White matter changes in mild cognitive impairment and AD:
A diffusion tensor imaging study

David Medina\textsuperscript{a}, Leyla deToledo-Morrell\textsuperscript{a,b}, Fabio Urresta\textsuperscript{a,1}, John D.E. Gabrieli\textsuperscript{a,e}, Michael Moseley\textsuperscript{f}, Debra Fleischman\textsuperscript{a,d}, David A. Bennett\textsuperscript{a,d}, Sue Leurgans\textsuperscript{a}, David A. Turner\textsuperscript{c}, Glenn T. Stebbins\textsuperscript{a,∗}

\textsuperscript{a} Department of Neurological Sciences, Rush University Medical Center, 1725 W. Harrison, Suite 309, Chicago, IL 60612, USA
\textsuperscript{b} Department of Psychology, Rush University Medical Center, Chicago, IL 60612, USA
\textsuperscript{c} Diagnostic Radiology, Rush University Medical Center, Chicago, IL 60612, USA
\textsuperscript{d} Rush Alzheimer’s Disease Center, Rush University Medical Center, Chicago, IL 60612, USA
\textsuperscript{e} Department of Psychology, Stanford University, Palo Alto, CA, USA
\textsuperscript{f} Department of Radiology, Stanford University, Palo Alto, CA, USA

Received 8 June 2004; received in revised form 2 August 2004; accepted 30 March 2005
Available online 7 July 2005

Abstract

Diffusion tensor imaging (DTI) can detect, in vivo, the directionality of molecular diffusion and estimate the microstructural integrity of white matter (WM) tracts. In this study, we examined WM changes in patients with Alzheimer’s disease (AD) and in subjects with amnestic mild cognitive impairment (MCI) who are at greater risk for developing AD. A DTI index of WM integrity, fractional anisotropy (FA), was calculated in 14 patients with probable mild AD, 14 participants with MCI and 21 elderly healthy controls (NC). Voxel-by-voxel comparisons showed significant regional reductions of FA in participants with MCI and AD compared to controls in multiple posterior white matter regions. Moreover, there was substantial overlap of locations of regional decrease in FA in the MCI and AD groups. These data demonstrate that white matter changes occur in MCI, prior to the development of dementia.

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Keywords: Aging; Cognition; Dementia; Fractional anisotropy; MRI

1. Introduction

Mild cognitive impairment (MCI) may be a transitional state between normal aging and Alzheimer’s disease (AD). Individuals with amnestic MCI differ from healthy elderly in their level of cognitive function, performing more poorly than controls on measures of memory. Despite impaired memory performance, individuals with MCI do not meet diagnostic criteria for dementia \cite{10,43,59-61}. MCI is associated with a significantly increased risk of developing AD compared to the elderly population without cognitive impairment \cite{14,23,59-61}. Neuropathological and neuroimaging studies report no significant difference in entorhinal volume \cite{26,29} or the extent of cell loss in layer II of the entorhinal cortex \cite{49} in individuals with cognitive complaints and in patients with MCI compared to those with a diagnosis of AD. Since the entorhinal cortex is one of the earliest sites of pathology in AD, these results indicate that patients with MCI may be in the incipient phase of the disease process. Thus, studies of individuals with MCI provide a unique opportunity to investigate prodromal AD.

Structural magnetic resonance imaging (MRI) techniques have been extensively used to investigate the pathophysiology of Alzheimer’s disease (AD) in vivo. Additionally, individuals with MCI are now being studied in order to identify...
anatomical changes that precede a clinical diagnosis and to
develop sensitive in vivo markers that may be predictive of
conversion to AD. The major emphasis of these studies has
been on the detection of atrophy in regions of interest known
to be pathologically involved in the disease process. Mesial
temporal lobe structures critically important for memory
function, such as the hippocampal formation and the entorhi-
nal cortex, have received special attention in these investiga-
tions [13,21,22,26–30,41,42,47,48] because a disturbance
in the acquisition of new information is a hallmark of MCI
and AD [26,27,29,47,48].

