Cognitive impairment with and without depression history: an analysis of white matter microstructure

Shantel L. Duffy, MDR (Hons); Matt Paradise, FRANZCP; Ian B. Hickie, FRANZCP; Simon J.G. Lewis, FRACP; Sharon L. Naismith, DPsych; Jim Lagopoulos, PhD

Duffy, Paradise, Hickie, Lewis, Naismith — Ageing Brain Centre, Brain & Mind Research Institute, University of Sydney, Camperdown, Australia; Duffy, Paradise, Hickie, Lewis, Naismith, Lagopoulos — Clinical Research Unit, Brain & Mind Research Institute, University of Sydney, Camperdown, Australia

Background: Mild cognitive impairment (MCI) and late-life depression are clinical syndromes that often co-occur and may represent an early manifestation of neurodegenerative disease. The present study examined white matter microstructure in patients with MCI with and without a history of major depression compared with healthy controls. **Methods:** Older adults with MCI and no history of major depression (MCI), adults with MCI and euthymic major depression (MCI-MD) and healthy controls underwent comprehensive medical, psychiatric and neuropsychological assessments. Participants also underwent diffusion tensor imaging, which was analyzed using tract-based spatial statistics. White matter hyperintensity (WMH) burden and medical burden were also quantified. **Results:** We enrolled 30 participants in the MCI group, 36 in the MCI-MD group and 22 in the control group. Compared with controls, participants in the MCI group had significantly reduced fractional anisotropy (FA) in the corpus callosum, superior longitudinal fasciculus (SLF), corona radiata and posterior thalamic radiation. Participants in the MCI-MD group had significantly reduced FA in the corpus callosum, internal capsule, external capsule, corona radiata, posterior thalamic radiation, sagittal striatum, fornix, SLF, uncinate fasciculus and right cingulum compared with controls. No significant differences in FA were observed between the MCI and MCI-MD groups. Participants in the MCI-MD group had greater medical burden (p = 0.020) and WMH burden than controls (p = 0.013). **Limitations:** Study limitations include the cross-sectional design and antidepressant medication use. **Conclusion:** To our knowledge, this study is the first to compare white matter microstructure in patients with MCI with and without a history of major depression and suggests that a common underlying structural white matter change may underpin cognitive impairment in both MCI groups. Further research is needed to delineate the pathophysiological mechanisms underlying these microstructural changes.

Introduction

Mild cognitive impairment (MCI) and late-life depression are common and disabling disorders and are both independently associated with an increased risk of dementia, including Alzheimer disease[1,2] and vascular dementia.[3] It is estimated that 1 in 5 people will have a major depressive episode (MDE) in their lifetime, and there is strong evidence that a single MDE can increase the risk of dementia up to 3-fold.[4] In addition to the constellation of mood and somatic symptoms associated with major depression (MD), studies have shown that at least half of older adults with MD also meet criteria for MCI, even in the remitted state.[3,5] Mild cognitive impairment is a clinical syndrome characterized by significant decrements in neuropsychological functioning in 1 or more cognitive domains and is widely recognized as a transitional stage between normal aging and dementia.[6] The condition can be present with or without a history of MD, and rates of

Correspondence to: S.L. Naismith, Ageing Brain Centre, 94 Mallett St., Camperdown NSW 2050 Australia; sharon.naismith@sydney.edu.au

J Psychiatry Neurosci 2014;39(2):135-43.

Submitted Apr. 30, 2013; Revised Sept. 6, Sept. 25, 2013; Accepted Oct. 1, 2013.

DOI: 10.1503/jpn.130079

conversion from MCI to Alzheimer disease of up to 45% over 5 years have been reported in the literature.[1] However, patients with MCI and a lifetime history of MD have more than twice the risk of dementia than those without a history of depression.[7] Despite data detailing the substantial overlap between MCI and MD, the 2 syndromes are usually examined separately. In particular, studies examining MCI usually exclude individuals with clinically significant depressive symptoms or history of MD. Such an approach neglects to consider that shared underlying etiological pathways may lead to cognitive decline in these groups.

The pathophysiological mechanisms underpinning the association between MD, MCI and dementia are complex and currently unclear. However, a common risk factor for both MCI and late-life MD is cerebrovascular disease.[3,7] Chronic, diffuse tissue ischemia resulting from vascular risk factors (VRFs) typically manifests as white matter hyperintensities (WMH) on T_2-weighted magnetic resonance imaging (MRI) scans.[8] White matter hyperintensities are believed to reflect broad changes to white matter microstructure, and previous imaging research has shown that both MCI and MD are associated with increased WMH burden in comparison to healthy controls.[3,8] White matter microstructure can be further analyzed using diffusion tensor imaging (DTI), an MRI technique used to examine the integrity of white matter tracts by measuring the diffusion of water through neural tissue. If water mobility is unrestricted in all directions, diffusion is described as isotropic. Conversely, if water mobility is restricted in any direction, diffusion is described as anisotropic. In the brain, anisotropy is created through the restriction of perpendicular movement by axon membranes and myelin sheaths in white matter tracts.[9] Fractional anisotropy (FA) is a quantitative index of diffusion derived from DTI and reflects the integrity of white matter microstructure.[10] Increased WMH burden, particularly in the periventricular and deep white matter,[3] and decreased microstructural white matter integrity measured using DTI[11] have led to a disconnection syndrome theory for the cognitive impairment seen in patients with MCI, MD and dementia.[12]

