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Pre-dementia Memory Impairment is Associated with White Matter Tract Affection

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Abstract

Mild cognitive impairment (MCI), especially amnestic, often represents pre-dementia Alzheimer's disease, characterized by medial temporal lobe atrophy, while white matter (WM) alterations are insufficiently described. We analyze both cortical morphometric and WM diffusivity differences in amnestic *versus* non-amnestic subtypes and ask if memory and WM tract affection are related independently of cortical atrophy. Forty-nine patients from a university-hospital based memory clinic with a score of 3 on the Global Deterioration Scale aged 43–77 years (45% female) were included. Two neuropsychologists have classified cases as amnestic (aMCI), non-amnestic (naMCI), or less advanced (laMCI), not satisfying criteria for aMCI/naMCI. Diffusion tensor imaging (DTI) WM tract and morphometric data of the temporal-parietal memory network were compared among patient subtypes and related to story, word list, and visual memory. WM radial and mean diffusivity (DR and MD), underlying the entorhinal cortex, were higher in aMCI compared with laMCI. WM DR and MD, underlying the entorhinal, parahippocampal, and middle temporal cortex, explained unique variance in word list and story memory, and this was not due to secondary effects of cortical thinning. DTI may thus potentially aid diagnosis in early disease stages. (*JINS*, 2011, *17*, 143–153)

Keywords: Alzheimer's disease, Mild cognitive impairment, Diffusion tensor imaging, Radial and mean diffusivity, Cortical thickness, Temporal-parietal memory network

INTRODUCTION

Mild cognitive impairment (MCI) was originally described as a condition with amnesia, representing an intermediate stage between normal aging and Alzheimer's dementia (Petersen et al., 1999), but has later been extended to encompass non-amnestic types (Petersen, 2003).

Subjects with amnestic MCI (aMCI) have subjective and objective (verified in cognitive testing or clinical assessment) memory impairment in either memory alone or both memory and other cognitive domains, but do not fulfill criteria for dementia (Petersen, 2004; Petersen, et al., 1999). Both MCI patients with impaired story or visual memory and patients with impaired word list memory convert to Alzheimer's disease (AD) at a higher rate than patients with only subjective memory loss (Rountree et al., 2007).

The majority of aMCI cases are pre-dementia AD cases (Nordlund et al., 2010). The etiology of cognitive impairment in these subjects may differ from non-amnestic MCI (naMCI) subtypes who often have deficits of language, attention and executive function (Whitwell, Petersen, et al., 2007). AD-like neuropathologic changes are more frequently present in aMCI cases (Petersen et al., 2006; Schneider, Arvanitakis, Leurgans, & Bennett, 2009), and 76% of MCI cases progressing to Alzheimer's dementia have aMCI (Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006). It is also known that approximately 20–40% of MCIs will revert to the normal range upon repeated testing (Bickel, Mosch, Seigerschmidt, Siemen, & Forstl, 2006; Fischer et al., 2007). Due to the heterogeneity of the MCI construct, both well-defined MCI-criteria (Jak, Bangen, et al., 2009; Jak, Bondi, et al., 2009) and knowledge about the clinical amnestic and non-amnestic

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subtypes are important for identification of pre-dementia cases (Petersen et al., 2009).

Impaired memory and hippocampal atrophy in MCI are commonly recognized indicators of incipient AD (Dubois et al., 2007; Jack et al., 1999). Gray matter loss in aMCI may be found in the medial temporal lobes (MTLs), including the amygdala, anterior hippocampus, entorhinal cortex, and the fusiform gyrus 3 years before the diagnosis of AD, and neuropathology spreads to include the middle temporal gyrus, the whole hippocampus and the parietal lobe one year before the diagnosis of AD (Whitwell, Przybelski, et al., 2007). The risk for AD may increase due to cerebrovascular disease (Snowdon et al., 1997). Small vessel ischemic disease is manifested by white matter (WM) lesions in conventional imaging studies, which are associated both with low cerebrospinal fluid (CSF) Abeta42, suggesting increased risk for AD (Stenset et al., 2006), and with AD-independent cognitive impairment (Stenset et al., 2008). It has been shown that those aMCI patients, who progressed to AD within 18 month of the magnetic resonance imaging (MRI), had bilateral gray matter loss in the medial/inferior temporal lobe, temporoparietal association neocortex, and frontal lobes, as well as higher frequency of lacunar infarcts than the control group (Whitwell et al., 2008).

