PAPER

Diffusion indices on magnetic resonance imaging and neuropsychological performance in amnesic mild cognitive impairment

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Background: Magnetic resonance diffusion tensor imaging (DTI) shows promise in the early detection of microstructural pathophysiological changes in the brain.

Objectives: To measure microstructural differences in the brains of participants with amnesic mild cognitive impairment (MCI) compared with an age-matched control group using an optimised DTI technique with fully automated image analysis tools and to investigate the correlation between diffusivity measurements and neuropsychological performance scores across groups.

Methods: 34 participants (17 participants with MCI, 17 healthy elderly adults) underwent magnetic resonance imaging (MRI)-based DTI. To control for the effects of anatomical variation, diffusion images of all participants were registered to standard anatomical space. Significant statistical differences in diffusivity measurements between the two groups were determined on a pixel-by-pixel basis using gaussian random field theory.

Results: Significantly raised mean diffusivity measurements ($p < 0.001$) were observed in the left and right entorhinal cortices (BA28), posterior occipital-parietal cortex (BA18 and BA19), right parietal supramarginal gyrus (BA40) and right frontal precentral gyri (BA4 and BA6) in participants with MCI. With respect to fractional anisotropy, participants with MCI had significantly reduced measurements ($p < 0.001$) in the limbic parahippocampal subgyral white matter, right thalamus and left posterior cingulate. Pearson's correlation coefficients calculated across all participants showed significant correlations between neuropsychological assessment scores and regional measurements of mean diffusivity and fractional anisotropy.

Conclusions: DTI-based diffusivity measures may offer a sensitive method of detecting subtle microstructural brain changes associated with preclinical Alzheimer's disease.

Substantial effort is currently being focused towards improving the diagnosis of early Alzheimer's disease. The term mild cognitive impairment (MCI) is often used to describe the transitional stage between normal ageing and dementia. Owing to the heterogeneity of MCI, not all participants with MCI will have predementia Alzheimer's disease.¹ Peterson *et al*² suggested the criteria for a subtype of MCI, so-called amnesic MCI, which is presumed to present a typical prodrome of dementia in Alzheimer's disease. People with amnesic MCI have a 10–15% annual conversion rate to Alzheimer's disease compared with 1–2% in the normal elderly population.² Neuroimaging studies conducted on participants with MCI using magnetic resonance imaging (MRI) morphological analysis have consistently reported atrophic changes primarily in the medial temporal lobe and, to a lesser extent, in the thalamus and cingulate gyrus.^{3–5} Furthermore, the degree of atrophy in temporal lobe structures correlates with performance on memory tasks³ and with density of neurofibrillar tangles at autopsy.⁶ These findings support the concept that MRI-based neuroimaging studies together with neuropsychological assessment may enable identification of participants with MCI which may progress to Alzheimer's disease, and evaluation of the efficacy of novel treatments.

Recent studies using diffusion tensor magnetic resonance imaging (DTI) have shown microstructural changes in the hippocampus of participants with MCI that may not be apparent using standard anatomical imaging.^{7–9} DTI

measures the random motion of bulk water in cerebral tissue. When the random motion of water is restricted preferentially in one direction when compared with the orthogonal planes, such as occurs in white matter, diffusion is referred to as anisotropic; in contradistinction, bulk water motion in the cerebrospinal fluid is equal in all directions and is thus referred to as isotropic. Fractional anisotropy, a quantitative measurement of the degree of anisotropy, can be used to probe the integrity of white matter fibre tracts.¹⁰ The mean diffusivity is a quantitative measurement of the bulk mean motion of water considered in all directions and is used to interrogate pathological changes in cerebral tissue, such as ischaemia in patients with stroke.¹⁰ DTI studies in patients with MCI have shown raised mean diffusivity in the hippocampus and other temporal lobe regions, using manually traced regions of interest (ROI).^{7–9} Although the precise neural correlates of altered mean diffusivity measurements are uncertain, increased mean diffusivity most likely results from loss of neurones, axons and dendrites, resulting in an increase in extracellular space and raised water diffusivity in these regions.⁷ It is unknown whether such microstructural changes, detectable by DTI, are due to amyloid or neurofibrillar tangle formation or some other neuropathological

Abbreviations: ARWMC, age-related white matter change; DTI, diffusion tensor imaging; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; RAVLT, Rey Auditory Verbal Learning Test; ROI, regions of interest

process in Alzheimer's disease. However, the finding of a negative correlation between hippocampal diffusivity and volume in people with MCI indicates that both measurements are sensitive to early Alzheimer's disease neuropathology.⁷ Using manually defined ROI analyses, a recent study has identified marked changes in volume, mean diffusivity and fractional anisotropy indices in the hippocampus in participants with MCI compared with age-matched controls.⁹ Specifically, compared with volume measurements, raised left hippocampal mean diffusivity was found to be a strong independent predictor of poor verbal memory performance in both controls and participants with MCI.