Accordingly, a review of DTI studies in patients with MD showed a consistent reduction in FA of frontal and temporal white matter tracts compared with controls in region of interest (ROI) studies.[3,11,13] Further reductions in the occipital and right parietal regions, putamen and caudate have also been demonstrated in studies using voxel based analysis (VBA).[13,14] Similar findings of decreased FA in frontal and temporal white matter have been demonstrated in patients with MCI without a history of depression.[11,15] Importantly, the white matter changes seen in patients with MCI and MD parallel those reported in patients with Alzheimer disease and vascular dementia, though more severe and extensive disruptions are seen in patients with advanced disease.[11] These findings support the notion that cognitive impairment may be underpinned by white matter pathology in these patient groups. However, previous studies have examined FA locally using ROI analysis or globally using VBA techniques, which have inherent limitations and biases. Tract-based spatial statistics (TBSS) is a global analysis technique that overcomes the need for a priori hypothesis in ROI analyses and minimizes the effects of misalignment associated with VBA, making this analysis technique more robust and sensitive.[16]

To our knowledge, no studies to date have concurrently compared the white matter microstructure of patients with MCI with no history of MD (MCI group) to patients with MCI and remitted late-life major depression (MCI-MD group). The aim of this study was to assess the microstructural integrity of white matter in these 2 MCI groups in comparison to age-matched healthy controls. For comparability with prior literature, we conducted these analyses with reference to information on VRFs, WMH and medical burden.

Methods

Participants

We recruited older adults with MCI or with MCI-MD from the Healthy Brain Aging Clinic at the Brain and Mind Research Institute (BMRI) in Sydney, Australia. All patients were attending this specialist early intervention clinic for new onset mood or cognitive problems. We recruited healthy control participants via community advertisement. Exclusion criteria were age younger than 50 years at the time of testing; suspected dementia; Mini Mental State Examination (MMSE) score < 24;[17] current DSM-IV major depression; history of neurologic or primary psychotic illness, stroke, head injury (with loss of consciousness > 30 minutes) or substance misuse; and medical contraindications to MRI scanning. The University of Sydney Institutional Ethics Committee approved our study protocol, and all participants gave written informed consent before participation.

Clinical assessment

Using a semi-structured interview, an old age psychiatrist recorded a full medical, clinical, psychiatric and medication history. For each participant, the psychiatrist used the Structured Clinical Interview for DSM-IV Disorders[18] to assess lifetime and current major depression and used the 17-item Hamilton Rating Scale for Depression (HAM-D)[19] to measure depressive symptoms. In addition, the psychiatrist rated psychosocial functioning using the Social and Occupational Functioning Assessment Scale[18] (SOFAS) and severity of medical burden using the Cumulative Illness Rating Scale[20] (CIRS) total score. The following vascular risk factors were rated as being present (1) or absent (0): history of diabetes, history of treated or untreated hypertension, past or present smoking history, cardiovascular disease and elevated cholesterol. Each risk factor was given an equal weighting and summed to give a total risk value (range 0–5).[21] Medication use was also recorded.

As detailed elsewhere,[22] a standardized neuropsychological assessment was conducted for each participant by a clinical neuropsychologist. The assessment covered a range of domains, including attention, working memory, processing speed, verbal and visual learning and memory, language,

and visuospatial and executive functioning. For reporting purposes, MMSE[17] was administered and premorbid intellect was estimated using the Wechsler Test of Adult Reading.[23] A clinical diagnosis of MCI was obtained using Petersen and Morris' criteria of cognitive decline of at least 1.5 standard deviations on neuropsychological tests relative to age- and (where available) education-adjusted normative data.[24] Per criteria, each participant was required to have subjective and objective cognitive decline, but with the preservation of gross functions (as reflected by a global deterioration score of 3).[25] The diagnoses of MCI were consensus-rated by an old age psychiatrist and 2 neuropsychologists based on clinical profile, neuropsychological assessment and with reference to structural MRI scans. The broad clinical definition of MCI was further categorized into amnestic MCI (aMCI) and non-amnestic MCI (naMCI) over single or multiple cognitive domains.[24] To be categorized as aMCI, participants were required to demonstrate clear evidence of deficits in memory consolidation (≥ 1.5 standard deviations), which was not considered to be due merely to poor encoding.

MRI acquisition

Imaging was conducted within 2 weeks of clinical assessment and took place at the BMRI imaging centre on a 3 T GE Discovery MR750 scanner (GE Medical Systems) using an 8-channel phased array head coil. The following images were acquired in order: (1) 3-dimensional sagittal whole-brain scout for orientation and positioning of subsequent scans; (2) T_1-weighted magnetization prepared rapid gradient-echo (MPRAGE) sequence producing 196 sagittal slices (repetition time [TR] 7.2 ms, echo time [TE] 2.8 ms, flip angle 10°, 256 × 256 matrix, 0.9 mm isotropic voxels) for anatomic reference and MCI diagnosis; (3) fluid attenuated inversion recovery (FLAIR) sequence (TR 10 000 ms, TE 130 ms, inversion time 2500 ms, 320 × 256 matrix, slice thickness 4 mm, flip angle 90°) for WMH assessment; and (4) diffusion weight imaging. The DTIs were acquired in 32 directions with the following echoplanar acquisition protocol: TR 8000 ms, TE 85 ms, 64 axial slices with 2.5 mm thickness, 128 × 128 matrix; field of view 24 cm. The effective diffusion weighting was b = 1000 s/mm^2. Two image volumes with no diffusion weighting (b = 0 s/mm^2) were also acquired at the beginning of each diffusion sequence. Acquisition of all b = 1000 s/mm^2 and b = 0 s/mm^2 images was repeated 34 times. The duration of the DTI scan was about 4 minutes, 30 seconds.