Cortical-subcortical and cortical-cortical disconnection may contribute to cognitive dysfunction due to WM tract disruption (Stenset et al., 2007). It has been shown that neocortical connections to the hippocampus may deteriorate due to the degeneration of critical MTL and associated fiber pathways in AD (Salat et al., 2010). Diffusion tensor imaging (DTI) is a method for delineating the anatomy of WM pathways by measuring the magnitude (mean diffusivity, MD) and directionality of water diffusion, which provides new insights into AD and MCI (Stebbins & Murphy, 2009). MD is a measure of non-directional diffusion providing an average of the three diffusion tensor eigenvalues (λ_1, λ_2, and λ_3). Directional diffusion can be quantified by fractional anisotropy (FA), calculated from the diffusion tensor eigenvalues (Charlton et al., 2006; Le Bihan et al., 2001), which describe diffusivity parallel (λ_1) or perpendicular (λ_2 and λ_3) to the axonal tracts (axial diffusivity, DA, or radial diffusivity, DR). FA reductions, likely reflecting differences in WM integrity, in MCI *versus* normal controls have been reported in several studies (Fellgiebel et al., 2005; Medina et al., 2006; Rose et al., 2006; Stenset et al., 2009; Zhang et al., 2007). In addition to FA, other DTI parameters, such as MD and DR, may provide more detailed information about pathological WM diffusivity changes. Parahippocampal WM degradation causes a disruption of multimodal input from entorhinal cortex to the hippocampus in aMCI (Rogalski et al., 2009), and alterations of diffusion properties, namely DR and DA, were found in parahippocampal WM and in regions with both direct and secondary connections to the MTL in AD (Salat et al., 2010). Decreased FA and increased MD of the MTL have been found in aMCI compared with subjects with normal cognition (Wang et al., 2009). Significantly lower posterior cingulate FA and higher DR values were observed in MCI patients with pathological T-tau levels at risk for AD compared to patients with normal CSF T-tau levels and controls (Stenset et al., 2009). In another study (Huang, Friedland, & Auchus, 2007), MCI subjects also had decreased FA/DA in temporal normal-appearing WM as well as decreased FA and increased DR in parietal WM. Relationships between DTI parameters and neuropathology are not well established, but comparing pre-operative imaging with electron microscopy analyses of surgically resected temporal lobes in cases with epilepsy and mesial temporal sclerosis, increased diffusivity was related to increased extra-axonal fraction, myelin rarefication, and reduced cumulative axonal membrane area (Concha, Livy, Beaulieu, Wheatley, & Gross, 2010). Although the literature is limited, these studies suggest that DTI parameters measure neuropathological parameters highly relevant for cognition, and that more attention should be paid to WM diffusivity changes in addition to gray matter changes to better understand pathological mechanisms in MCI.

The temporal-parietal memory network has been shown to be affected in MCI and AD (Chetelat et al., 2003; De Santi et al., 2001; Fjell et al., 2010; Jack et al., 2004, 2008; Karas et al., 2008; Walhovd et al., 2009). In a study, where MCI patients from a sample overlapping with the present were compared to normal controls (Walhovd et al., 2009), the morphometric variables were found to have superior diagnostic sensitivity when compared to FA of the temporal and parietal areas, comprising the hippocampus, entorhinal, parahippocampal, retrosplenial, posterior cingulate, precuneus, supramarginal, inferior parietal, and middle temporal cortices. FA still explained unique variance in verbal memory function in the MCI group. In the current study, we use the same regions of interest (ROIs), but, differently from the study of Walhovd et al. (2009), WM diffusivity data have been processed using Tract-Based Spatial Statistics and FSL method (Smith et al., 2004), shown to be a promising method in examining the degeneration of neurofiber tracts in MCI and AD (Liu et al., 2009). This method makes this study unique also when compared to another of our publications (Grambaite et al., 2010), containing a sample overlapping with the present, where DTI data have been processed using the nICE Basis and Diffusion Module and nine ROIs have been manually drawn in the FA map. In that study, the patients have been stratified by CSF T-tau pathology, and the results indicate that the size of hippocampus volume (HcV) and memory performance may differ according to levels of T-tau pathology. In the current study, we classify our MCI sample according to neuropsychological performance into the aMCI, naMCI and laMCI (less advanced MCI, not satisfying criteria for either aMCI or naMCI) subtypes to characterize typical DTI and morphometric alterations in aMCI compared to other MCI subtypes. To better understand the relationship between memory and chosen temporal-parietal regions, known to be involved in episodic memory retrieval (Buckner & Wheeler, 2001; Wagner, Shannon, Kahn, & Buckner, 2005; Walhovd et al., 2009), we relate episodic memory (story, word list, and visual) to morphometric and WM diffusivity measures. Memory-related cortical changes

in pre-dementia stages are relatively well described (Fjell, Walhovd, et al., 2008; Karas et al., 2008; Whitwell et al., 2009), and the relations between memory and WM alterations in MCI have been found in a few DTI studies (Bosch et al., 2010; Huang et al., 2007; Rogalski et al., 2009; Rose et al., 2006; Walhovd et al., 2009). Still, these relationships need to be verified across different DTI methods (e.g., ROI-based and TBSS methods) as well as different episodic memory domains, including both verbal and non-verbal recall aspects. Furthermore, it remains unclear to which degree the relations between WM diffusivity and memory may be accounted for by the secondary effects of cortical gray matter atrophy.

The study aims are as follows: (1) to compare an aMCI group with other neuropsychologically derived clinical MCI subgroups (naMCI and laMCI) with respect to cortical morphometric and DTI measures of the underlying WM tracts (FA, MD, and DR) in the temporal-parietal memory network; (2) to determine clinical significance of WM tract affection by investigating the relationships between imaging parameters and story, word list and visual memory performance; and (3) to analyze whether WM diffusivity measures have unique contributions to memory performance, independently of cortical atrophy.