Although most imaging studies of MCI and mild AD have
focused on gray matter alterations, a number of post-mortem
investigations have documented white matter pathology asso-
ciated with AD [18,19,31,44,45]. White matter changes asso-
ciated with AD may reflect different underlying causes or
mechanisms. First, white matter changes in AD may be
indicative of anterograde Wallerian degeneration, especially
in regions close to cortical areas with the greatest pathologi-
cal burden. Secondly, there may be white matter rarefaction
[31] with axonal damage and gliosis. This type of change is
diffuse, does not follow the regional extension of pathologi-
cally involved gray matter, and may be vascular or ischemic
in origin. Third, it has recently been suggested that myelin
breakdown is an important component of the disease process
in AD [4–6]. According to this hypothesis, damage to oligo-
dendrocytes may be a critical initiating step in the disease.
Furthermore, since late developing oligodendrocytes may be
more vulnerable, late-myelinating association areas are pre-
dicted to be more susceptible to myelin breakdown.

The results of imaging studies tend to support post-mortem
findings of white matter abnormalities in MCI and AD. Increased white matter hyperintensities (WMH) have been
found in both MCI and AD using either semi-quantitative
radiologic ratings scales [2,51] or quantitative measurements
[5,12,24,32]. The role of WMH in the pathology or disease
severity of MCI or AD is not established, however. Indepen-
dence between WMH and diagnosis or cognitive impairment
has been reported by some authors [12,46,51], while others
report significant correlations between WMH and diagnosis
or cognitive impairment [2,24,32]. These discrepancies may
be due to differences in the sample studied, analytic methods,
or sensitivity of the MRI methodology.

A recently developed structural MRI technique, diffu-
sion tensor imaging (DTI), provides increased sensitivity to
alterations in the microstructure of white matter in vivo and
is especially indicative for diseases causing axonal damage
and demyelination [7–9,52,70]. DTI detects microstructural
alterations in white matter by measuring the directionality
of molecular diffusion (fractional anisotropy: FA). Highly
organized white matter tracts have high FA because diffu-
sion is highly constrained by the tract’s cellular organization.
As white matter is damaged, FA decreases due to decreased
anisotropic diffusion.

Previous investigations of white matter changes in AD
or MCI using diffusion weighted MRI have reported
changes in mean diffusivity and anisotropic diffusion
[15,16,33,36,37,39,46,64,65,74]. Most of these studies have
been based on analyses of a priori defined regions of interest.
The exact regions of alterations in diffusivity or anisotropic
diffusion vary between studies, with some reporting greater
anterior differences (e.g. [15]) in AD, while others demon-
strate posterior or temporal lobe changes in AD and MCI
[33,39,46,64,65].

These conflicting results from prior studies may be due to
multiple causes such as differences in sample composition
(e.g., mild versus moderate cognitive impairment in AD;
amnestic MCI versus MCI involving other cognitive
domains), imaging technique (diffusion weighted [16,36,37,
46,65] versus diffusion tensor imaging [15,33,39,68,74]) or
location of brain regions chosen for examination of MRI
differences. Most studies used a “region-of-interest”
(ROI) approach to examine MRI differences between groups.
This approach can be subjective with inconsistent defini-
tions of anatomical borders across studies [20] and poor
reproducibility [3]. Even when applied by trained individ-
uals with established reliability and reproducibility, dif-
erential regional placement of ROIs across studies could
contribute to inconsistent reports of differences in DTI
indices.

Whole-brain, voxel-based methods applied to the analy-
sis of DTI differences between samples provide a global and
comprehensive assessment un-complicated by the potential
biases of ROI approaches. These techniques are automated
and, therefore, are not subject to issues of human based trac-
ing reliability and/or reproducibility. In addition, voxel-based
analyses assess regional changes in DTI parameters indepen-
dent of a priori constraints and may reveal differences that
are not encompassed by specific ROIs.

In the present study, we examined white matter changes
in patients with probable mild AD and in those with amnes-
tic MCI compared to controls using whole-brain, voxel-

2. Materials and methods

2.1. Subjects

Data reported here were obtained from the following three
groups of participants: (1) 21 elderly control subjects (NC)
with no cognitive impairment, (2) 16 patients who met crite-
rion for amnestic MCI, and (3) 14 patients diagnosed with
mild AD. All participants were recruited from the Rush
Alzheimer’s Disease Center (RADC, Chicago, IL), the com-

the Religious Order Study (ROS), a longitudinal,
clinico-pathologic investigation of aging and AD in older
nuns, priests and brothers who have agreed to annual evaluations and to brain autopsy at the time of death [11,58]. To be included in the study, participants had to be 65 years of age or older.

