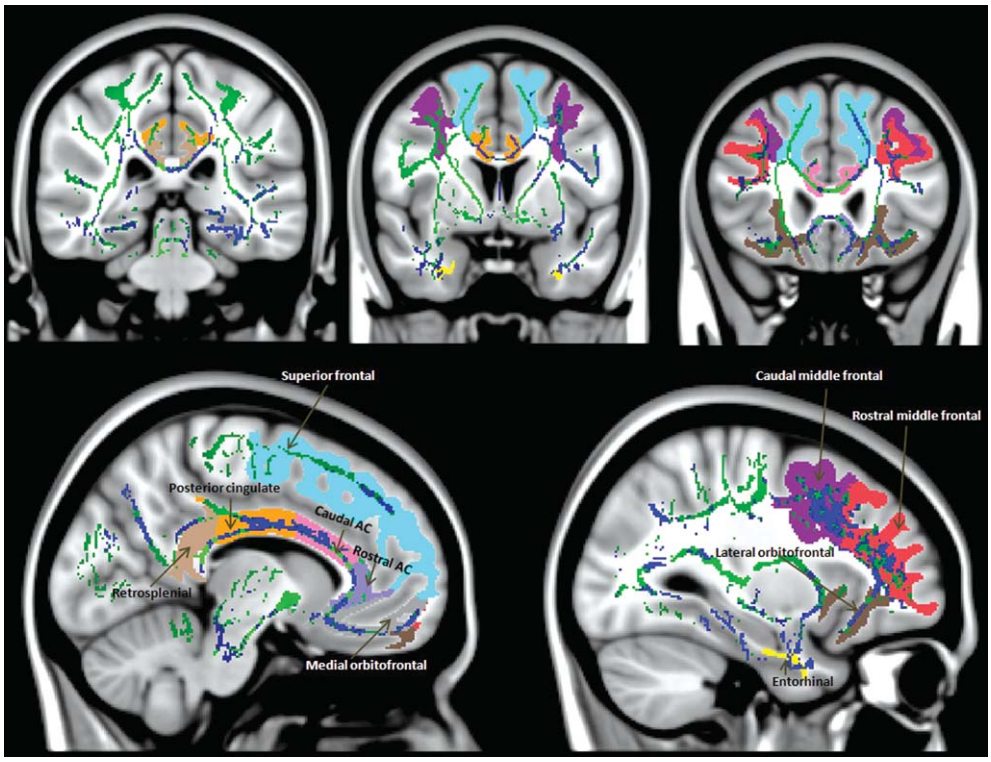

Fig. 1. Statistical map of voxels in the fractional anisotropy skeleton (blue/green) for which radial diffusivity is significantly ($p < 0.05$) higher (blue; green not significantly different) in a/e MCI patients compared to controls, corrected for multiple comparisons. Coronal and sagittal planes of images are shown. The chosen regions of interest are color-coded. Abbreviation: AC = anterior cingulate.

whole brain, and highlights voxels in the FA skeleton in which DR differs significantly between the groups.

Widespread WM tract affection was shown in the whole brain analysis in the a/e MCI group as compared to controls; DR was significantly higher in a/e MCI than controls for 53% of all voxels in the FA skeleton. The most marked DR differences can be seen in the temporal and frontal lobes, with less prominent changes in the parietal and occipital lobes.

Figure 2 shows the percentage of voxels in the FA skeleton (by WM ROI and hemisphere) in which DR was significantly higher for the a/e MCI group than the control group (affected voxels).

The percentage of affected voxels was higher or approximately the same in the left and the right hemisphere for all WM ROIs. In both hemispheres, the entorhinal region had the highest percentage of affected voxels. DR was significantly higher for the a/e MCI group than the control group for 55% of the voxels in the chosen WM ROIs [the ROIs cover 35% of all voxels in the FA skeleton].

Only minor areas showing low levels of significance where the cortex was thinner in a/e MCI than controls were found. A statistical map showing these areas may be found in Supplementary Fig. 1 (data available online: http://www.j-alz.com/issues/27/vol27-2.html#supplementarydata06).

Figure 3 shows group values for the various CTH and WM DR ROIs.

WM DR, underlying rostral middle frontal, medial orbitofrontal, caudal AC, posterior cingulate, retrosplenial and entorhinal cortices, was significantly higher for the a/e MCI than the control group. WM MD differed significantly between the groups for the same ROIs (data not shown). CTH did not differ significantly between the groups for any ROI.