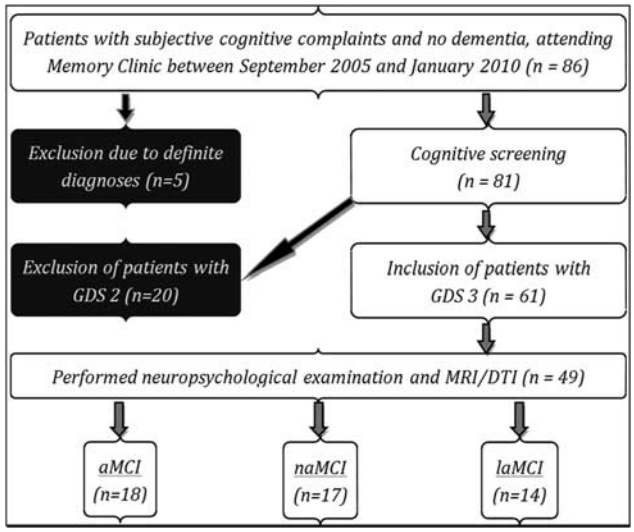

Fig. 1. Schematic overview of the study participants. In total, 86 patients were candidates for inclusion. Five participants were excluded after initial investigations due to definite diagnosis (i.e., normal pressure hydrocephalus, frontotemporal dementia and Lewy body disease). Patients with mild cognitive impairment (MCI; Global Deterioration Scale score = 3), verified on cognitive screening tests, who have performed both neuropsychological and magnetic resonance imaging/diffusion tensor imaging examinations, were included in the current study ($n = 49$). The patients were further classified into three neuropsychological subtypes (amnestic [aMCI], non-amnestic [naMCI], and less advanced [laMCI]).

METHODS

Research Participants

The study participants are shortly described in a schematic summary, provided in Figure 1.

Patients with subjective cognitive complaints lasting 6 months or longer attending a university-based memory clinic between September 2005 and January 2010 were assessed for inclusion.

Inclusion criteria were preserved general intellectual function, no or very mild activities of daily living problems and Global Deterioration Scale (GDS) score 3 (Auer & Reisberg, 1997; Reisberg, Ferris, de Leon, & Crook, 1988) as determined from a clinical interview and screening tests. Screening tests included parameters 13–20 (memory, disorientation, abstract thinking, visuospatial ability, language, sensory aphasia, visual agnosia, and apraxia) from the stepwise comparative status analysis—STEP (Edman, Mahnfeldt, & Wallin, 2001; Wallin et al., 1996), word fluency, interference, and numeral-letter items from the I-flex (Royall, Mahurin, & Gray, 1992), and items from the Neurobehavioral Cognitive Status Examination – Cognistat (Kiernan, Mueller, Langston, & Van Dyke, 1987), as well as Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). To be classified as GDS 3, subjects had to score ≥ 26 on MMSE, ≤ 1 on STEP variables, ≤ 2 on I-FLEX variables, and there were more than one Clinical Dementia Rating (Morris, 1993) domain where they scored 0.5, albeit none where they scored 1. Criteria for exclusion were established psychiatric disorder, cancer, drug abuse, solvent exposure, or anoxic brain damage. The project was approved by the South-Eastern Norway committee for medical research ethics. Participants' consent was obtained according to the Declaration of Helsinki (Declaration of Helsinki, 1991).

Neuropsychological Assessment

Neuropsychological examination was performed by a psychologist within three months of the MRI scan date. General cognitive ability, memory, language, attention/executive and visuospatial function have been assessed. For the assessment of *general cognitive ability, vocabulary* was measured using vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) and nonverbal abstract problem solving was measured using *Matrix reasoning* either from WASI or Wechsler Adult Intelligence Scale—Third Edition (WAIS-III; Wechsler, 2003). T-scores, based on norms for these tests, are reported in Table 1.

The *memory tests* included Logical Memory Subtest from the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987), the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996) and visual reproduction from the Rey Complex Figure Test (RCFT; Meyers & Meyers, 1995). T-scores, based on norms for these tests, are provided in Table 1. The *language* tests used were the Boston Naming Test (BNT; Kaplan Goodglass, & Weintraub, 1983) and the Controlled Verbal Fluency Task (FAS; Spreen & Strauss, 1998). The *attention/executive*

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Table 1. Demographic and neuropsychological data comparison among groups