In this study, we investigated whether mean diffusivity and fractional anisotropy measurements differed between participants with MCI and age-matched controls, using an optimised DTI protocol¹¹ and a fully automated voxel-by-voxel method of data analysis. This approach assesses the entire brain, rather than just one structure, and circumvents any operator-introduced errors in the manual selection of ROI for analysis. In addition, we investigated the relationship between measurements of water diffusivity and performance on memory and other cognitive tasks across participants.

METHODS

Patients

Participants were 17 healthy elderly adults (7 women and 10 men, mean age 73.59 (standard deviation (SD) 9.06) years, median Mini-Mental State Examination (MMSE) score 28 (range 27–30)) and 17 people with MCI (7 women and 10 men, mean age 73.58 (SD 8.96) years, median MMSE score 26 (range 24–29)). The local ethics committee approved the study and all participants gave informed consent. In this study, participants were categorised on the basis of combination of medical history, clinical and radiological examination and neuropsychological assessment by consensus meeting of a neurologist and two neuropsychologists. Participants were excluded from the study if there was evidence of prior head trauma, a primary psychiatric diagnosis, infectious or endocrine cause of cognitive dysfunction, a Geriatric Depression Scale score >16, alcohol consumption >30 g/day in men and >20 g/day in women, or a history of habituation to drugs such as benzodiazepines or narcotics. Controls and participants with MCI were recruited from newspaper advertisements and were all community dwelling. All underwent neuropsychological testing on a battery of tests devised to detect cognitive impairment in elderly adults, including a 7-subtest short form of the Wechsler Adult Intelligence Scale—3rd edition,^{12,13} the Logical Memory, Paired Associates and Face Recognition subtests of the Wechsler Memory Scale—3rd edition,¹⁴ Rey Auditory Verbal Learning Test,¹⁵ Boston Naming Test,¹⁶ letter and category verbal fluency,¹⁵ Trail Making Test forms A and B,¹⁷ the Number Location, Dot Counting and Cube Analysis subtests of the Visual Object and Space Perception Battery,¹⁸ and Stroop Neuropsychological Screening test.¹⁵

Amnesic MCI was diagnosed according to the Mayo Clinic Alzheimer's Disease Research Centre criteria,^{19,20} and required the following: (a) subjective memory impairment according to the patient or an informant; (b) objective memory

impairment indicated by a delayed recall score on the Wechsler Memory Scale—3rd edition Logical Memory subtest and a Rey Auditory Verbal Learning Test (RAVLT) score of at least 1.5 SD from age-adjusted and education-adjusted norms;¹⁹ (c) relatively normal performance on other tests measuring other cognitive domains; and (d) relatively normal activities of daily living. Participants were excluded if they satisfied a diagnosis for dementia as defined by either NINCDS-ADRDA criteria²¹ or Diagnostic and statistical manual—4th edition.²² Hachinski scores, in addition to Wahlund age-related white matter change (ARWMC) scores, were recorded for all participants.²³ Wahlund scores were obtained from high-resolution T2-weighted FLuid Attenuation Inversion Recovery scans. The mean (SD) duration between neuropsychological testing and DTI acquisition was 57 (24) and 84 (61) days for participants with MCI and controls, respectively. Participants with MCI were not given any cognitive enhancing agents during the course of the study.

MRI methods

DTI was carried out with a 1.5-T Siemens Sonata scanner (Siemens Sonata, Erlangen, Germany) using an optimised diffusion tensor sequence.¹¹ The imaging parameters were 45 axial slices, field of view 23 cm, repetition time/echo time 6000/106 ms, 2.5 mm slice thickness with 0.25 mm gap, acquisition matrix 128×128 and 60 images acquired at each location consisting of 16 low-diffusion-weighted ($b = 0$) and 44 high-diffusion-weighted images ($b = 1100$ s/mm²) in which the encoding gradient vectors were uniformly distributed in space using the electrostatic approach described previously.¹¹ The reconstruction matrix was 256×256, resulting in an in-plane resolution of 890×890 μ m. The total scan time was 8 min. The mean diffusivity, a rotationally invariant measurement of diffusion equal to one third of the trace of the diffusion tensor, was used for analysis.