Tract based spatial statistics

After DTI acquisition, data were transferred offline for post-processing using the FSL software package (FMRIB Centre). The DTI analysis was performed following the standard procedure for voxel-wise analysis of multi-subject diffusion data.[16] Briefly, raw DTI images were corrected for motion and eddy current distortions by applying an affine alignment of the diffusion-weighted image to the b = 0 image. The DTIFIT algorithm was then used to fit the tensor model and to compute the FA maps. The resulting FA maps were processed using TBSS to facilitate voxel-wise statistical analysis. All individual FA maps were nonlinearly registered to the FMRIB58 template and then spatially transformed into standard Montreal Neurological Institute space.[16] A mean white matter skeleton was generated based on the mean FA image of all participants, which was then thresholded by an FA value of 0.2 to limit the effect of misalignment across participants and reduce the likelihood of grey matter and cerebrospinal fluid inclusion in skeleton voxels.[16] Each participant's aligned FA image was then projected onto a mean FA skeleton, and voxel-wise group comparisons of FA values were conducted along the skeleton. In all cases the distribution was built up over 5000 permutations, and significance was tested at $p < 0.05$, corrected for multiple comparisons.

Visual rating of WMH

Visual rating of WMH was assessed on FLAIR images using the Fazekas rating scale.[26] Briefly, scores of 3 areas (periventricular, deep and subcortical white matter) were rated and an overall global rating (average of the 3 scores) was determined. Scores ranged from 0 (no WMH) to 3 (large confluent areas of WMH) in each area. The ratings were performed and consensus-rated by 2 scorers (S.D. and S.N.), one of whom has previously published work in this area.[27,28] Raters were blind to the experimental group.

Statistical analysis

Data were analyzed using SPSS (version 20 for Mac). Comparisons between the MCI, MCI-MD and control groups were analyzed using 1-way analysis of variance (ANOVA) and the Scheffe post hoc test for contrasts. Sex and MCI subtype comparisons were analyzed using a χ^2 test. Associations between age at onset of MD, number of depressive episodes and FA in the MCI-MD group were conducted using Pearson correlations, and we applied Bonferroni correction for multiple comparisons. All analyses were 2-tailed and used an α level of 0.05.

Results

Participants

We enrolled 30 participants in the MCI group (mean age 68.1 ± 8.4 [range 52–82] yr), 36 in the MCI-MD group (mean age 64.6 ± 8.2 [range 52–82] yr) and 22 in the control group (mean age 64.3 ± 8.7 [range 50–84] yr). Participants with MCI were further categorized into aMCI (n = 21) and naMCI (n = 45) groups over single (n = 19) or multiple (n = 47) cognitive domains.[24]

The demographic and clinical characteristics for this sample are presented in Table 1. There was no significant difference in age, sex, years of education, depressive symptom severity (HAM-D) and premorbid IQ among the groups. As expected, MMSE scores were significantly lower in the MCI group and depression scores were significantly higher in

MCI-MD group. In total, summed vascular risk factors did not differ significantly between groups. Chronic medical burden (CIRS total score) was greater in both MCI and MCI-MD groups than the control group; however, only the MCI-MD group reached statistical significance. Psychosocial functioning (SOFAS) was also significantly reduced in the MCI-MD group compared with the control group. The MCI and MCI-MD groups did not differ from one another in any of the demographic or clinical characteristics described. In addition, the proportions of patients having aMCI or naMCI subtypes did not significantly differ between the MCI and MCI-MD groups.

In total, 32 participants reported antidepressant use: 26 in the MCI-MD group, 4 in the MCI group and 2 in the control group. The reasons for antidepressant use in the MCI and control groups included the treatment of subthreshold depression (n = 4) and anxiety symptoms (n = 1) and the treatment of chronic pain (n = 1). Antidepressants included selective serotonin reuptake inhibitors (n = 13), serotonin noradrenaline reuptake inhibitors (n = 13), tricyclic antidepressants (n = 3), noradrenaline reuptake inhibitors (n = 1), monoamine oxidase inhibitors (n = 1) and noradrenergic and specific serotonergic antidepressants (n = 1). Furthermore, at the time of assessment 7 patients were taking a mood stabilizer, 7 were taking an adjunctive antipsychotic and 7 were taking benzodiazepines (2 on an as required basis).

All patients in the MCI-MD group reported an MDE in the 5 years preceding the study but were euthymic at time of testing (as per inclusion criteria). The mean age at onset of MD was 44.7 ± 17.7 (range 18–77, median 47.0) years, and the mean number of lifetime depressive episodes was 3.4 ± 4.2 (range 1–20, median 2). Twenty participants reported their first depressive episode before age 50 (early-onset depression; EoD) and 16 after age 50 (late-onset depression; LoD).

Diffusion Tensor Imaging

As shown in Fig. 1 and Table 2, patients in the MCI group had significantly reduced FA in the splenium, body and genu of the corpus callosum, the bilateral SLF, the superior, anterior and posterior corona radiata bilaterally and the left posterior thalamic radiation compared with controls.

On the other hand, patients in the MCI-MD group had significantly reduced FA in the genu and body of the corpus callosum, bilaterally in the internal capsule, external capsule, anterior and superior corona radiata, posterior thalamic radiation, sagittal striatum, the fornix, SLF, uncinate fasciculus and the right cingulum compared with controls.

There were no significant differences in FA between the MCI and MCI-MD groups, and there were no regions where controls had significantly reduced FA in comparison to participants in the MCI or MCI-MD groups. Furthermore, there was no significant difference in FA between the aMCI and naMCI subgroups. In the MCI-MD group, age at onset of MD and number of MD episodes did not significantly correlate with FA values in any region analyzed.