Association between attention/executive subfunctions and imaging findings

Table 2 presents correlations between a/e subfunctions and WM DR in different ROIs. Similar results were obtained with WM MD (data not shown).

For the a/e MCI group increased WM DR/MD in at least one of the ROIs correlated with lower scores for response inhibition and response inhibition/switching (CWIT condition 3 and 4) after Bonferroni-correction.

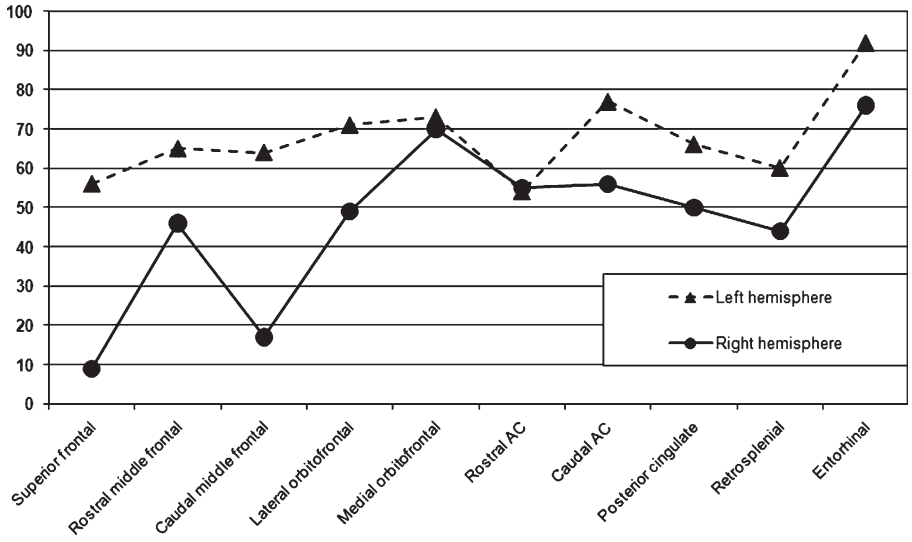

Fig. 2. Percent of voxels in the fractional anisotropy skeleton for which radial diffusion is significantly ($p < 0.05$) increased in a/e MCI patients as compared to controls. Abbreviation: AC = anterior cingulate.