Neuropsychological assessment

The participants in this study are part of an ongoing longitudinal investigation on MCI receiving serial neuropsychological assessments at 12-monthly intervals. The neuropsychological tests used in this study have been previously reported in another study.²⁴ We have recently shown that semantic measures such as category fluency, when used in conjunction with a test of episodic memory, may increase the sensitivity for detecting preclinical Alzheimer's disease.²⁴ To test whether mean diffusivity and fractional anisotropy measurements correlated with cognitive function, we examined the correlation of DTI with three tasks that are sensitive to MCI—namely, the RAVLT,¹⁵ the Boston Naming Test¹⁶ and a category fluency test.²⁵

Data analysis

As all participants in this study had different brain sizes and varying degrees of cortical atrophy, it was imperative that the effects of anatomical variation be minimised to enable accurate voxel-by-voxel statistical comparison between the two groups. This was achieved by the rigorous non-linear

Table 1 Demographic characteristics of participants, including performance on neuropsychological tests

Participants	Age (years)	Education	GDS	MMSE	RAVLT	BNT	Semantic fluency
Controls	73.59 (9.06)	11.29 (2.87)	4.82 (4.33)	28.24 (1.25)	52.47 (7.24)	55.17 (3.83)	17.12 (5.11)
MCI	73.58 (8.96)	9.71 (3.06)	7.41 (4.91)	26.12 (2.21)	39.27 (5.09)	48.69 (6.22)	12.06 (3.32)
p Value	NS	NS	NS	0.006	<0.001	0.006	0.009

Values are mean (SD).

BNT, Boston Naming Test; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NS, not significant; RAVLT, Rey Auditory Verbal Learning Test.

Table 2 Mean Hachinski and age-related white matter change scores in participants

Participants	Hachinski score	Wahlund score (ARWMC)				
		Frontal	Parieto-occipital	Basal ganglia	Infratentorial	Temporal
Controls	1.13 (1.26)	0.56 (0.96)	0.69 (0.95)	0 (0)	0.06 (0.25)	0.31 (0.48)
MCI	1.00 (1.17)	0.65 (0.79)	0.59 (0.80)	0 (0)	0.18 (0.39)	0.12 (0.33)

Values are mean (SD).

ARWMC, age-related white matter change; MCI, mild cognitive impairment.

registration of diffusion images of all participants into the same standard anatomical space. Although MRI studies are normally based on the use of T1-weighted three-dimensional volumetric scans, with DTI, several T2-weighted images without any diffusion encoding ($b = 0$ images) are inherently acquired as part of the acquisition sequence. These $b = 0$ scans are in the same raw image space as the generated mean diffusivity and fractional anisotropy maps, and can be used to register individual data into standard anatomical space to enable voxel-by-voxel statistical analysis of diffusivity indices between groups. A similar approach was successfully used to investigate diffusivity changes in patients with schizophrenia compared with those in controls.^{26, 27} Normalisation of $b = 0$ images was achieved by rescaling the intensities between 0 and 100 using two histogram per cent critical thresholds. All pixel values that lie outside the lower and upper 0.1 centile range were assigned values of 0 and 100 pixels, respectively. Normalised $b = 0$ images of participants were non-linearly registered using mutual information to the Montreal Neurological Institute template known as the ICBM152.²⁸ The ICBM152 was generated from 152 T1-weighted brain volumes. A hierarchical fitting strategy with a minimum step size of 2 mm was used for this registration procedure.²⁹ A two-sample t test was used to determine significant difference between the two groups. Statistical significance, corrected for multiple comparisons, was determined using gaussian random field theory using a blurring kernel of 5 mm (full-width at half-maximum).³⁰ A value of $t > 4.095$ was considered to be significant ($p < 0.001$). Voxels from the mean diffusivity and fractional anisotropy maps with $t > 4.096$ were automatically extracted and classified as a ROI when ≥ 20 voxels were contiguous. Pearson's correlation coefficients calculated across both groups for each generated ROI were used to determine the relationship between mean diffusivity and fractional anisotropy measurements and neuropsychological assessment scores. Bonferroni correction for multiple comparisons was applied to maintain the total type I error rate at a sufficient level. In this case, only corrected correlations of $p < 0.01$ were considered significant. The mean diffusivity measurement from each ROI was used to derive the correlation coefficients.

RESULTS

Table 1 gives the demographic information of participants, including group mean neuropsychological scores. Between the MCI cohorts and controls, there were no significant differences in age, sex ratio, education level or extent of depressive symptoms. Neuropsychological tests showed significant differences in cognitive function between the groups, as expected. Table 2 shows ARWMC scores found on high-resolution FLuid Attenuation Inversion Recovery MRI for the two cohorts. We found no significant difference in Hachinski scores between the two groups or in Wahlund scores for several different brain regions.