2.2. Clinical work-up and subject selection

All evaluations were carried out by members of the RADC as previously described [28,72]. Briefly, the evaluation incorporated the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD [57]) procedures and included a medical history, neurological examination, neuropsychological testing, informant interview and blood tests. The MRI scans of all participants in the present study were reviewed by a neuroradiologist to assess the presence of stroke or other exclusionary brain abnormalities. The clinical diagnosis of probable AD followed NINCDS/ADRDA guidelines [53]; exclusion criteria for dementia. Exclusion criteria for both patients with mild probable AD and MCI were evidence of other neurologic, psychiatric or systemic conditions that could cause cognitive impairment (e.g., stroke, tumor, alcoholism, major depression, a history of temporal lobe epilepsy).

Control subjects received the same work-up as the two patient groups. Selection as an elderly control subject required a normal neurological examination, normal cognition and a Mini Mental State Examination (MMSE [34]) score ≥ 27. Exclusion criteria for the controls were the same as those used for the patient groups. Informed consent was obtained from all participants according to the rules of the Institutional Review Board of Rush University Medical Center.

2.3. Acquisition and processing of MRI data

Scans were performed on a 1.5T GE scanner (General Electric, Milwaukee, WI, USA) equipped with fast gradient Echospeed upgrades (Rev. 8.4). Single-shot echoplanar diffusion-weighted imaging was used with the following parameters: repetition time, $T_R = 8000$, echo time, $T_E = 97$, gradient duration $\delta = 20$ ms, acquisition matrix $128 \times 128$ zero-filled to $256 \times 256$, field of view (FOV) = 240, slice thickness = 6 mm, 0 gap, 19 axial slices. Two degrees of diffusion weighting ($b$ values) were used: $b = 0$ and $b = 800$ s/mm$^2$. These diffusion weights were applied in six non-collinear directions $(x, y, z, -x, -y, -z)$ with two repetitions of $b = 0$ and four replications of each diffusion weighted image. Images were transferred to an off-line workstation (Sun Microsystems, Palo Alto, CA) for processing.

The first step in post-acquisition processing of diffusion tensor-MRI images (DT-MRI) involved the unwarping of eddy currents. Eddy currents are geometric distortions introduced by the echo planar diffusion weighting gradients and can cause distortions in shear, magnification and/or pixel shifts. A set of CSF nulled inversion recovery images ($T_I \sim 2100$ ms) are acquired with $b=0$ as a reference for unwarping eddy current effects in the diffusion weighted images [25,38]. Processing of unwarped DT images involved the calculation of the six diffusion coefficients defining the six elements of the diffusion tensor [9]. Eigenvectors, defining the three principle directions of diffusion for each voxel were derived from the diffusion tensor. The magnitude of diffusivity in each direction was represented by the eigenvalues for the three eigenvectors. The mean diffusivity (DW) and the fractional anisotropy (FA) were derived from the eigenvalues [7–9]. From this post-processing, three values were constructed for each slice: DW, FA and $b = 0$ (0 weighted image = T2 image).

2.4. MRI data analyses

Individual participant slice images for DW, FA and T2 acquisitions were concatenated into whole-brain volumes in acceptable format using software developed by Russ Poldrack, Ph.D. (http://sourceforge.net/projects/spm-toolbox). Whole-brain volumes were imported into Statistical Parametric Mapping software [35] (version SPM99) for analysis. To facilitate voxel-by-voxel comparisons between groups, all images were spatially normalized to a standard template. To avoid the geometric distortions associated with diffusion weighted echoplanar imaging, we used the 0 diffusion weighted (e.g., T2) image obtained during the scanning sequence for normalization. The T2 weighted image was normalized to the standard T2 template in SPM99 using a 12 iteration linear transformation and a non-linear transformation with $7 \times 8 \times 7$ basis functions. The adequacy of transformation of each participant’s T2 weighted image to the T2 template was assessed by visual inspection. Parameters from this transformation were then applied to the remaining DT images and statistical maps were created for DW and FA values. This normalization processing re-sampled the volumes into a 2 mm$^3$ voxel size.