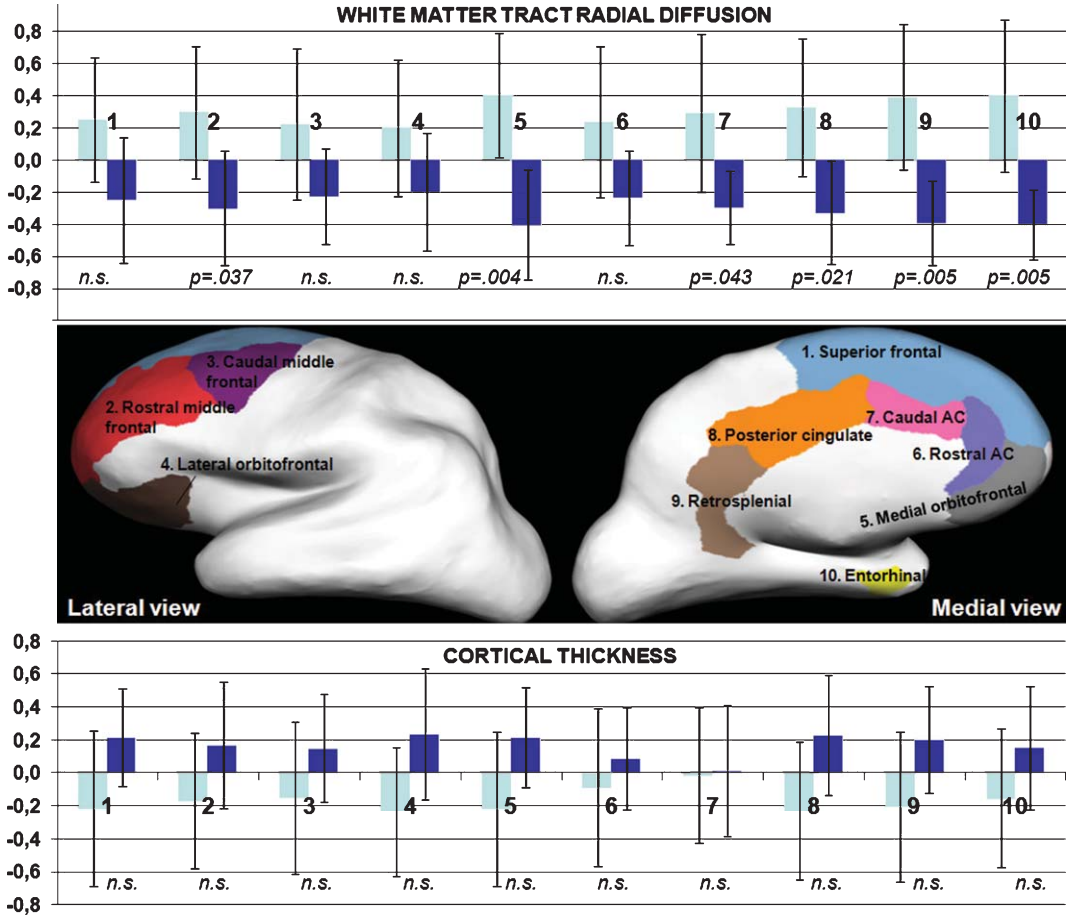

Fig. 3. Imaging data for white matter radial diffusion and cortical thickness by region. The scale for thickness is in millimeters. The effects of age and sex were regressed out, and the standardized residuals are depicted (z-scores). Error bars represent 95% CI. The Student's *t*-test was used for group comparison. Abbreviation: AC = anterior cingulate.

Table 2
Correlations between attention/executive subfunctions and white matter radial diffusivity by region of interest

	Superior frontal	Rostral MF	Caudal MF	Lateral orbit.	Medial orbit.	Rostral AC	Caudal AC	Posterior cingulate	Retro–splenial	Entor–hinal
TMT-A	–0.16	–0.13	0.00	–0.31	–0.28	–0.15	0.00	0.03	–0.26	–0.06
	–0.25	–0.26	–0.38	–0.17	–0.18	–0.20	–0.38	–0.20	–0.30	0.08
TMT-B	–0.26	–0.16	–0.02	–0.24	–0.30	–0.15	–0.07	–0.05	–0.29	0.01
	–0.14	–0.24	–0.29	–0.20	–0.31	–0.34	–0.42*	–0.27	–0.22	–0.17
L-N	0.01	–0.19	0.03	0.00	–0.09	–0.23	–0.16	–0.06	–0.22	0.00
	0.06	0.12	0.21	–0.02	0.05	0.06	–0.05	–0.11	0.20	–0.16
COWAT-	–0.24	–0.29	–0.29	–0.26	–0.22	–0.19	–0.12	–0.33	–0.36	–0.24
FAS	0.03	–0.08	–0.13	–0.11	–0.16	–0.17	–0.38	0.05	–0.36	–0.04
CWIT 3	–0.53**	–0.50**	–0.35	–0.48*	–0.43*	–0.34	–0.30	–0.33	–0.46*	–0.10
	0.16	0.02	0.20	0.26	0.03	–0.01	–0.22	–0.13	–0.14	0.13
CWIT4	–0.63**	–0.55**	–0.39	–0.64**	–0.54**	–0.52*	–0.45*	–0.40	–0.58**	–0.10
	0.04	0.04	0.09	0.07	0.07	0.13	–0.05	–0.04	0.00	0.25

Abbreviations: AC, anterior cingulate; MF, middle frontal; L-N, Letter-Number Sequencing subtest; COWAT-FAS, the Controlled Oral Word Association Test; CWIT 3 and 4, Color-Word Interference Test conditions 3 and 4. Pearson correlation coefficients between white matter radial diffusivity and cognitive parameters are listed. For each test, the numbers presented in the first line (uncolored) indicate the results for a/e MCI group ($n = 23$) and the numbers presented in the second line (gray shaded) indicate the results for the control group ($n = 23$). The effects of age and gender are regressed out for all variables. Significant correlations are marked as $*p < 0.05$ and $**p < 0.01$. The underlined characters indicate significance level $p < 0.008$ (these correlations have passed Bonferroni adjustment for the number of cognitive variables).

No correlations survived Bonferroni-correction in the control group.

For the a/e MCI group cortical thinning in the caudal middle frontal ROI correlated with low scores for attention and divided attention (TMT-A and TMT-B) after Bonferroni-correction. Cortical thinning in rostral middle frontal and the lateral orbitofrontal ROIs correlated ($p < 0.05$) with attention and divided attention, but these correlations did not survive Bonferroni-correction. No correlations were found in the control group. To control for the possibility that reduced processing speed contributed to poor performance in the task of divided attention (TMT-B), a score (TMT-B minus TMT-A) was computed. When this score was used instead of TMT-B, the significance levels of correlations with different ROIs remained the same.