After controlling for atrophic and anatomical variation by non-linearly registering each participant's images to ICBM152 stereotactic space, we found no significant differences ($p < 0.001$) on the normalised T2-weighted MRI ($b = 0$) between the two groups for any brain region indicating a high level of accuracy for image registration. Figure 1 shows the accuracy of the normalisation procedure for the $b = 0$ images. Compared with controls, we found several regions in the brains of the participants with MCI with significantly increased measurements of mean diffusivity. Table 3 gives the stereotactic coordinates and mean of mean diffusivity measurements for each group. The mean diffusivity was increased in the left and right entorhinal cortices (BA28), the occipital-parietal lobe boundaries (BA18 and BA19), right supramarginal gyrus (BA40) and right frontal lobe precentral gyri (BA4 and BA6). These regions have been overlaid on the average mean diffusivity model constructed from the participants' data and a T1-weighted averaged model (fig 2). We found no significant differences in the controls between measurements of mean diffusivity in either the left or right entorhinal cortices. However, for the participants with MCI, we found a significant increase in mean diffusivity in the left entorhinal cortex when compared with that in the right ($p < 0.011$).

We found significantly decreased fractional anisotropy ($p < 0.001$) in the MCI group in parahippocampal white matter structures and right thalamus compared with controls (fig 3). Table 4 gives the stereotactic coordinates and mean fractional anisotropy measurements for the MCI group and

Table 3 Regional mean diffusivity measurements for participants with mild cognitive impairment and age-matched controls

Region	Talairach coordinate				Mean (SD) diffusivity ($\times 10^6$ mm ² /s)	
	x	y	z	t Value	Control	MCI
L entorhinal cortex (BA28)*	-24	-7	-32	4.2	860 (95)	1081 (147)
R entorhinal cortex (BA28)	27	-8	-30	4.3	875 (64)	1006 (115)
R occipital/parietal cortex (BA18/BA19)	18	-84	33	4.5	898 (96)	1049 (117)
R parietal lobe supramarginal gyrus (BA40)	38	-48	42	4.5	743 (53)	898 (96)
R frontal lobe precentral gyrus (BA4)	38	-19	47	4.3	925 (88)	1245 (211)
R frontal lobe precentral gyrus (BA6)	31	-3	49	4.1	860 (21)	1175 (172)

L, left; MCI, mild cognitive impairment; R, right.

Data presented are from regions of interest consisting of ≥ 20 contiguous pixels.

*Kolmogorov-Smirnov test showed that mean diffusivity measures in the entorhinal cortex were normally distributed and that the difference between mean diffusivity measures between controls and participants with MCI was significant ($D = 0.824$, $p < 0.001$).

Figure 1 A representative plot of normalised $b=0$ signal intensity for a column of pixels transversing the left hippocampal formation through the region of the entorhinal cortex with an increased mean diffusivity measurement for controls (solid line) and participants with mild cognitive impairment (dashed line) in ICMB152 standard space. The plots represent averaged (with SD) pixel signal intensity for all participants in each group. The stereotaxic coordinates of the column are $x=25$ and $y=-7$, with pixels ranging from $z=-36$ to -22 .

controls. We found no significant differences in fractional anisotropy measurements between left and right parahippocampal subgyral white matter within the MCI cohort. We also found significant negative correlations between mean regional mean diffusivity measurements and scores from the MMSE, RAVLT, Boston Naming Test and Category Fluency tests within the entorhinal cortices, right parietal supramarginal gyrus and right frontal precentral gyrus calculated across both participant groups. Table 5 gives Pearson correlation coefficients for regional mean of mean diffusivity measurement and neuropsychological assessment scores. The highest correlation coefficients were found for mean diffusivity measurements within the left entorhinal cortex. The RAVLT was the neuropsychological test most strongly correlated with the regional mean diffusivity measurements. We found no significant correlations between age and the mean of mean diffusivity measurement in any region.

We found significant positive correlations for regional mean fractional anisotropy measurements and neuropsychological scores primarily for parahippocampal white matter, right thalamus and left posterior cingulate gyri calculated across all participants. Table 5 also gives correlation coefficients for regional mean fractional anisotropy measurements and neuropsychological assessment scores. Of all neuropsychological tests, the highest correlation coefficients were found between the RAVLT and regional mean fractional anisotropy measurements. We found no significant correlations between age and any regional mean fractional anisotropy measurement. When comparing group differences, we found no evidence of significantly reduced mean diffusivity or raised fractional anisotropy measurements in any cortical or white matter area in the MCI group.