	aMCI, $n = 18$	naMCI, $n = 17$	laMCI, $n = 14$	p 1	p 2
Age 43–77 (*SD*), y	63.1 (7.7)	58.3 (8.1)	60.2 (5.4)	.12	.22
Education 7–18 (*SD*), y	11.8 (3.4)	12.6 (2.2)	12.2 (3.0)	.28	.62
Gender, *n* male (%)	8 (44%)	11 (65%)	8 (57%)	.23	.48
Handedness, n right (%)	17 (94%)	17 (100%)	11 (79%)	.32	.18
APOE-ε 4, *n* carriers (%)	9 (50%)	5 (29%)	7 (50%)	.21	1.0
General Cognitive Ability					
MMSE (*SD*)	27.4 (1.5)	27.6 (1.4)	28 (1.0)	.93	.32
Matrix reasoning (*SD*)	51.1 (9.9)	56.2 (8.2)	59.5 (9.8)	.13	.03
Vocabulary (*SD*)	53.1 (7.5)	51.9 (12.7)	57.6 (9.3)	.62	.11
Memory					
Story memory, immediate (*SD*)	38.9 (7.8)	48.0 (9.5)	52.5 (11.3)	.01	.00
Story memory, long-term (*SD*)	37.4 (8.6)	48.9 (8.5)	54.3 (10.1)	.00	.00
Word list memory, short-term (*SD*)	31.0 (8.0)	46.1 (12.1)	45.9 (9.6)	.00	.00
Word list memory, long-term (*SD*)	30.6 (7.5)	48.9 (12.0)	45.5 (9.8)	.00	.00
Visual memory, short-term (*SD*)	29.3 (7.0)	47.9 (10.3)	45.7 (11.8)	.00	.00
Visual memory, long-term (*SD*)	25.4 (5.4)	47.0 (8.4)	45.3 (11.7)	.00	.00

Note. MCI = mild cognitive impairment; aMCI = amnestic MCI; naMCI = non-amnestic MCI; laMCI = less advanced MCI; APOE = apolipoprotein E; MMSE = Mini-Mental State Examination (max score, 30). T-scores, presented for all neuropsychological tests, except MMSE, are age-corrected test-specific normative data. The comparison of gender, handedness and APOE 4 among groups were made with a χ^2 test (Pearson χ^2 test p value is shown). Mann-Whitney *U*-test was used to compare the groups for the remaining variables in the table. p 1 = significance aMCI *versus* naMCI; p 2 = significance aMCI *versus* laMCI.

tests were comprised of Trail Making Test (TMT) A and B (Spreen & Strauss, 1998), the Digit Symbol subtest of the WAIS-III, D-KEFS (Delis-Kaplan Executive Function System) Color-Word Interference Test (Delis, Kaplan, & Kramer, 2001), and The Letter-Number Sequencing task from WAIS-III. RCFT copy trial was used to assess *visuospatial* function.

Subject Classification

Two experienced clinical neuropsychologists, who were blinded for other data than neuropsychological test results, including normative scores, age, and education, have classified the subjects into either aMCI or naMCI or laMCI subtypes. The clinicians worked independently of each other and finally compared their answers to assure that the subjects were classified correctly. Criteria for classification of subjects were similar to those used by Whitwell and colleagues (Whitwell, Petersen, et al., 2007).

To be classified as *aMCI*, a subject had to be impaired on at least two memory tests, based on norms for these tests, irrespectively of impairment on other non-memory tests. The T-score had to be ≤ 37 for the mean score of short- and long-term recall on RAVLT or/and RCFT, or/and $\leq$ the 10th percentile for the long-term recall of Logical Memory, reflecting a score of 1.3 or more standard deviations (*SD*) below the control mean. When the results on RAVLT and RCFT were close to the cut-off and doubtful, then the long-term recall was used for classification. To be classified as *naMCI*, a subject had to be unimpaired on memory tasks, but impaired on at least two of the non-memory tests. The same cut-off (T = 37 or percentile = 10) as for the judgment of amnestic impairment was used. Subjects, who did not meet the criteria for aMCI or naMCI because of relatively intact performance on neuropsychological tests, were classified as *laMCI*.

Memory Variables

Three memory variables, used in the analyses were termed: *story memory* (WMS-R), *word list memory* (RAVLT), and *visual memory* (RCFT). The mean scores of the short term and 30 min recall were calculated for word list and visual memory and the mean score of the immediate and 30 min recall was calculated for story memory to reduce the number of variables. The standardized residuals, after regressing out age, gender, and education (and also copy trial for visual memory) from the raw scores, were computed and used in all analyses.

ROIs and MRI/DTI Acquisition

The same ROIs as in a previous publication on a subset of this material were used (Walhovd et al., 2009): the hippocampus, entorhinal, parahippocampal, retrosplenial, posterior cingulate, precuneus, inferior parietal, supramarginal and middle temporal cortices, and the underlying WM. A three-dimensional illustration of all these regions may be found in Figure 2. For HcV, the sum of the right and the left sides, and for other ROIs, mean scores of the right and the left sides, have been used in the analyses.

For practical reasons, two different 1.5 Tesla (T) MRI scanners were used in this study (site 1/2: 14/43 subjects), which are described in detail elsewhere (Stenset et al., 2009). In another study, where the same MR scanners were used and six subjects were scanned on both scanners, correlations across scanners for different morphometric measures were close to 1.00, indicating that change of scanner did not introduce bias in the data (Fjell, Walhovd, et al., 2008). In our data set, correlations (the Pearson coefficients) between MR site and the chosen ROIs of cortical thickness and HcV were not significant ($p > .05$) and varied from −.15 to .26.