Table 1: Demographic and clinical characteristics of participants with MCI and no depression history (MCI), MCI and a history of major depression (MCI-MD) and healthy controls

	Group; mean ± SD*				
Characteristic	MCI n = 30	MCI-MD n = 36	Control n = 22	Statistic†	p value
Sex, female; no. (%)‡	11 (36.7)	19 (52.8)	14 (63.6)	3.9	0.14
Age, yr	68.1 ± 8.4	64.6 ± 8.2	64.3 ± 8.7	1.9	0.16
Education, yr	14.3 ± 3.5	13.9 ± 3.6	13.5 ± 2.8	0.3	0.71
Mini Mental State Examination	28.0 ± 2.0§	28.5± 2.0	29.4 ± 0.9	4.1	0.019
WTAR — Predicted IQ	106.9 ± 9.2	108.2 ± 8.6	107.4 ± 7.3	1.8	0.84
SOFAS	75.4 ± 10.2	69.1 ± 9.9¶	82.3 ± 9.6	11.1	< 0.001
HAM-D	3.4 ± 3.4	7.7 ± 4.6¶	1.9 ± 2.2	18.3	< 0.001
CIRS, total score	5.2 ± 2.7	5.8 ± 3.4§	3.5 ± 2.0	4.2	0.019
Vascular risk factors, no. (%)‡					
Diabetes	2 (6.7)	6 (16.7)	3 (13.6)	1.6	0.45
Hypertension	15 (50.0)	14 (38.9)	5 (22.7)	3.1	0.21
Smoking history	20 (66.7)	21 (58.3)	12 (54.5)	1.3	0.53
Cardiovascular disease	4 (13.3)	2 (5.5)	0 (0.0)	3.8	0.15
Hypercholesterolemia	10 (33.3)	20 (55.5)	7 (31.8)	4.0	0.14
Total	1.8 ± 1.1	1.8 ± 1.0	1.4 ± 0.7	1.5	0.23
Fazekas White Matter Ratings					
Periventricular white matter	1.2 ± 0.8	1.5 ± 0.9	1.0 ± 1.0	2.7	0.07
Deep white matter	0.8 ± 0.7	1.2 ± 1.0§	0.6 ± 0.8	3.6	0.032
Subcortical white matter	0.7 ± 0.5	1.0 ± 0.9	0.6 ± 0.7	2.4	0.10
Global rating	0.9 ± 0.7	1.3 ± 1.0§	0.6 ± 0.7	4.7	0.012

CIRS = Cumulative Illness Rating Scale; HAM-D = Hamilton Rating Scale for Depression; MCI = mild cognitive impairment; MD = major depression; SD = standard deviation; SOFAS = Social and Occupational Functioning Assessment Scale; WTAR = Wechsler Test of Adult Reading.
*Unless otherwise indicated.
†Statistics represent 1-way analysis of variance with Scheffe post hoc test, unless otherwise stated.
‡χ^2 statistic.
§Post hoc paired comparisons showed significant ($p < 0.05$) group difference compared with controls.
¶Post hoc paired comparisons showed significant ($p < 0.01$) group difference compared with patients with MCI and controls.

White matter hyperintensities

Compared with controls, participants in the MCI-MD group had significantly greater WMH burden on ratings of global severity and in the deep white matter. No significant differences were found between the MCI and MCI-MD groups, or between the MCI and control groups.

Discussion

To our knowledge, this study is the first to examine concurrently the microstructural integrity of white matter in patients with MCI with and without a history of MD. In comparison to healthy controls, we found that MCI (without lifetime depressive history) was associated with reduced FA in frontal and midbrain regions. Participants who had MCI and remitted MD also demonstrated this pattern and additional white matter changes in temporal regions. Furthermore, we found that in comparison to controls, participants in the MCI-MD group had significantly greater chronic medical burden and (visually rated) WMH burden, especially in the deep white matter, and impaired psychosocial functioning. Interestingly, we did not find any significant differences in white matter microstructure between the MCI and MCI-MD groups.

From a clinical perspective, our finding of significantly reduced FA in major white matter tracts in patients with MCI and those with MCI-MD supports the hypothesis that brain disconnection plays a critical role in the pathophysiology of MCI.[29] We found significantly reduced FA in the splenium, body and genu of the corpus callosum; SLF; the superior, anterior and posterior corona radiata; and the left posterior thalamic radiation in the MCI group compared with the control group. These findings are aligned with those of previous studies that report significantly reduced FA in the hippocampus, genu and splenium of the corpus callosum; posterior cingulum; corona radiata; SLF; and frontal and temporal white matter of patients with MCI compared with controls.[11,15] The only region that differs between our findings and previous ones is that of reduced FA in the posterior thalamic radiation. To our knowledge, no previous studies have found significantly reduced FA in the posterior thalamic radiation of patients with MCI; however, this finding is not surprising given that a recent resting-state functional MRI study reported significantly disrupted connectivity between the thalamus and several brain regions in patients with MCI.[30]