DISCUSSION

Several novel findings were obtained from this study. After controlling for variations in brain size due to atrophy and carefully assessing differences in vascular risk factors and age-related white matter changes, we found significantly increased mean diffusivity and reduced fractional anisotropy measures within anatomical regions associated with early Alzheimer's disease neuropathology in a group of participants considered at risk of developing Alzheimer's disease. These findings were derived using fully automated postprocessing and analytical methods. A potential problem with the analytical approach is that non-optimised image registration associated with anatomical variation and geometric distortion of diffusion images may result in raised mean diffusivity

Figure 2 Representative coronal images showing regions of considerably altered diffusivity levels between participants with mild cognitive impairment and age-matched controls overlaid on the averaged mean diffusivity model (top) and an averaged T1-weighted control model (bottom). Increased mean diffusivity was found in the left and right entorhinal cortices, BA28 ($y=-3$ and -7 mm), in addition to the right frontal precentral gyrus, BA6 ($y=-3$ mm) and BA4 ($y=-19$ mm). Areas with increased mean diffusivity were also found in the right parietal supramarginal gyrus, BA40 ($y=-48$ mm), and in the occipital-parietal lobe boundaries, BA18 and BA19 ($y=-84$ mm).

measurements in the MCI group owing to cerebrospinal fluid inclusion in various anatomical locations. To test the accuracy of our registration procedure, we evaluated the null hypothesis—that is, whether there were any significant differences between the normalised anatomical T2-weighted ($b=0$) images between the two participant groups. As this test showed no significant difference between the two groups for any brain region, we believe that altered measurements of diffusivity detected in this study are due to microstructural changes in brain tissue and not because of indirect measurements of regional brain atrophy due to registration error. This condition is true only if $b=0$ images of all participants are accurately normalised. To test this premise for all participants, we plotted the normalised $b=0$ signal intensity for a column of pixels transversing the left hippocampus at the level of the entorhinal cortex with raised mean diffusivity measurement (fig 1). This plot shows that grey matter pixels for this region are normalised across participants, thus enabling appropriate statistical analysis of $b=0$ images and true assessment of the accuracy of the image registration procedure.

As shown in fig 2, regions with markedly raised mean diffusivity were found to lie within grey matter structures. Furthermore, the mean of mean diffusivity measurements found in this study closely correlated with mean diffusivity

Table 4 Regional mean fractional anisotropy values for patients with mild cognitive impairment and age-matched controls

Region	Talairach coordinate			t Value	Mean (SD) fractional anisotropy	
	x	y	z		Control	MCI
L limbic lobe (temporal subgyral WM)	−27	−6	−27	4.1	0.24 (0.02)	0.19 (0.02)
R limbic lobe (temporal subgyral WM)	35	−6	−25	4.1	0.27 (0.02)	0.20 (0.02)
R limbic lobe (parahippocampal gyrus WM)*	25	−9	−25	4.2	0.24 (0.03)	0.19 (0.02)
R temporal lobe (subgyral WM)	34	−7	−12	4.1	0.48 (0.03)	0.44 (0.04)
R thalamus	19	−31	9	4.3	0.34 (0.03)	0.28 (0.04)
L limbic lobe (posterior cingulate)	−24	−66	18	4.3	0.42 (0.05)	0.34 (0.05)

L, left; MCI, mild cognitive impairment; R, right; WM, white matter.
Data presented are from regions of interest >20 pixels in volume.
*Kolmogorov–Smirnov test found that mean diffusivity measurements within parahippocampal white matter were normally distributed and that the difference in mean diffusivity measurements between controls and participants with MCI was significant ($D=0.882$, $p<0.001$).

values derived from hippocampal and occipitoparietal regions in participants with MCI reported in independent studies using manually derived ROI.^{8–9} By evaluating data on a pixel-by-pixel basis using an automated approach, we have confirmed changes in diffusivity localised to both the left and right entorhinal cortices, with noticeably higher mean diffusivity localised to the left entorhinal cortex. Such regions are associated with early Alzheimer’s disease. In addition, the mean regional mean diffusivity measurements were found to correlate significantly with neuropsychological assessment scores, in particular the RAVLT, a test of episodic memory.