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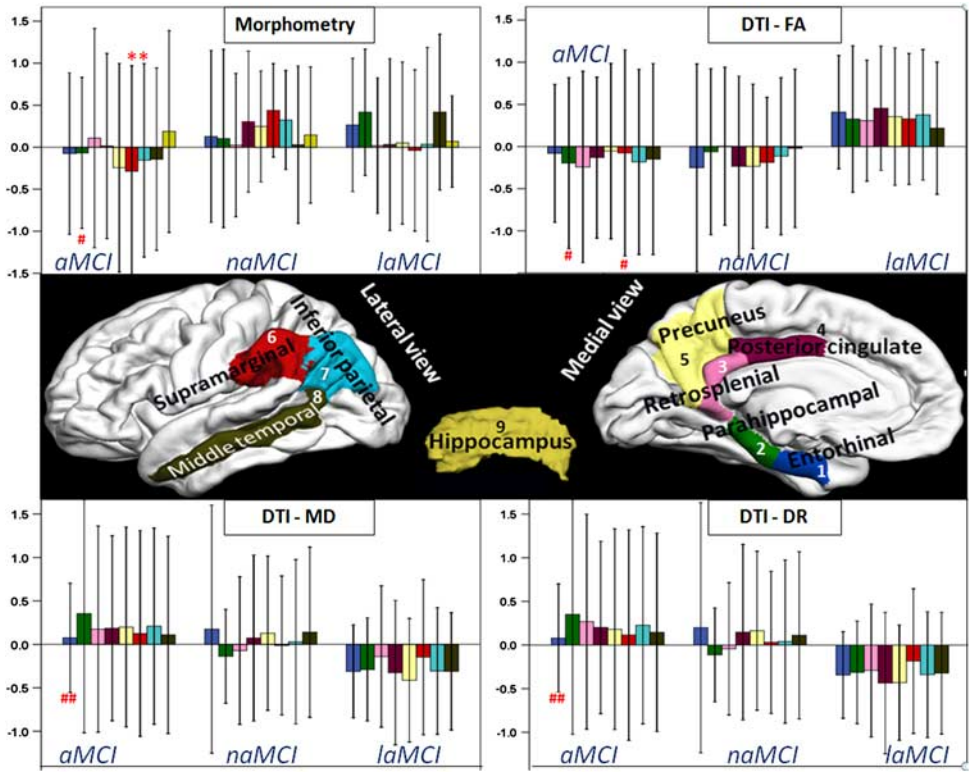

Fig. 2. Group values for the different regions of interest for morphometric and diffusion tensor imaging (DTI) measurements. The standardized residuals are depicted. The effects of age and gender (and intracranial volume [ICV] for hippocampus volume [HcV]) were regressed out for morphometric variables. The effects of age, gender, and DTI site were regressed out for fractional anisotropy/mean diffusivity/radial diffusivity [FA/MD/DR]. Significance of the differences between amnestic mild cognitive impairment (aMCI, $n = 18$) and non-amnestic MCI (naMCI, $n = 17$) is marked: $^{**}p < .05$ and $^{*}p < .10$. Significance of the differences between aMCI and less advanced MCI (laMCI, $n = 14$) is marked: $\#\#p < .05$ and $\#p < .10$. Error bars represent standard deviations.

Contrarily, the Pearson coefficients between DTI-site and FA parameters were highly significant ($p < .01$) and varied from .39 to .73 in our data set. Therefore, DTI variables were regressed on age, gender and also MRI site, and the residuals were used in all analyses, except for the supplementary analyses provided in Supplementary Table 1. Age, gender, and intracranial volume (ICV) were regressed out for HcV; age and gender were regressed out for cortical thickness.

Supplementary Materials

To review these additional data and analyses, please access the online-only supplementary Table 1. Please visit journals.cambridge.org/INS, then click on the link "Supplementary Materials" at this article.

MRI Segmentations and Analyses

Morphometric and DTI data were processed by the same physician at Akershus University Hospital (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 (Fischl et al., 2002) and parcellation of the cortical surface (Fischl et al., 2004) according to a parcellation scheme (Desikan et al., 2006). This labels cortical sulci and gyri, and thickness values are calculated in the ROIs.

DTI data were processed using FSL version 4.1 (Smith et al., 2004; Woolrich et al., 2009). Initially, an affine registration was done for each DTI volume to the low-b ($b = 0$) image using FLIRT (Jenkinson & Smith, 2001). 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 ($(\lambda_2 + \lambda_3)/2$), and MD as the mean of all three eigenvalues ($(\lambda_1 + \lambda_2 + \lambda_3)/3$). Further processing of the FA, DR, and MD data was carried out using TBSS (Tract-Based Spatial Statistics) version 1.2 (Smith et al., 2006), part of FSL. FA images were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using BET (Smith, 2002). All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT (Andersson, 2007), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to all subjects in the group. Each subject's

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aligned FA data were then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. DR and MD data were then extracted from each subject according to the skeletonized FA map. WM ROIs based on the FreeSurfer WM parcellations were then extracted for FA, DR and 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 FA, DR, and MD data from each WM ROI (Fjell, Westlye, et al., 2008).