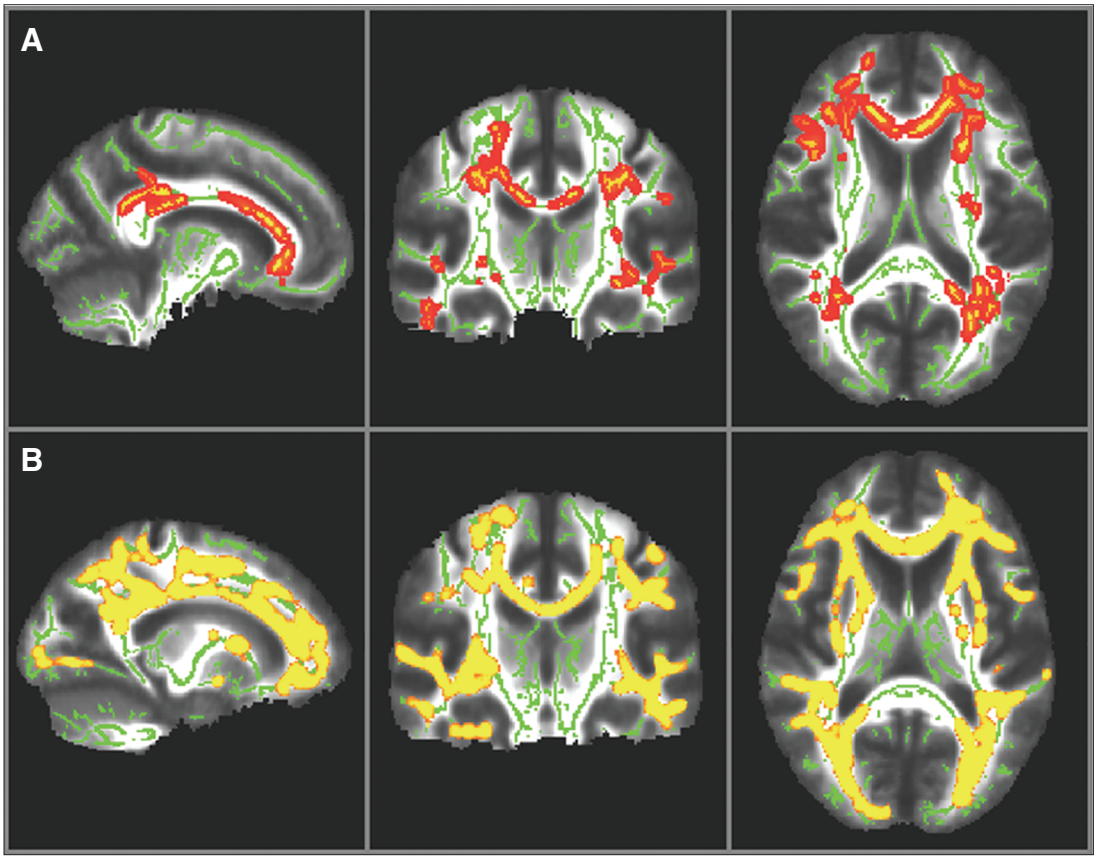

Fig. 1: Fractional anisotropy (FA) in patients with mild cognitive impairment (MCI) and those with MCI and major depression (MCI-MD) in comparison to healthy controls (panels **A** and **B**, respectively). All images show the mean FA image overlaid with the skeleton image (green; FA > 0.2). The yellow and red colours indicate areas that have significantly decreased FA values (red indicates $p < 0.05$ and yellow indicates $p < 0.01$, corrected for multiple comparisons) in comparison to controls. There were no differences in FA between the MCI and MCI-MD groups.

Our study also demonstrated widespread areas of reduced white matter microstructural integrity in the MCI-MD group. In comparison with controls, patients in the MCI-MD group had significantly reduced FA in the same regions as patients in the MCI group; however, white matter integrity was also compromised in the internal and external capsule, sagittal striatum, the fornix, uncinate fasciculus and the right cingulum. Importantly, patients in the MCI-MD group also recorded significantly greater WMH and chronic medical burden than controls. Our findings are consistent with those of previous studies examining white matter microstructure in depressed patients, despite our patients being euthymic at the time of testing. Furthermore, we used a global analysis technique that did not require a priori hypotheses, further strengthening previous ROI and VBA findings.[14]

Interestingly, we found no significant differences in white matter microstructure or clinical measures between patients in the MCI group and those in the MCI-MD group. Although

Table 2: Average fractional anisotropy measurements and Montreal Neurological Institute coordinates for participants with MCI and no history of depression (MCI), MCI and a history of major depression (MCI-MD) and healthy controls

		Group; fractional anisotropy, mean ± SD			
Anatomic region	MNI coordinates (*x, y, z*)	MCI-MD, *n* = 36	MCI, *n* = 30	Control, *n* = 22	*p* value*
MCI v. controls					
Corpus callosum					
Genu	103, 151, 91	—	0.6447 ± 0.0616	0.6898 ± 0.0624	0.035
Body	103, 138, 99	—	0.6056 ± 0.0588	0.6689 ± 0.0528	0.034
Splenium	104, 90, 98	—	0.8263 ± 0.0462	0.8399 ± 0.0511	0.033
Left posterior thalamic radiation	124, 75, 83	—	0.5236 ± 0.0711	0.5458 ± 0.1134	0.034
Anterior corona radiata					
Left	113, 155, 73	—	0.5651 ± 0.0876	0.6076 ± 0.0882	0.044
Right	65, 155, 73	—	0.5336 ± 0.0820	0.5597 ± 0.0615	0.041
Posterior corona radiata					
Left	116, 98, 99	—	0.5283 ± 0.0567	0.5358 ± 0.0478	0.034
Right	65, 98, 99	—	0.5262 ± 0.0726	0.5534 ± 0.0847	0.047
Superior corona radiata					
Left	116, 109, 103	—	0.4928 ± 0.0452	0.5111 ± 0.0510	0.030
Right	63, 109, 103	—	0.4898 ± 0.0498	0.5184 ± 0.0297	0.033
Superior longitudinal fasciculus					
Left	132, 77, 80	—	0.5779 ± 0.0719	0.5921 ± 0.0855	0.033
Right	47, 77, 80	—	0.6461 ± 0.0599	0.6669 ± 0.0840	0.048
MCI-MD v. controls					
Corpus callosum					
Genu	103,151, 91	0.6373 ± 0.0921	—	0.6898 ± 0.0624	0.020
Body	103,138, 99	0.6240 ± 0.0852	—	0.6689 ± 0.0528	0.020
Splenium	73, 88, 98	0.7693 ± 0.0808	—	0.7838 ± 0.0586	0.028
Posterior thalamic radiation					
Left	124, 65, 79	0.4958 ± 0.0823	—	0.5327 ± 0.0992	0.027
Right	56, 65, 79	0.5020 ± 0.0998	—	0.5163 ± 0.0997	0.024
Anterior corona radiata					
Left	112, 153, 73	0.6042 ± 0.1220	—	0.6547 ± 0.1051	0.025
Right	66, 153, 73	0.5522 ± 0.1070	—	0.6070 ± 0.0789	0.022
Posterior corona radiata					
Left	108, 85, 104	0.4317 ± 0.0852	—	0.4644 ± 0.0894	0.029
Right	64, 85, 104	0.4062 ± 0.0777	—	0.4430 ± 0.0629	0.022
Superior corona radiata					
Left	118,115, 96	0.5600 ± 0.0585	—	0.5753 ± 0.0524	0.025
Right	60,115, 96	0.5414 ± 0.0748	—	0.5682 ± 0.0436	0.040
Superior longitudinal fasciculus					
Left	131, 75, 80	0.5616 ± 0.0942	—	0.5845 ± 0.0580	0.031
Right	54, 75, 80	0.5349 ± 0.1077	—	0.5573 ± 0.0923	0.026
Uncinate fasciculus					
Left	125, 125, 58	0.6099 ± 0.0820	—	0.6345 ± 0.0756	0.035
Right	57, 131, 60	0.6604 ± 0.0710	—	0.6831 ± 0.0730	0.028
Fornix					
Left	120, 102, 66	0.6189 ± 0.0882	—	0.6196 ± 0.1004	0.025
Right	59, 102, 66	0.5686 ± 0.0890	—	0.6036 ± 0.1076	0.035
Sagittal striatum					
Left	129, 84, 65	0.5385 ± 0.0711	—	0.6017 ± 0.0754	0.023
Right	50, 84, 65	0.5910 ± 0.0752	—	0.6417 ± 0.0761	0.023
External capsule					
Right	55, 121, 62	0.5384 ± 0.0735	—	0.5688 ± 0.0666	0.023
Left	124, 121, 62	0.6115 ± 0.1023	—	0.6449 ± 0.1094	0.035
Internal capsule					
Right	75, 134, 79	0.6315 ± 0.0770	—	0.6866 ± 0.0696	0.023
Left	105, 134, 79	0.6188 ± 0.1057	—	0.6724 ± 0.0927	0.023
Right cingulum	65, 99, 54	0.5214 ± 0.0965	—	0.5805 ± 0.0644	0.046