Several other neuroanatomical structures with increased diffusivity measurements were observed—namely, regions in the right occipital–parietal lobe boundary (BA18 and BA19), right parietal (BA40) and frontal lobes (BA4 and BA6). Evidence in the literature suggests that temporal, occipitoparietal and parietal lobe regions, believed to be associated with visual recognition and memory, may be associated with

the early breakdown of neural networks in patients with MCI.³¹ Reduced visual attention has been reported in both patients with MCI and in those with Alzheimer’s disease.^{31–32} Within regions BA18 and BA19, we did not find any correlations between the mean of mean diffusivity measurements and neuropsychological performance. The absence of relationships between the diffusivity measurements and neuropsychological scores is probably because of their not depending heavily on visual selective attention for successful performance. Although the neural correlates of dynamic visual attention remain undetermined, possible mechanisms seem to involve perturbed connective feedback loops between posterior parietal and superior temporal lobe areas³³ and visual cortices,³² regions with raised mean diffusivity measurements.

The experimental finding of increased mean diffusivity in frontal lobe regions (BA4 and BA6), believed to be associated with higher motor function, is intriguing. Previous DTI studies on patients with Alzheimer’s disease have shown preservation of white matter tracts that project into motor cortical regions.^{34–35} In our MCI group, we found no significant difference in fractional anisotropy measurements within pyramidal tracts projecting into the frontal cortex. As patients with MCI and those with Alzheimer’s disease have shown impaired motor function to both fine and complex motor tasks,³⁶ the findings of microstructural changes in the supplementary motor and motor cortices in participants with MCI suggest that raised measurements of mean diffusivity in BA4 and BA6 may be more sensitive markers of the neural correlates of impaired motor function than reduced fractional anisotropy measurements in white matter tracts projecting into these cortical regions. Neuropathological studies have reported considerable synaptic loss in BA6³⁷ and the presence of senile plaques and neurofibrillar tangle formations in the motor cortex³⁸ in the brains of patients with Alzheimer’s disease, giving further evidence of altered cytoarchitecture in these cortical regions.

Another novel finding from this study was the markedly decreased fractional anisotropy in parahippocampal and parietal cortices and thalamus, providing evidence of involvement of microstructural white matter damage in participants with MCI. Furthermore, regions with reduced mean fractional anisotropy measurements correlated significantly with neuropsychological performance. The findings of reduced mean fractional anisotropy in the thalamus and posterior cingulate are consistent with MRI morphological studies on MCI.⁵ However, it should be noted that the size of the smoothing kernel used in the analysis can affect voxel-based morphological analyses of fractional anisotropy data.²⁷ In our participant cohort, changing the size of the smoothing kernel (3–8 mm) had limited effect on the anatomical locations with markedly raised mean diffusivity or reduced fractional anisotropy measurements. Analysis of mean

Figure 3 Representative coronal fractional anisotropy maps showing regions of significantly altered anisotropy levels between the patients with mild cognitive impairment and age-matched controls. Reduced fractional anisotropy was found in the left and right temporal subgyral white matter ($y = -6$ mm) and along the right parahippocampal gyrus ($y = -9$ mm). Areas with reduced fractional anisotropy were also found in the right thalamus ($y = -31$ mm) and left posterior cingulate ($y = -66$ mm).

Table 5 Pearson's correlation coefficients between regional mean diffusivity (top), fractional anisotropy (bottom) measurements and neuropsychological assessment scores, calculated across both participant groups

Region	Age	MMSE	RAVLT	BNT	Semantic fluency
L entorhinal cortex (BA28)	0.321	-0.446*	-0.732*	-0.585*	-0.588*
R entorhinal cortex (BA28)	0.340	-0.280	-0.652*	-0.508*	-0.428
R occipital/parietal cortex (BA18/BA19)	0.032	-0.067	0.017	0.136	-0.039
R parietal lobe supramarginal gyrus (BA40)	0.046	-0.552*	-0.689*	-0.460*	-0.557*
R frontal lobe precentral gyrus (BA4)	0.122	-0.550*	-0.671*	-0.216	-0.263
L limbic lobe (temporal subgyral WM)	-0.163	0.373	0.731*	0.392	0.281
R limbic lobe (temporal subgyral WM)	-0.096	0.449*	0.793*	0.430*	0.347
R limbic lobe (parahippocampal gyrus WM)	-0.133	0.381	0.649*	0.203	0.209
R temporal lobe (subgyral WM)	-0.137	0.219	0.397	0.328	0.194
R thalamus	-0.336	0.534*	0.534*	0.384	0.619*
L limbic lobe (posterior cingulate)	-0.306	0.103	0.534*	0.313	0.211

Data presented are from regions of interest >20 pixels in volume.

BNT, Boston Naming Test; L, left; MMSE, Mini-Mental State Examination; R, right; RAVLT, Rey Auditory Verbal Learning Test; WM, white matter.