To confirm that the voxels in the mean FA skeleton actually were derived from the correct tract-center points in all subjects, these voxels were projected back from their position on the skeleton to the nearby position at the center of the nearest tract in the subject's FA image in standard space (i.e., after the FA image had been nonlinearly registered to the target image). Furthermore, these points were then "inversely warped" back into the subject's native space by inverting the nonlinear registration that was originally applied. The voxels were then manually inspected in both standard and native space. There was a generally satisfactory overlap between tract centers and back projected voxels. Furthermore, the selected WM ROIs from the FreeSurfer parcellation of the standard space T1 volume MNI152 were also projected back to both standard and native space and manually inspected for accuracy.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS 16.0) was used for all statistical analyses. To compare group demographic characteristics Mann-Whitney *U*-test and χ^2 test were used. A linear regression model was used to perform a parametric correction to the data. The variables, the effects of which we regressed out, are listed in the sections "Memory variables" and "ROIs and MRI/DTI Acquisition." The obtained standardized residuals were further treated as a new dataset before the group analyses were performed. The Mann-Whitney *U*-test was further used to analyze group differences with regard to neuropsychological performance, WM diffusivity and morphometry. Non-parametric approach was used due to small and unequal sample sizes. To estimate effect sizes, Cohen's *d,* defined as the difference between two means divided by the pooled standard deviation for the data, was calculated. As pooled standard deviation, the square root of the average of the squared standard deviations was used (Cohen, 1988). Pearson's correlation method was used to test for associations between imaging and cognitive variables. Both uncorrected and Bonferroni-corrected *p* values for the number of memory variables (story, word list, visual) investigated were obtained for the correlation analyses. Hierarchic regression method was used to analyze the predictive value of WM diffusivity, namely DR and MD of the regions significantly correlating with memory, to memory variance after controlling for possible effects of cortical thickness in the corresponding ROIs. The terms "statistically significant" and "significant," used in this article, refer to the *p* value smaller than .05. The term "significant at trend level" refers to the *p* value smaller than .10.

RESULTS

The patient groups were quite similar according to their demographics as seen from Table 1. None of the listed variables, except the memory variables as expected by the definitions used, differed significantly between the aMCI and naMCI. When aMCI was compared to laMCI, performance on matrix reasoning test as well as memory variables were significantly better in the laMCI group, but performance on the vocabulary subtest as well as other listed demographical variables did not differ significantly between the groups.

HcV, cortical thickness, FA, MD, and DR for different ROIs were compared among the groups, and the results are presented in Figure 2.

Comparison of aMCI and naMCI Groups

Inferior parietal and supramarginal thickness were lower at trend level in aMCI compared to naMCI. Neither HcV nor FA/DR/MD values differed significantly between the groups. To check how much the correction of data and application of standardized residuals impacted the results, the analyses of group differences were performed with the uncorrected data. Significant group differences, the raw score means, standard deviations, and effects sizes are provided in a supplementary table (Supplementary Table 1).

Comparison of aMCI and laMCI Groups

HcV in the aMCI was smaller than in the laMCI group, but the differences were not statistically significant. Parahippocampal cortex was thinner at trend level in the aMCI compared to laMCI. For the underlying WM tracts, parahippocampal and supramarginal FA values were lower at trend level and entorhinal DR/MD were significantly higher in the aMCI group compared to the laMCI group. Group analyses for the uncorrected data may be found in Supplementary Table 1. Relationships between imaging and memory measures are presented in Table 2.

As shown, parahippocampal MD/DR correlated significantly with story, word list, and visual memory. Parahippocampal FA was significantly related with story and word list memory, and parahippocampal thickness was significantly related with visual memory. Entorhinal and middle temporal thickness/MD/DR, and also entorhinal FA, correlated significantly with story memory. The relationships were negative between memory and MD/DR and positive between memory and cortical thickness/FA. The correlations were adjusted for three comparisons applying the Bonferroni correction to account for the fact that three memory variables

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Table 2. The relationships between ROIs and memory

	Story memory				Word list memory				Visual memory			
Measure	TH/V	FA	MD	DR	TH/V	FA	MD	DR	TH/V	FA	MD	DR
Entorhinal	**.36***	**.36***	**−.41****	**−.43****	.08	.16	.03	−.01	.24	−.17	−.02	.00
Parahippocampal	**.21**	**.31***	**−.45****	**−.43****	**.16**	**.32***	**−.42****	**−.41****	**.30***	.09	**−.30***	**−.29***
Retrosplenial	.20	.20	−.21	−.24	.21	.09	−.03	−.08	.23	.06	−.08	−.10
Poster. cingulate	.07	.09	−.14	−.13	.05	.08	−.15	−.13	.12	−.10	.03	.07
Precuneus	.04	.04	−.12	−.11	.21	.05	−.04	−.05	.16	−.09	.11	.11
Inferior parietal	.14	.06	−.05	−.05	.24	−.01	.07	.07	.18	−.19	.19	.20
Supramarginal	.05	.16	−.25	−.24	.15	.17	−.21	−.21	.12	−.04	.06	.06
Middle temporal	**.29***	.23	**−.34***	**−.35***	.08	.21	−.16	−.19	.12	−.15	.21	.19
Hippocampus	.19				.15				.06			