MCI = mild cognitive impairment; MD = major depression; MNI = Montreal Neurological Institute; SD = standard deviation.
*Tract-based spatial statistics.

in this small clinical sample we may have lacked power to detect subtle changes between these groups, this finding suggests that common structural brain changes may underpin at least some degree of cognitive impairment in both groups. Our findings are consistent with previous research showing topological alterations to white matter networks in patients with remitted late-life depression (R-LLD) and no MCI and those with aMCI.[31] Significant decrements in regional connectivity were shown in both patient groups compared with the control group; however, results showed altered connectivity characteristics between the posterior cingulate gyrus and prefrontal regions between the patient groups. While it is widely accepted that MCI is a predementia syndrome,[1,6] it is unclear whether MD is an independent risk factor for or an early symptom of dementia.[4,7] Certainly, our study shows that MCI, regardless of depression history, is associated with significant white matter pathology; however, we are unable to discern whether MCI in patients with and without a history of MD share the same etiological pathways. Differences in FA between patient groups and controls could be the result of changes in axon density, axonal diameter, myelination, the coherence of the fibre tract and localized water content, which could result from any number of different pathological processes.[9] In this study, the MCI-MD group had significantly greater WMH burden in the deep white matter than the control group, corroborating previous findings in MD cohorts[3] and suggesting that the white matter changes seen in the MCI-MD group may arise from microvascular origins.[8] This finding is clinically significant, as increased WMH burden is predictive of cognitive decline, functional disability, poorer longitudinal disease course and treatment resistance.[3] Our data also showed significantly impaired psychosocial functioning in the MCI-MD group compared with the control group, although MMSE did not differ significantly between these groups. Further research investigating the prognostic utility of WMH burden and FA abnormalities in this clinical sample would further enhance our findings.

Surprisingly, VRFs did not differ significantly between patients and controls. Vascular risk factors are postulated to play a key role in the pathogenesis of both LLD and MCI, with cerebrovascular disease shown to predispose, precipitate and perpetuate both conditions.[7,32] However, recent epidemiological studies suggest that the association between MCI and depressive symptoms is not attributable solely to vascular disease or risk.[33–35] Alternatively this association may, at least in part, be linked to underlying Alzheimer pathology. It has been postulated that LLD, MCI and dementia lie on a continuum; neuropathic burden in the form of β-amyloid deposition or tau pathology, in combination with depressed mood leads to a reduction in cognitive reserve and the subsequent manifestation of MCI.[7] Thus, depression without clinically significant cognitive impairment may be a harbinger of a neurodegenerative disease and/or depression may unmask the clinical manifestations of MCI in individuals with limited cognitive reserve.[7] A previous study examining white matter connectivity in patients with R-LLD showed similar global reductions compared with patients with aMCI.[31] However, our study found no significant difference between the MCI and MCI-MD groups. As such, the findings of our study indicate that common changes to white matter microstructure underlie MCI regardless of depression history and do not support a continuum theory.

Conversely, MD may be linked etiologically to neurodegeneration and the development of MCI and dementia. It has been postulated that MD could lead to hippocampal damage through a glucocorticoid cascade.[3,4,7] In this pathway, activation of the hypothalamic–pituitary–adrenal (HPA) axis and excess glucocorticoid production damages the hippocampus and results in a downregulation of glucocorticoid receptors.[4,7] This impairs negative feedback to the HPA axis and results in chronic elevation of glucocorticoid levels. In individuals who accumulate Alzheimer disease neuropathology, this hippocampal damage may reduce cognitive reserve and result in the expression of MCI earlier than would otherwise be the case, thus increasing the likelihood of dementia progression.[7] Alternatively it has been suggested that chronic inflammation may play a central role in the pathophysiology of MD and dementia. Increased levels of cytokines associated with MD may lead to a decrease in anti-inflammatory regulation and an increase in proinflammatory changes in the central nervous system.[3,4,36] These proinflammatory cytokines may then interfere with serotonin metabolism and reduce synaptic plasticity and hippocampal neurogenesis. While we are unable to ascertain if any of these potential pathways contribute to the white matter microstructure change observed in this sample, these avenues warrant further evaluation.