To limit our analysis to DW and FA values in white matter, we created individual subject mask volumes that were used to exclude voxels representing white matter abnormalities based on T2 signal, voxels from gray matter, CSF, and extra-cranial space. The first step in creating the masks was to segment the normalized T2 images into CSF, gray matter, and white matter compartments. The segmentation algorithms for defining white matter were based on a probability of greater than 0.80 for white matter classification. This process allowed us to not only exclude voxels from gray matter, CSF and extra-cranial space, but also to exclude areas of white matter in which the T2 signal was altered due to white matter lesions, atrophic changes or other abnormalities on an individual participant basis. Thus, only voxels surviving this threshold were included in the group analyses. The individual white mat-
**Table 1**

Demographic variables and white matter mask volumes of clinical groups (means ± S.D.)

<table>
<thead>
<tr>
<th></th>
<th>NCI (N=21)</th>
<th>MCI (N=14)</th>
<th>AD (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>77.3 ± 10.1</td>
<td>78.4 ± 5.6</td>
<td>77.4 ± 6.8</td>
</tr>
<tr>
<td>Range</td>
<td>62–96</td>
<td>64–86</td>
<td>70–89</td>
</tr>
<tr>
<td>Education (years)</td>
<td>78.0</td>
<td>78.5</td>
<td>76.5</td>
</tr>
<tr>
<td>Female/male</td>
<td>11/10</td>
<td>11/3</td>
<td>9/5</td>
</tr>
<tr>
<td>MMSE score</td>
<td>29.3 ± 0.7</td>
<td>26.9 ± 2.1</td>
<td>24.5 ± 1.9</td>
</tr>
<tr>
<td>Cardiovascular risk factors (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>11.8</td>
<td>0</td>
<td>21.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.9</td>
<td>14.3</td>
<td>0</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>38.5</td>
<td>35.7</td>
<td>42.9</td>
</tr>
<tr>
<td>White matter volumes</td>
<td>4075.8 ± 1255.7</td>
<td>42027.1 ± 1244.4</td>
<td>44386.9 ± 949.7</td>
</tr>
</tbody>
</table>

* Significantly different from NCI (p<0.001).
** Significantly different from both NCI (p<0.001) and MCI (p<0.001).

3. Statistical methods

Differences between the three groups of participants in demographic and disease related measures, as well as volumes of white matter masks, were assessed by one-way analyses of variance (ANOVA) followed by post hoc tests (Fisher’s). χ²-tests were used to determine the relationship between variables such as gender or cardiovascular risk factors, and diagnostic classification.

Voxel-wise group differences in FA and DW were assessed using the ANOVA module in SPM99 followed by group-wise t-tests. For these comparisons, significance was determined with a p-value of <0.01 (corrected for multiple comparisons at the cluster level) with a seven-voxel extent threshold.

Determination of the location of voxels demonstrating significantly different DTI values was accomplished by converting the x, y, z coordinates for the peak voxel within a cluster from the Montreal Neurological Institute (MNI) coordinates used in SPM99 analyses, to Talairach coordinates [69] using the MNItoTAL software (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). The resultant Talairach coordinates were entered into a software program that identifies lobar and Brodmann area locations [50].

4. Results

Demographic and cognitive status information on the participants is listed in Table 1. Two participants with the diagnosis of MCI were excluded from analyses because of radiologically confirmed cerebral vascular accidents. The age of participants was equitably distributed among the three diagnostic groups (F(2,46) = 0.02, p = 0.974), with similar medians and ranges. Analyses of independence revealed no significant relationships between diagnostic groups and variables such as gender (χ²[2]= 2.488, p = 0.288) or the presence of cardiovascular risk factors; i.e. myocardial infarction (χ²[4]= 6.784, p = 0.148), diabetes (χ²[4]= 5.754, p = 0.218) and high blood pressure (χ²[4]= 3.606, p = 0.462) (see Table 1). However, the groups were significantly different on MMSE scores [F(2,46) = 37.67, p < 0.001]. Pairwise comparisons showed that the control group had significantly higher scores than patients with MCI or AD (p<0.001 for both). Similarly, participants with MCI had significantly higher scores than patients with AD (p < 0.001). There were no significant differences in the volumes of the white matter masks between the groups [F(2,46) = 2.34, p = 0.14).