Note. Pearson correlation coefficients between ROIs and memory are listed. $N = 49$. ROI = region of interest; TH = cortical thickness; V = volume; FA = fractional anisotropy; DR = radial diffusivity; MD = mean diffusivity; ICV = intracranial volume; HcV = hippocampus volume. The effects of age, gender, and education (and copy trial for visual memory) were regressed out for memory variables. The effects of age and gender (and ICV for HcV) were regressed out for morphometric variables. The effects of age, gender and DTI-site were regressed out for FA/MD/DR. Bold characters indicate * $p < .05$ and ** $p < .01$ uncorrected, and underlined characters indicate $p < .05$ Bonferroni-corrected for three comparisons (story, word list, visual).

were correlated to the imaging variables of the temporal-parietal memory network. Due to carefully chosen imaging variables, which were interdependent, and relatively small sample, stronger corrections were deemed to be too strict. After the Bonferroni corrections, story memory was still significantly related to entorhinal thickness/FA/MD/DR, parahippocampal MD/DR, as well as middle temporal MD/DR. The relationships between word list memory and parahippocampal MD/DR also remained significant.

Hierarchic regression analyses (Table 3) were further performed with cortical thickness and DR/MD of the ROIs, correlating significantly with memory function (shown in Table 2), as the independent variables. The chosen thickness variable was entered in step 1 (the first block) and DR or MD (one per model) in the underlying WM tract was entered in step 2. That was to analyze if DR/MD could serve as unique predictors of the variance in episodic memory after controlling for the possible effect of cortical thickness.

Table 3. Hierarchic regression analyses with memory function as the dependent variable

	Story memory					Word list memory					Visual memory				
	β	*p*	R^2	F	Cp	β	*p*	R^2	F	Cp	β	*p*	R^2	F	Cp
Step 1a/b															
Parahipp. TH	.23	.12	.05	2.5	.12	.17	.26	.03	1.3	.26	.30	.04	.09	4.6*	.04
Step 2a															
Parahipp. TH	.11	.44				.06	.69				.24	.10			
Parahipp. DR	−.42	.00	.22	6.2*	.00	−.39	.01	.17	4.7*	.01	−.22	.14	.13	3.5*	.14
Step 2b															
Parahipp. TH	.09	.50				.05	.74				.23	.11			
Parahipp. MD	−.45	.00	.24	6.9*	.00	−.41	.01	.18	5.0*	.01	−.22	.13	.14	3.6*	.13

	Story memory						Story memory				
	β	*p*	R^2	F	Cp		β	*p*	R^2	F	Cp
Step 1a/b						Step 1a/b					
Entorhinal TH	.37	.01	.14	7.2*	.01	Middle temporal TH	.28	.05	.08	4.0	.05
Step 2a						Step 2a					
Entorhinal TH	.24	.12				Middle temporal TH	.19	.19			
Entorhinal DR	−.33	.02	.23	6.7*	.02	Middle temporal DR	−.30	.04	.16	4.3*	.04
Step 2b						Step 2b					
Entorhinal TH	.25	.09				Middle temporal TH	.19	.19			
Entorhinal MD	−.31	.04	.22	6.2*	.04	Middle temporal MD	−.29	.05	.15	4.1*	.05

Note. $N = 49$. TH = cortical thickness; DR = radial diffusivity; MD = mean diffusivity; Cp = *p* for F-change. *Indicates significant model ($p < .05$). The effects of age and gender (and intracranial volume for hippocampus volume) were regressed out for morphometric variables. The effects of age, gender, and diffusion tensor imaging site were regressed out for MD/DR.

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In the analyses with story, word list, and visual memory as the dependent variables, both DR and MD in the parahippocampal WM tract explained unique variance ($p < .05$) in story and word list memory beyond that which could be explained by cortical thickness in the corresponding ROI. Contrarily, parahippocampal MD/DR did not show superior predictive value in explaining unique variance ($p > .05$) in visual memory beyond that which could be explained by parahippocampal thickness. Further analyses were performed with story memory as the dependent variable and cortical thickness and DR/MD in either the entorhinal or middle temporal WM tracts as the independent variables. DR and MD in these ROIs could also explain unique variance ($p < .05$) in story memory after controlling for the possible effects of cortical thickness in the corresponding ROIs.

DISCUSSION

Two main conclusions can be drawn from the present study. First, clinical aMCI and laMCI subgroups could be distinguished by DTI WM diffusivity measures, but aMCI and naMCI groups could not be distinguished by these variables. Second, memory performance in the total MCI sample could be explained by diffusion characteristics in specific WM tracts, which was not due to secondary effects of gray matter thinning.

Our results suggest that increased DR and MD, underlying the entorhinal cortex, differentiate the aMCI group from the laMCI, the latter group comprising MCI patients not satisfying criteria for either aMCI or naMCI subtypes. These findings are partially in accord with the results of Pievani and colleagues, who have found increased DR in the limbic network in aMCI patients compared with healthy elderly, although MD and FA values were not different (Pievani et al., 2010). Adding to the findings concerning group differences, we show that changes in DR and MD of the WM tracts underlying the entorhinal cortex have unique predictive value for story memory performance even after controlling for cortical thickness. Similarly, the results from our study show that DR and MD of the WM tracts, underlying parahippocampal and middle temporal cortex, are unique predictors of story and word list memory, independently of cortical thickness. In another recent study it has been shown that the statistical effect on WM diffusivity changes in temporal and parahippocampal regions remained after controlling for gray matter degeneration as measured by HcV (Salat et al., 2010). Here, by controlling WM tract parameters for cortical thickness in each of the corresponding regions in the temporal-parietal memory network, we were able to show that the relationships between WM integrity and memory parameters were not secondary effects of cortical gray matter atrophy. The results from another DTI study, where TBSS method was applied, showed that most DTI-derived changes, except some MD and DR increases in posterior associative pathways, were secondary to gray matter atrophy in aMCI and AD (Bosch et al., 2010). Furthermore, FA values were the only DTI measure significantly related to memory in aMCI and AD, while we find that both DR and MD serve as significant predictors of episodic memory impairment.

