Posterior brain white matter abnormalities in older adults with probable mild cognitive impairment

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Abstract

Objective—Much of the mild cognitive impairment (MCI) neuroimaging literature has exclusively focused on regions associated with Alzheimer's disease. Little research has examined white matter abnormalities of other brain regions, including those associated with visual processing, despite evidence that other brain abnormalities appear in these regions in early disease stages.

Method—Diffusion tensor imaging (DTI) was utilized to examine participants ($n = 44$) that completed baseline imaging as part of a longitudinal healthy aging study. Participants were divided into two groups based on scores from the Montreal Cognitive Assessment (MoCA), a brief screening tool for MCI. Participants who scored < 26 were defined as "probable MCI" while those who scored   26 were labled cognitively healthy. Two DTI indices were analyzed including fractional anisotropy (FA) and mean diffusivity (MD). DTI values for white matter in the lingual gyrus, cuneus, pericalcarine, fusiform gyrus and all four lobes were compared using MANOVA. Regression analyses examined the relationship between DTI indices and total MoCA score.

Results—Results revealed significantly lower FA in the probable MCI group in the cuneus, fusiform, pericalcarine and occipital lobe, and significantly higher MD in the temporal lobe. Fusiform FA and temporal lobe MD were significantly related to total MoCA score after accounting for age and education.

Conclusions—Results indicate that there are posterior white matter microstructural changes in individuals with probable MCI. These differences demonstrate that white matter abnormalities are evident among individuals with probable MCI in regions beyond those commonly associated with Alzheimer's disease and anterior brain aging patterns.

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Mild Cognitive Impairment (MCI) has been described as a transitional state between "normal" age-related cognitive decline and dementia, usually Alzheimer's disease (AD; Petersen et al., 2001). Core criteria for this condition were recently redefined to include individuals for whom there is concern about a decline in cognition, and impairment on objective measures in one or more cognitive domains (Albert et al., 2011). This cognitive impairment is not of sufficient severity to impede independence in daily functional abilities and therefore does not meet the requirements for dementia. The prevalence of MCI is typically reported as 15–20% of adults over 65 years of age in epidemiological studies (Lopez et al., 2003; Petersen et al., 2010; Plassman et al., 2008). Individuals with MCI are considered to be at a higher risk to develop dementia, with annual conversion rates ranging from 3% to 20% (Albert et al., 2011; Farias, Mungas, Reed, Harvey & DeCarli, 2010; Petersen, 2011).

MCI has become an important area of interest for both researchers and clinicians, with a particular focus on identifying biomarkers that would allow for earlier identification of this condition and intervention. Neuroimaging provides a non-invasive biomarker for identifying structural brain changes that indicate the development and progression of MCI (Mueller et al., 2008). Diffusion tensor imaging (DTI) has emerged over the past decade as a useful imaging technique for examining microstructural brain integrity, and is an emerging biomarker in the identification of MCI and AD (Huang, Friedland & Auchus, 2007; Medina et al., 2006; Stebbins & Murphey, 2009). DTI measures the movement (diffusion) of water molecules throughout the brain and is particularly sensitive to variations in white matter microstructure (Le Bihan et al., 2001).

Primary indices of DTI include fractional anisotropy (FA) and mean diffusivity (MD). FA refers to a scalar measure of directional dependency of diffusion, calculating the extent that water diffuses in restricted directions. A value of zero signifies complete isotropy, indicating an equal diffusion rate in all directions. MD is the average rate of diffusion of water molecules within a voxel, independent of direction-specific restrictions such as membranes and tissues. FA and MD are recognized as sensitive to microstructural change. Low MD values and high FA values are generally associated with increased microstructural integrity and neuronal density (Alexander, Lee, Lazar & Field, 2007; Le Bihan et al., 2001).

Much of the MCI literature utilizing DTI has focused on areas vulnerable to AD pathology, such as the hippocampus, parahippocampal white matter, the posterior cingulum, and the medial temporal lobe (Stebbins & Murphey, 2009). Previous studies have reported significant increases in MD and significant decreases in FA in these areas in MCI versus controls, with changes in FA most frequently reported (Fellgiebel et al., 2004; Fellgiebel et al., 2005; Medina et al., 2006; Rose et al., 2006; Zhang et al., 2007). Importantly, these changes demonstrate greater ability to predict conversion from MCI to AD over that of changes in volumes (Scola et al., 2010).

The above results support the existence of microstructural changes in the brains of individuals with MCI. Although consistent patterns of changes have been reported in memory-related areas of the brain (Stebbins & Murphey, 2009), less is known about brain regions and networks outside of those heavily linked to AD among individuals with MCI.

Brain regions that significantly contribute to cognitive functions outside of memory can also impact the development and progression of MCI. Further, microstructural changes in regions outside of those linked to AD could signal global neural degeneration associated with MCI (Mapstone, Steffenella, & Duffy, 2003).

AD pathology is present in visual processing brain regions even in the mild to moderate stages of the disease (Braak & Braak, 1991). Research has demonstrated that early neuropathological features of AD extend from the hippocampus and entorhinal cortex to cortical regions, including visual association areas (Brodmann areas 18 and 19), in mild to moderate stages. These visual association areas of the brain include the lingual gyrus and cuneus. At autopsy, patients with MCI present with AD pathology in the visual association cortex (McKee et al., 2006).