Irrespective of the pathophysiological mechanisms that may account for the increased risk of dementia posed by a history of MD, it is important to emphasize that this study found no significant difference in white matter pathology when compared with patients with MCI only. By contrast, recent research has shown that depressive symptoms and/or LLD result in significant regional differences in grey matter volume in patients with aMCI. Differences in frontal, parietal and temporal grey matter volume have been demonstrated using data-driven analysis techniques,[37,38] and longitudinal tracking indicates that depressive symptoms in patients with aMCI are predictive of a greater rate of grey matter atrophy.[37] The examination of grey matter microstructure was beyond the scope of this study; however, future research examining the relationship between grey and white matter microstructure in patients with MCI with and without MD is now indicated. Examination of grey and white matter differences between patients with MCI-MD and those with LLD may further elucidate the structural changes underlying MCI and allow us to better identify those at risk for progression to dementia.

Limitations

This study provides important insights into the white matter pathology underlying cognitive decline in older adults; however, it is not without limitations. This study was cross-sectional in design, which has not allowed follow-up of patients to determine disease trajectory. In addition, a proportion of patients reported antidepressant use. The specific effects of antidepressant medication on white matter

microstructure are unclear; however, an animal study indicates they may prevent oligodendrocyte and myelin loss.[39] As such, antidepressant medications may mediate changes to FA in patients with MCI-MD. Furthermore, the sample included both men and women with a broad age range. Further research investigating the effect of these variables on FA in this cohort is now indicated. This study would have also benefited from the inclusion of a patient group with only MD to contrast the MCI-MD findings. Previous findings have shown that R-LLD is associated with similar regional deficits in white matter connectivity as aMCI,[31] and further investigation of MD without MCI as a risk factor for dementia is warranted. Finally, this sample of patients with MCI was rather heterogeneous, as it incorporated an admixture of both aMCI and naMCI subtypes, as well as EoD and LoD subtypes. Thus, it is not easily compared with studies including homogeneous groups, such as those with aMCI. However, our study strengthens previous findings by showing that these changes to white matter microstructure are present in more diverse patient cohorts. Previous DTI analyses in MCI samples have focused predominantly on patients with aMCI, as research indicates that these patients are the most likely to progress to Alzheimer disease.[1,6] However, vascular dementia is typically associated with impairments that do not include the memory domain,[32] and as such, the inclusion of patients with naMCI as well as those with aMCI in this study, particularly in the MCI-MD subgroups, allows us to examine those at risk for both Alzheimer disease and vascular dementia. In addition, most DTI research on depression has been conducted in patients with LoD who are currently depressed. Our findings show that in patients with MCI, the white matter microstructure compromise associated with LLD is also present in the remitted state. Although FA did not differ significantly between aMCI and naMCI subgroups in our study, future research using TBSS is now needed to examine FA in large cohorts of patients with aMCI and naMCI and with LoD and EoD.

Conclusion

To our knowledge, our study is the first to compare white matter microstructure in patients with MCI with and without a history of MD and suggests that while the phenotypes may differ according to depressive history, common underlying structural white matter change may underpin cognitive impairment. Further research is now required to delineate the pathophysiological mechanisms that underlie the white matter pathology identified in this study and to determine whether white matter microstructural change is a marker of illness trajectory. Finally, this study suggests that regardless of phenotype, early intervention strategies for dementia must incorporate older people with mood and/or cognitive problems if the underlying shared mechanisms to neurodegenerative disease are to be targeted.[40]

Acknowledgements: We gratefully acknowledge the generosity of the patients and control participants who undertook this research. We also thank old age psychiatrist Dr. Louisa Norrie and the clinical neuropsychologists, including Dr. Zoe Terpening, for their assistance with assessments and clinical consensus ratings.

Funding: S. Duffy is supported by an Australian Rotary Health/Rotary Club of Parkes Funding Partners scholarship. I. Hickie and M. Paradise are supported by a National Health and Medical Research Council (NHMRC) Australian Fellowship awarded to I. Hickie. S. Lewis is supported by an NHMRC Practitioner Fellowship. S. Naismith is supported by an NHMRC Career Development Award. J. Lagopoulos is supported by Dreikurs bequest supporting Alzheimer's research.

Competing interests: None declared.

Contributors: S. Duffy, I. Hickie, S. Lewis, S. Naismith and J. Lagopoulos designed the study. S. Duffy, M. Paradise, S. Naismith and J. Lagopoulos acquired the data, which S. Duffy, I. Hickie, S. Lewis, S. Naismith and J. Lagopoulos analyzed. S. Duffy, S. Naismith and J. Lagopoulos wrote the article, which all authors reviewed and approved for publication.