Previously, it has been shown that severe destruction of the entorhinal pre-[alpha] layer, which is accompanied by comparatively minor changes in the hippocampus, occur before major neocortical destruction in AD (Braak & Braak, 1996). Therefore, small HcV differences in groups are probably not surprising in early disease stages. Whitwell, Przybelski, and colleagues (2007) found hippocampus atrophy in aMCI compared to the matched healthy subjects, while HcV in aMCI, defined using similar MCI-subtyping procedure, did not differ significantly from HcV of non-amnestic subtypes in our study, where no control group was included. In another study, Whitwell, Petersen, and colleagues (2007) found gray matter loss in hippocampus even in the naMCI group. These findings may possibly explain small HcV differences in amnestic *versus* non-amnestic MCI in our study, although it is important to mention that different MRI post-processing techniques were used for morphometry. Furthermore, the mean age of the aMCI subjects in the studies of Whitwell, Petersen, et al. (2007) and Whitwell, Przybelski, et al. (2007) were 76–78 years. Our aMCI subjects are younger (mean age is 63 years) and may have different pattern of cortical and WM changes than older aMCI patients. Possible explanation may be that our relatively young aMCI group consists of AD patients very early in the disease progression, and HcV is, therefore, less affected than it is usually expected in older aMCIs. These questions need to be addressed in the future research.

By using comprehensive diagnostic criteria, including three different memory tasks, we have shown pathological differences concerning WM tract affection (DR and MD) in the aMCI compared with the laMCI subtype. The amnestic group probably represents incipient AD. Non-amnestic groups are heterogeneous and may contain both patients with AD or other incipient dementias and normal aging subjects. MCI patients with relatively normal neuropsychological function (laMCI) may possibly represent a group of "normals." Of interest, the frequency of the apolipoprotein E ε 4 carriers is equal in aMCI and laMCI groups (data are shown in Table 1). The results from the meta-analysis of Wisdom, Callahan, and Hawkins (2009) show that APOE ε 4 and cognition are negatively related also in healthy subjects. Thus, the laMCI group may also be at risk for developing aMCI. We have focused on an episodic memory network, and naMCI is defined as having non-memory deficits. Memory is complex, and we have chosen a few defining memory parameters in this study, although that does not mean that there may not be deficits in other parameters or in only one test. Therefore, the groups may be overlapping in memory function. It follows that both group analyses and analyses of different memory parameters should be performed together to better understand AD-related pathology.

This study has some important strengths. First, carefully defined inclusion criteria were used. In addition to cognitive screening measures, we used neuropsychological criteria to further divide our "MCI" subjects into subgroups and were able to demonstrate group differences in otherwise similar

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individuals. Second, by studying cortical morphometric parameters together with diffusivity parameters (FA/DR/MD) of the underlying WM tracts, we were able to provide consistent findings regarding the importance of both cortical and WM changes in the underlying tracts and their relation to different aspects of the episodic memory. To the best of our knowledge, most studies were focused on ROIs and no former data, except for data from this study and recent study of Bosch and colleagues (2010), are available providing multiple DTI measures (FA, MD, and DR) in aMCI using TBSS, known to improve the sensitivity, objectivity and interpretability of analysis of multi-subject DTI studies (Smith et al., 2006). There are also some important limitations. First, MCI subgroups contained relatively small number of participants. Second, Alzheimer and dementia are progressive processes, and using age-corrected residuals can result in failing to detect group differences. As can be seen in Table 1, the aMCI group is 5 years older than the naMCI group. Supplemental Table 1 shows that group differences are significant for some uncorrected variables. Although we have chosen this conservative approach, it is not necessary correct. Third, we do not know how many patients go on to be demented and the results need to be verified with longitudinal data.

The results of the present study showed more pronounced relationships between memory and DR/MD, than with FA. Experimental and clinical studies have shown that increases in DR may be associated with demyelination and myelin degeneration and axonal atrophy (Concha et al., 2010; Song et al., 2003, 2005). Interpretation of putative pathological underpinnings of the DR/MD findings should be made with caution as the specific neurobiology relating to DTI parameters is still unclear (Paus, 2009).

Memory function is dependent on memory network. In addition to atrophy in this network, the fiber integrity in key areas may contribute to memory dysfunction. Our main findings indicate that DTI DR and MD may differentiate aMCI from laMCI. A few memory aspects are related to these WM alterations in MCI, suggesting that the structural group differences have cognitive correlates, and so verifying the importance of using more than one memory tests and DTI WM diffusivity measures for identification of incipient AD.

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