4.1. Voxel-based comparisons

Voxel-wise comparison for DW failed to reveal reliable group differences. In contrast, voxel-wise analysis of regional differences in white matter FA between the NC, MCI and AD groups using a p<0.01 threshold showed sig-

**Table 2**

Talairach space-derived distribution of white matter regions with decreased intra-voxel diffusion anisotropy (FA) in MCI subjects compared to age-matched controls.

<table>
<thead>
<tr>
<th>Cortical voxel</th>
<th>Z</th>
<th>Area</th>
<th>Correspondent anatomical location</th>
</tr>
</thead>
<tbody>
<tr>
<td>−28</td>
<td>−11</td>
<td>17</td>
<td>4.74 405 Left sub-lobar extra-nuclear</td>
</tr>
<tr>
<td>−28</td>
<td>−31</td>
<td>8</td>
<td>4.31 20  Left sub-lobar extra-nuclear</td>
</tr>
<tr>
<td>−16</td>
<td>−19</td>
<td>53</td>
<td>4.23 187 Left frontal lobe sub-gyral</td>
</tr>
<tr>
<td>−30</td>
<td>−41</td>
<td>30</td>
<td>3.91 19  Left parietal lobe sub-gyral</td>
</tr>
<tr>
<td>−16</td>
<td>−11</td>
<td>45</td>
<td>3.65 21  Left frontal lobe sub-gyral</td>
</tr>
<tr>
<td>16</td>
<td>25</td>
<td>37</td>
<td>3.63 21  Right cingular gyrus</td>
</tr>
<tr>
<td>16</td>
<td>42</td>
<td>36</td>
<td>3.48 27  Right cingular gyrus</td>
</tr>
<tr>
<td>−28</td>
<td>−15</td>
<td>21</td>
<td>3.44 56  Right sub-lobar extra-nuclear</td>
</tr>
<tr>
<td>−20</td>
<td>−7</td>
<td>10</td>
<td>3.41 14  Left frontal lobe sub-gyral</td>
</tr>
<tr>
<td>−16</td>
<td>8</td>
<td>44</td>
<td>3.32 37  Left cingular gyrus</td>
</tr>
<tr>
<td>−22</td>
<td>47</td>
<td>39</td>
<td>3.13 7   Left parietal lobe sub-gyral</td>
</tr>
<tr>
<td>26</td>
<td>20</td>
<td>16</td>
<td>3.08 13  Right frontal lobe sub-zygual</td>
</tr>
</tbody>
</table>

* Talairach coordinates.
significant regional group differences. The majority of these were in posterior areas with few regions anterior to the anterior commissure. Approximately 13% of all voxels showing significant differences between the groups were in anterior regions and the remaining 87% were in posterior regions (12.7% anterior versus 87.3% posterior: $\chi^2[1] = 827$, $p < 0.0001$). NC versus MCI group contrasts revealed significant decrease in FA in the MCI participants in 12 regions.

Fig. 1. Representative regions of significantly reduced fractional anisotropy (FA) in patients with mild cognitive impairment (MCI) compared to age-matched healthy control participants. Three dimensional volumes were created from contiguous individual slices and normalized to a common standardized brain volume using SPM99 [35]. Differences were analyzed using a two-sample $t$-test statistic. Significance thresholds were set for $p < 0.01$. Voxels evidencing significant differences between groups are displayed on representative coronal sections on a canonical brain image. The color scale indicates the magnitude of $Z$ values with lowest appearing in dark red and the highest in bright yellow/white. The left side of the images represents the left side of the brain.
versus AD comparison was in the posterior cingulate sub-gyral white matter (voxel size = 11, Z score = 3.07, Talairach coordinates x: 16, y: −4, z: 46).