References

1. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. *Lancet* 2006;367:1262-70.
2. Xie H, Mayo N, Koski L. Predictors of future cognitive decline in persons with mild cognitive impairment. *Dement Geriatr Cogn Disord* 2011;32:308-17.
3. Naismith SL, Norrie LM, Mowszowski L, et al. The neurobiology of depression in later-life: Clinical, neuropsychological, neuroimaging and pathophysiological features. *Prog Neurobiol* 2012;98:99-143.
4. Byers AL, Yaffe K. Depression and risk of developing dementia. *Nat Rev Neurol* 2011;7:323-31.
5. Yeh Y-C, Tsang H-Y, Lin P-Y, et al. Subtypes of mild cognitive impairment among the elderly with major depressive disorder in remission. *Am J Geriatr Psychiatry* 2011;19:923-31.
6. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment — clinical characterization and outcome. *Arch Neurol* 1999;56:303-8.
7. Panza F, Frisardi V, Capurso C, et al. Late-life depression, mild cognitive impairment, and dementia: possible continuum? *Am J Geriatr Psychiatry* 2010;18:98-116.
8. Chui H. Vascular dementia, a new beginning — shifting focus from clinical phenotype to ischemic brain injury. *Neurol Clin* 2000;18:951-78.
9. Beaulieu C. The basis of anisotropic water diffusion in the nervous system — a technical review. *NMR Biomed* 2002;15:435-55.
10. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson B* 1996;111:209-19.
11. Sexton CE, Kalu UG, Filippini N, et al. A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* 2011;32:2322.e5-18.
12. Delbeuck X, Van der Linden M, Collette F. Alzheimer's disease as a disconnection syndrome? *Neuropsychol Rev* 2003;13:79-92.
13. Colloby SJ, Firbank MJ, Thomas AJ, et al. White matter changes in late-life depression: a diffusion tensor imaging study. *J Affect Disord* 2011;135:216-20.
14. Sexton CE, Mackay CE, Ebmeier KP. A systematic review of diffusion tensor imaging studies in affective disorders. *Biol Psychiatry* 2009;66:814-23.
15. Thillainadesan S, Wen W, Zhuang L, et al. Changes in mild cognitive impairment and its subtypes as seen on diffusion tensor imaging. *Int Psychogeriatr* 2012;24:1483-93.
16. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 2006;31:1487-505.
17. Folstein MF, Folstein SE, McHugh PR. Mini-mental state — practical method for grading cognitive state of patients for clinician. *J Psychiatr Res* 1975;12:189-98.
18. First M, Spitzer R, Gibbon M, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders - Patient Edition (SCID-I/P, 1/2007 Revision)*. New York (NY): Biometrics Research Department; 2007.

19. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.
20. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research — application of the cumulatiive illness rating-scale. *Psychiatry Res* 1992;41:237-48.
21. Hickie I, Scott E, Naismith S, et al. Late-onset depression: genetic, vascular and clinical contributions. *Psychol Med* 2001;31:1403-12.
22. Naismith SL, Rogers NL, Hickie IB, et al. Sleep well, think well: sleep-wake disturbance in mild cognitive impairment. *J Geriatr Psychiatry Neurol* 2010;23:123-30.
23. Wechsler D. *Manual for the Wechsler Adult Intelligence Scale 3rd ed*. 1997, San Antonio: The Psychological Corporation.
24. Petersen RC, Morris JC. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol* 2005;62:1160-3.
25. Reisberg B, Ferris SH, Deleon MJ, et al. The global deterioration scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;139:1136-9.
26. Fazekas F, Chawluk JB, Alavi A, et al. MR signal abnormalities at 1.5-T in Alzheimer dementia and normal aging. *AJR Am J Roentgenol* 1987;149:351-6.
27. Hickie I, Naismith S, Ward PB, et al. Vascular risk and low serum B12 predict white matter lesions in patients with major depression. *J Affect Disord* 2005;85:327-32.
28. Hickie IB, Naismith SL, Ward PB, et al. Psychomotor slowing in older patients with major depression: Relationships with blood flow in the caudate nucleus and white matter lesions. *Psychiatry Res* 2007;155:211-20.
29. Medina D, DeToledo-Morrell L, Urresta F, et al. White matter changes in mild cognitive impairment and AD: a diffusion tensor imaging study. *Neurobiol Aging* 2006;27:663-72.
30. Wang Z, Jia X, Liang P, et al. Changes in thalamus connectivity in mild cognitive impairment: evidence from resting state fMRI. *Eur J Radiol* 2012;81:277-85.
31. Bai F, Shu N, Yuan Y, et al. Topologically convergent and divergent structural connectivity patterns between patients with remitted geriatric depression and amnestic mild cognitive impairment. *J Neurosci* 2012;32:4307-18.
32. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. *Lancet Neurol* 2003;2:89-98.
33. Barnes DE, Alexopoulos GS, Lopez OL, et al. Depressive symptoms, vascular disease, and mild cognitive impairment — findings from the cardiovascular health study. *Arch Gen Psychiatry* 2006; 63:273-9.
34. Panza F, Capurso C, D'Introno A, et al. Impact of depressive symptoms on the rate of progression to dementia in patients affected by mild cognitive impairment. The Italian Longitudinal Study on Aging. *Int J Geriatr Psychiatry* 2008;23:726-34.
35. Lopez OL, Jagust WJ, Dulberg C, et al. Risk factors for mild cognitive impairment in the Cardiovascular Health Study cognition study part 2. *Arch Neurol* 2003;60:1394-9.
36. Paradise MB, Naismith SL, Norrie LM, et al. The role of glia in late-life depression. *Int Psychogeriatr* 2012;24:1878-90.
37. Lee GJ, Lu PH, Hua X, et al. Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease-related regions. *Biol Psychiatry* 2012;71:814-21.
38. Xie C, Li W, Chen G, et al. The co-existence of geriatric depression and amnestic mild cognitive impairment detrimentally affect gray matter volumes: voxel-based morphometry study. *Behav Brain Res* 2012;235:244-50.
39. Bi X, Zhang Y, Yan B, et al. Quetiapine prevents oligodendrocyte and myelin loss and promotes maturation of oligodendrocyte progenitors in the hippocampus of global cerebral ischemia mice. *J Neurochem* 2012;123:14-20.
40. Naismith SL, Glozier N, Burke D, et al. Early intervention for cognitive decline: Is there a role for multiple medical or behavioural interventions? *Early Interv Psychiatry* 2009;3:19-27.