*Correlation is significant at the 0.01 level.

diffusivity measurements using voxel-based morphometry techniques is less sensitive to filter size owing to the data being more normally distributed.²⁷⁻³⁹ However, to test whether the mean diffusivity and fractional anisotropy measurements in the hippocampal formation with markedly altered diffusivity measurement were normally distributed, we analysed the diffusivity indices in these regions using a Kolmogorov-Smirnov test. As shown in tables 3 and 4, the non-parametric Kolmogorov-Smirnov analysis showed that the mean diffusivity and fractional anisotropy measurements were normally distributed and that there was a significant difference in the diffusivity indices between the controls and participants with MCI for these regions.

Apart from the small sample size, this study has several limitations. A recent study has highlighted the effect of the method of subject recruitment and levels of cognition in participants with MCI.⁴⁰ As we recruited our participants from newspaper advertisements, the volunteers may not be truly representative in terms of their disease aetiology, which in MCI is heterogeneous, or in terms of general demographic characteristics. They may also possess insight into their condition that motivated them to volunteer and, therefore, may be of higher functioning than patients referred to community clinics. However, we used stringent definitions and diagnostic criteria for amnesic MCI¹⁹ and were careful to assess vascular risk factors and ARWMC between participants with MCI and controls. Another limitation of our study was the duration between neuropsychological testing and acquisition of MRI data, which was approximately 2 months. In this time frame, although we cannot rule out that MCI in some participants may have progressed to early Alzheimer's disease, their neuropsychological performance may have varied, which could potentially affect the correlations between DTI measurements and cognitive scores. Uncertainty regarding the precise neural correlate of raised mean diffusivity measurement is also problematic, although the negative correlation between increased mean diffusivity and atrophic change in the hippocampus reported in participants with MCI indicates that these measurements may relate to a similar altered neuropathological state.⁷ A much larger study design would also enable correlation of diffusivity measurements and performance with neuropsychological tests, exclusively in an MCI group. Such an approach would provide conclusive evidence of the relationship between DTI-based indices and cognitive performance, which has the potential to improve identification of people at risk of developing Alzheimer's disease. Clearly, further DTI-based MCI studies incorporating a reference Alzheimer's disease group are required to fully elucidate the utility of this imaging modality.

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REFERENCES

- Visser PJ, Scheltens P, Verhey FRJ. Do MCI criteria in drug trials accurately identify subjects with predementia Alzheimer's disease? *J Neurol Neurosurg Psychiatry* 2005;**76**:1348-54.
- Peterson RC, Doody R, Kurtz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol* 2001;**58**:1985-92.
- Jack CR, Shiung MM, Gunter JL, et al. Comparison of different MRI brain atrophy rate measures with clinical progression in AD. *Neurology* 2004;**62**:591-600.
- Karas GB, Scheltens P, Rombouts SARB, et al. Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. *NeuroImage* 2004;**23**:708-16.
- Pennanen C, Testa C, Laakso MP, et al. A voxel based morphometry study on mild cognitive impairment. *J Neurol Neurosurg Psychiatry* 2005;**76**:11-14.
- Csernansky JG, Hamstra J, Wang L, et al. Correlations between antemortem hippocampal volume and postmortem neuropathology in AD participants. *Alzheimer's Dis Assoc Disord* 2004;**18**:190-5.
- Kantarci K, Petersen RC, Boeve BF, et al. DWI predicts future progression to Alzheimer's disease in amnesic mild cognitive impairment. *Neurology* 2005;**64**:902-4.
- Fellgiebel A, Wille P, Muller MJ, et al. Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study. *Dement Geriatr Cogn Disord* 2004;**18**:101-8.
- Muller MJ, Greverus D, Dellani PR, et al. Functional implications of hippocampal volume and diffusivity in mild cognitive impairment. *NeuroImage* 2005;**28**:1033-42.
- Basser PJ, Jones DK. Diffusion-tensor MRI: theory, experimental design and data analysis—a technical overview. *NMR Biomed* 2002;**15**:456-67.
- Jones DK, Horsfield MA, Simmons A. Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging. *Magn Reson Med* 1999;**42**:515-25.
- Axelrod BN, Ryan JJ, Ward LC. Evaluation of seven-subtest short forms of the Wechsler Adult Intelligence Scale-III in a referred sample. *Arch Clin Neuropsychol* 2001;**16**:1-8.
- Wechsler D. *Wechsler Adult Intelligence Scale*. 3rd edn. New York: Psychological Corporation, 1997.
- Wechsler D. *Wechsler Memory Scale*. 3rd edn. New York: Psychological Corporation, 1997.
- Spren O, Strauss E. *A compendium of neuropsychological tests*. 2nd edn. New York: Oxford University Press, 1998.
- Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test*. Philadelphia: Lea & Febiger, 1983.
- Reitan RM, Wolfson D. *The Halstead-Reitan neuropsychological test battery: theory and clinical interpretation*. Tucson, AZ: Neuropsychology Press, 1993.
- Warrington EK, James M. *The visual object and space perception battery*. Bury St Edmunds, UK: Thames Valley Test Company, 1991.
- Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment. *Arch Neurol* 1999;**56**:303-8.
- Petersen RC, Thomas RG, Grunman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005;**352**:2379-88.