5. Discussion

In the present study we characterized in vivo changes in normal-appearing white matter microstructural integrity of patients with MCI and mild AD using whole brain diffusion tensor imaging. We found significant regional decreases of white matter anisotropy in the two patient groups compared to age-matched healthy controls in voxel-by-voxel comparisons. While no differences in regional molecular diffusion variables were detected between the MCI and mild AD groups, the anatomical pattern of white matter anisotropy changes (FA) was similar for both patient groups with greater posterior than anterior involvement. Moreover, decreases in posterior FA were not due to differential age or gender distributions among the groups, increased cardiovascular risk factors (e.g., diabetes, myocardial infarct, hypertension) in the cognitively impaired groups, or differential volume sizes of the DTI measures.

Our results are consistent with those of previous studies demonstrating impaired white matter integrity in MCI and AD using diffusion weighted MRI. The published findings have been based on both diffusion weighted imaging [16,36,37,46,65], which does not develop a full tensor and is, thus, susceptible to artifacts from differential head positions, and diffusion tensor imaging [15,33,39,64,68,74], a technique that is invariant to head position. Most of the published studies on MCI and AD have inferred impaired white matter integrity from findings of both increased free-molecular diffusion (mean diffusivity) and decreased directional diffusion (anisotropic diffusion), although some studies have only reported increases in free-molecular diffusion [36,39,46] and have failed to find any significant differences [16].

Diffusion weighted and diffusion tensor imaging studies have demonstrated various regional abnormalities of white matter integrity in patients with MCI and AD. The location of these anomalies differs across studies depending upon the exact placement of the ROIs. For example, some studies have investigated limited regions such as the corpus callosum [36], posterior cingulum [74], or temporal lobe regions [37], but others have investigated multiple ROIs in the frontal lobes, temporal lobes, cingulum, parietal lobes, and occipital lobes [15,16,33,39,46,64,65,68]. The most consistent findings across studies are of impaired white matter integrity in the corpus callosum, temporal lobe, parietal lobe, and the cingulum, with greater posterior than anterior involvement [39,65,68].

The variability of previous results may be due to multiple factors. These factors could include effects of different head positions in those studies that did not develop a position-invariant tensor, inclusion of MCI with mixed cognitive domain impairments, and/or differential placement of ROIs across studies. In contrast to these potential influences...
on determination of anisotropic changes in MCI and AD, we developed position-invariant diffusion indexes derived from a full tensor, studied amnestic MCI only, and used a whole-brain voxel-based analytic method. Additionally, we separated the 0 diffusion weighted images (T2 relaxation time) into CSF, gray matter and white matter segments. The WM segment image was then applied to each individual DW and FA maps to avoid "contamination" of the DW or FA maps using SPM99 [35]. Differences were analyzed using a two-sample $t$-test statistic. Significance thresholds were set for $p < 0.01$. Voxels evidencing significant differences between groups are displayed on representative coronal sections on a canonical brain image. The color scale indicates the magnitude of $Z$ values with lowest appearing in dark red and the highest in bright yellow/white. The left side of the images represents the left side of the brain.

Fig. 2. Representative regions of significantly reduced fractional anisotropy (FA) in patients with Alzheimer’s disease (AD) compared to age-matched healthy control participants. Three dimensional volumes were created from contiguous individual slices and normalized to a common standardized brain volume using SPM99 [35]. Differences were analyzed using a two-sample $t$-test statistic. Significance thresholds were set for $p < 0.01$. Voxels evidencing significant differences between groups are displayed on representative coronal sections on a canonical brain image. The color scale indicates the magnitude of $Z$ values with lowest appearing in dark red and the highest in bright yellow/white. The left side of the images represents the left side of the brain.
by elements other than white matter, such as hyperintensities, CSF, gray matter, and extra-cerebral matter. The exclusion of cortical gray matter decreases the potential artifact of echo planar distortions at brain/air/bone interfaces, most notable at the frontal pole and inferior temporal regions.

In our study, strikingly similar regions of decreased white matter integrity were found in the MCI and AD groups, with most regions of significantly decreased FA located posterior to the anterior commissure. The presence of these regional alterations in MCI that are shared by participants with AD are consistent with findings in volumetric studies of gray matter changes, in which specific patterns of mesial temporal atrophy are seen in both groups and can predict longitudinally the conversion from MCI to AD [27,29,47,48].