DISCUSSION

This is the first case-control study evaluating both DTI WM and cortical morphometric changes in MCI with impaired a/e functions. The study objectives were met and the hypotheses confirmed. We found that patients with a/e MCI had WM DR/MD increase in frontal, cingulate and entorhinal regions, but CTH was not different from controls in any of the regions. WM tract degeneration in frontal and cingulate regions and cortical thinning in caudal middle frontal region were associated with executive impairment.

WM DR/MD of the WM underlying rostral middle frontal, medial orbitofrontal, caudal anterior cingulate, posterior cingulate, retrosplenial and entorhinal cortices were higher for the a/e MCI than the control group. Frontal and temporal WM diffusivity changes have been previously described in amnestic MCI patients [15]. Here, we show similar findings for patients with a/e MCI. In another study of our MCI cohort, we found increased DR/MD of the WM underlying the entorhinal cortex for patients with memory impairment [25]. Thus, it is possible that changes in this region are typical for MCI patients in general and that patients in the a/e MCI group will develop memory problems. The fact that we found WM DR/MD changes in both the anterior and posterior cingulate regions suggests that both regions may contribute to a/e impairment in MCI [49]. The cingulate cortex projects into the striatum [13], and both the anterior and posterior cingulate cortices receive mediodorsal thalamic afferents [21], which are part of fronto-subcortical circuits, involved in executive function. Brain pathology may spread from the anterior to the posterior cingulate regions, so that changes in both posterior and anterior regions contribute to clinical symptoms [21]. The proportion of affected voxels (increased WM DR) in the whole brain (53%) did not differ from that in the chosen ROIs (55%), indicating diffuse brain changes that affect different parts of the brain (particularly frontal and temporal) and that the observed changes are not specific to the regions tested.

Cortical thinning (lower CTH values) seemed to be more pronounced in the a/e MCI than in the control group in all ROIs, but the differences were not significant in any ROI. Small CTH differences may be explained by a slightly smaller sample size and different post-processing techniques used for morphometry in this study when compared to the other studies of a/e MCI [8, 9]. The lack of correspondence between reduction in WM integrity and reduction in CTH have been recently reported in amnestic MCI [15]. Our findings that CTH in a/e MCI was not significantly different from the control group may suggest that cortical thinning occurs after WM changes. Experimental and clinical studies have shown that increases in DR/MD may be associated with demyelination and myelin degeneration and axonal atrophy [50, 51].

Some a/e subfunctions correlated significantly with imaging findings in frontal and cingulate regions in the a/e MCI group, but no significant correlations were found in controls. In a/e MCI, response inhibition was associated with WM DR/MD underlying superior frontal cortex and response inhibition/switching was associated with WM DR/MD underlying superior frontal, rostral middle frontal, lateral/medial orbitofrontal and retrosplenial cortices. Test scores for attention and divided attention were associated with cortical thinning of the caudal middle frontal region. Working memory and verbal fluency were not associated with changes in any specific frontal or cingulate region. The differences in correlations between a/e subfunctions and regional affection point to a dependence on partly different brain regions. Earlier, it has been shown that executive function is related to WM tract integrity in normal aging [52] and traumatic brain injury [53], in accord with our observations on patients with a/e MCI in the current study. The study results thus support the results from previous MCI studies, where associations between prefrontal changes and a/e impairment have been reported [7, 11, 20]. In addition, the results confirm that cingulate changes are associated with executive impairment in MCI [21].

This study has some important limitations. The first limitation concerns definition of a/e MCI group. We have used tests for a/e subfunctions, which are commonly used in clinical practice, but do not cover all aspects of executive function. It may be questioned if verbal fluency test (COWAT) is an executive test as it is often defined as a language test [10]. Further, this study did not compare a/eMCI with other MCI groups, and we do therefore not know whether the observed changes can distinguish this particular group from other subgroups. The third limitation is that white matter hyperintensities (WMH) could not be directly assessed with the present methodology and its effects on patterns of DTI group differences and associations between WM diffusivity and a/e functions are unclear.

The concept a/e MCI should be further validated to achieve a consensus criterion for future research. The studied group is probably heterogeneous and contains, among other conditions, early stage AD and non-AD pre-dementia with executive impairment [7, 8, 10].

Continued follow-up of these study participants will provide information about whether such a subgroup of MCI can be characterized as a clinical entity with a specific pathophysiology and prognosis.

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Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=928).

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