- 21 **McKhann G**, Drachmann D, Foldstein M, *et al*. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRADA Work Group under auspices of Department of Health and Human Services Task Force of Alzheimer's Disease. *Neurology* 1984;**34**:939–44.
- 22 **American Psychiatric Association**. *Diagnostic and statistical manual of mental disorders*. 4th revised edn. Washington, DC: American Psychiatric Association, 1994.
- 23 **Wahlund LO**, Barkhof F, Fazekas F, *et al*. A new rating scale for age related white matter changes applicable to MRI and CT. *Stroke* 2001;**32**:1318–22.
- 24 **O'Dowd B**, Chalk JB, de Zubicaray G. Quantitative and qualitative impairments in semantic fluency, but not phonetic fluency, as a potential risk factor for Alzheimer's disease. *Brain Impairment* 2004;**5**:177–86.
- 25 **Lucas JA**, Smith RJ, Bohac DI, *et al*. Mayo's older American normative studies: category fluency norms. *J Clin Exp Neuropsychol* 1998;**20**:194–200.
- 26 **Park HJ**, Westin CF, Kubicki M, *et al*. White matter hemisphere asymmetries in healthy subjects and in schizophrenia: a diffusion tensor MRI study. *NeuroImage* 2004;**23**:213–23.
- 27 **Jones DK**, Symms MR, Cercignani M, *et al*. The effect of filter size on VBM analyses of DTI-MRI data. *NeuroImage* 2005;**26**:546–54.
- 28 **Mazziotta J**, Toga A, Evans A, *et al*. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philos Trans R Soc Lond B Biol Sci* 2001;**356**:1293–322.
- 29 **Collins DL**, Neelin P, Peters TM, *et al*. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *Comput Assist Tomogr* 1994;**18**:192–205.
- 30 **Worsley K**, Lao CH, Aston J, *et al*. A general statistical approach for fMRI data. *Neuroimage* 2002;**15**:1–15.
- 31 **Perry RJ**, Hodges JR. Dissociation between top-down attentional control and time course of visual attention as measured by attentional dwell time in patients with mild cognitive impairment. *Eur J Neurosci* 2003;**18**:221–6.
- 32 **Kavcic V**, Duffy CJ. Attentional dynamics and visual perception: mechanisms of spatial disorientation in Alzheimer's disease. *Brain* 2003;**126**:1173–81.
- 33 **Clower DM**, West RA, Lynch JC, *et al*. The inferior parietal lobule is the target of output from the superior colliculus, hippocampus and cerebellum. *J Neurosci* 2001;**21**:6283–91.
- 34 **Rose SE**, Chen F, Chalk JB, *et al*. Loss of connectivity in Alzheimer's disease: an evaluation of white matter tract integrity with colour coded MR diffusion tensor imaging. *J Neurol Neurosurg Psychiatry* 2000;**69**:528–30.
- 35 **Bozzali M**, Falini A, Franceschi M, *et al*. White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. *J Neurol Neurosurg Psychiatry* 2002;**72**:742–6.
- 36 **Kluger A**, Gianutsos JG, Golomb J, *et al*. Patterns of motor impairment in normal aging, mild cognitive decline and early Alzheimer's disease. *J Gerontol B Psychol Sci Soc Sci* 1997;**52**:28–39.
- 37 **Clinton J**, Blackman SE, Royston MC, *et al*. Differential synaptic loss in the cortex in Alzheimer's disease: a study using archival material. *Neuroreport* 1994;**12**:497–500.
- 38 **Suva DS**, Favre I, Kraftsik R, *et al*. Primary motor cortex involvement in Alzheimer's disease. *J Neuropathol Exp Neurol* 1999;**58**:1125–34.
- 39 **Pajevic TE**, Basser PJ. Parametric and non-parametric statistical analysis of DTI-MRI data. *J Magn Res* 2003;**161**:1–14.
- 40 **Arnaiz E**, Almkvist O, Ivnik RJ, *et al*. Mild cognitive impairment: a cross-national comparison. *J Neurol Neurosurg Psychiatry* 2004;**75**:1275–80.