The present results demonstrate significantly decreased FA in the fasciculi of the cortico-thalamic and thalamocortical connections through the internal capsule (superior and posterior thalamic peduncles) in both MCI and AD compared to controls. Additionally, the white matter fibers located deep in the posterior white matter, such as the superior longitudinal fasciculus and the posterior cingulum bundle, were particularly affected in patients with AD and MCI compared to controls. Indeed, the only region showing decreased white matter integrity unique to the AD group was in the posterior cingulum bundle.

Specific interest has been given to the cingulum bundle in DTI investigations of WM integrity in patients with AD because of the existing evidence of the early involvement of the posterior cingulate in the progression of the disease. Neuropathological, MRI-volumetric [21], and especially brain metabolism studies [56,62,63,71] have indicated that the posterior cingulate is involved very early in the course of AD. Moreover, behavioral measures of mental status are significantly correlated with DTI-based diffusion values in the posterior cingulate gyrus among patients with AD [74].

The underlying white matter pathway of the cingulum gyrus is an important part of the cholinergic system [66]. Alterations of the cholinergic system in AD results from the loss of neurons of the nucleus basalis of Meynert (nBM), with a subsequent depletion of cortical acetylcholine and cholinergic fibers [54,55]. Additionally, a significant relationship between the presence of WMH in the cholinergic pathways and level of cognitive impairment has been reported with the severity of WMH in cholinergic fibers accounting for a specific impairment in executive functions, regardless of an equivalent global cognitive impairment rating [67]. Thus, our finding of decreased FA in the cingulum bundles in MCI and AD compared to NC could reflect increased vulnerability of this cortical cognitive system to damage of cholinergic pathways in incipient AD, as well as progressive damage in this region in those with AD.

The alterations in the microstructural integrity of normal-appearing WM in AD and MCI found in the present study may represent a complex result of co-existing pathological processes. One pathological process contributing to decreased anisotropy in cortico-cortical and subcortico-cortical white matter tracts may be the presence of subclinical ischemic changes. Vascular risk factors and ischemic events, common in the elderly population, are known to increase the risk of AD [44]. As indicated in the introduction, alterations in microvasculature are commonly seen in brains of patients with AD [45]. In addition, there may be white matter rarefaction with axonal damage and gliosis [31]. In the present study however, the occurrence of clinically relevant cardiovascular risk factors (e.g., diabetes, myocardial infarct, hypertension) was similar across the three groups.

Another pathological process contributing to the loss of white matter integrity in MCI and AD may be increased susceptibility of oligodendrocytes to free-radical and other metabolic damage [4]. According to this theory, later myelinated regions (cortical association areas) have fewer oligodendrocytes supporting greater numbers of axons compared to earlier myelinated regions (primary cortical regions). Because of the high metabolic demands of oligodendrocytes in the cortical association areas needed to maintain the widely distributed axons, formation of ferritin-released iron is increased and may amplify pathological processes due to oxidative stress. These, and other metabolic processes may lead to decreased white matter integrity in association cortical regions due to damage to the supporting oligodendrocytes. In general, our findings of decreased white matter integrity in later-myelinating regions in patients with MCI and AD support this hypothesis.

In the early stages of AD, there is increased gray matter pathology in posterior brain regions relative to anterior regions [1,17]. Our finding of decreased posterior DTI indices of white matter integrity in MCI and early AD demonstrates that this pathological process occurs in white matter as well. The white matter changes in the cognitively impaired groups are independent of the presence of cardiovascular risk factors such as diabetes, myocardial infarct or hypertension and cannot be accounted for by differences in age distributions between the groups. Therefore, our results suggest that posterior white matter damage is specific to the pathological processes of AD. The occurrence of significant regional changes of whole brain WM anisotropy in both MCI and AD groups, compared to controls, suggests that posterior regional anisotropy changes in normal-appearing white matter of patients with MCI could occur before the onset of overt dementia and may play a role in the progression towards AD.

Acknowledgement

We thank all participants for their enthusiastic support of our efforts and for their diligence in complying with the evaluations. We also thank the staff of the RADC clinic, especially Barbara Eubler, for an outstanding job in recruiting participants in the study, and the reviewers for their insightful comments on an earlier draft of the paper.
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