Despite evidence that brain abnormalities are present in visual association areas in early stages of the disease, few studies have focused on regions associated with visual processing in MCI. Consequently, there is no established pattern of DTI alterations in the primary or associated visual processing brain regions of individuals with MCI. Identifying these patterns would contribute to the growing literature on the progression of decline in neural integrity throughout the brain in MCI. The purpose of the present study was to examine the microstructural integrity of visual processing brain regions in older adults with probable MCI. We hypothesized that individuals with probable MCI would exhibit significantly decreased FA in all analyzed regions relative to cognitively healthy older adults, and significantly increased MD. We also hypothesized that there would be a greater number of group differences in FA than MD.

Methods

All data were collected in compliance with regulations of the Institutional Review Board (IRB) of the University of Missouri – Saint Louis. Each participant provided informed consent and was compensated for participation in the study.

Participants

Forty-four individuals were enrolled in the present study. Participants included both male and female English-speaking individuals over the age of 50 recruited from both the local community and from the Participant Registry of Washington University Instititue of Clinical and Translational Sciences. Exclusion criteria included neurological conditions (e.g., current diagnosis of dementia, stroke, or Parkinson's disease), diabetes requiring medication (i.e., not diet-controlled), head injury with loss of conscious >5 min, past or current substance abuse, a major psychiatric condition (e.g., Schizophrenia, untreated anxiety or depression, bipolar disorder) or other medical conditions that could affect cognition including thyroid disease, HIV, epilepsy, multiple sclerosis, or cancer within the last 10 years.

All participants were administered the Lawton Instrumental Activities of Daily Living (IADL) to confirm independence in daily functioning (Lawton & Brody, 1969).

Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is a brief test to determine cognitive status and has demonstrated sensitivity to MCI and early AD (Nasreddine et al., 2005). The MoCA consists of 13 tasks that assess several cognitive domains including visuospatial (visuoconstruction), naming, memory, attention, language, abstraction, delayed recall and orientation. The scores for each task are summed for a total score of 30 points. The education correction was applied for participants with 12 years of education or less that scored fewer than 30 total points. Older adults were subdivided based on the total score on the MoCA. Following conventional cutoffs, individuals with scores < 26 ($N = 25$) were classified as probable MCI. Those with scores 26 ($N =19$) were classified as cognitively healthy. This cut-off is commonly used in the literature and demonstrates a sensitivity of 90% in detecting MCI (Nasreddine et al., 2005).

Neuroimaging Data Acquisition

Structural images were acquired on a 3 Tesla MRI scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) at Washington University in Saint Louis within 30 days of the neuropsychological assessment (M=23 days). Structural MRI scans of the whole brain were collected using: a T1-weighed magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) sequence (176 slices on the sagittal plane, TR=2,100 ms, TE = 3.93 ms, TI = 1,000 ms [non-selective inversion], flip angle = 7°, voxel size = $1.05 \times 1.05 \times 1.05$ mm^3), and a double-echo proton-density (PD)/T2-weighted turbo spin echo (TSE) sequence (43 slices in the transverse plane, TR = 8,040 ms, TE$_1$ = 18 ms, TE$_2$ = 105 ms, voxel size = $1.0 \times 1.0 \times 3.0$ mm^3.

Diffusion-weighted imaging (DWI) acquisition—A custom single-shot multislice echo-planar tensor-encoded pulse sequence was used to acquire axial diffusion-weighted images. Diffusion-encoding gradients were applied in 31 non-collinear directions consisting of 24 main directions (diffusion weighing of b= 996 s/mm^2) and 5 baseline I$_0$ acquisitions (b=0 s/mm^2). A TR of 7.82 s, TE of 86.2 ms, 64 contiguous 2.0-mm slices, and a 128×128 acquisition matrix with a FOV of 256×256 mm isotropic ($2.0 \times 2.0 \times 2.0$ mm) voxels were used as acquisition parameters. Custom image reconstruction was used to reconstruct raw (k-space) data into floating-point DWIs.

Neuroimaging Data Analyses

Diffusion volumes were skull-stripped with FSL BET and corrected for motion and eddy current artifacts with FSL FLIRT (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady & Smith, 2002). Diffusion tensors were fit using linear least squares, and FA and MD were computed for each voxel. Affine transforms were computed between T1-weighted and DTI data using FSL FLIRT. The T1 volumes were parcellated with the Desikan-Killiany atlas using Freesurfer version 5.1.0, and the computed white matter parcellations were registered to diffusion space using the affine transformations and nearest neighbor interpolation. Mean FA and MD were computed in each white matter region of each subject. To calculate the scalar metrics by lobe, the Desikan-Killiany regions were grouped to form bilateral

occipital, parietal, temporal, and frontal regions and a similar procedure was performed to compute lobar mean FA and MD.

Total white matter volumes were taken from aseg.stats output files and corrected for intracranial volume.

Statistical Analyses

All analyses were completed using IBM SPSS Statistics software v. 21 (IBM corp., Armonk, NY). Independent samples t-tests were used to examine group differences in demographic data, MoCA subtest scores and total white matter volume. Two multivariate analyses of variance (MANOVA) were performed to assess whether individuals with MoCA scores <26 (probable MCI) differed on neuroimaging indices compared to individuals with scores 26 (cognitively healthy). The first MANOVA analyzed FA of selected regions and lobes and the second MANOVA analyzed MD of selected regions and lobes. Primary and association areas of visual processing were chosen as imaging variables for the analysis. These regions included the white matter of the occipital lobe, pericalcarine (V1), cuneus, lingual gyrus and fusiform gyrus. Frontal, temporal and parietal white matter were also included to examine the whole-brain pattern of results. All imaging variables were bilateral, calculated by averaging data for those regions from the left and right hemispheres. We used an alpha level of <.05 to determine initial statistical significance. A subsequent false discovery rate (FDR; Benjamini & Hochberg, 1995) analysis was employed to correct for multiple comparisons.

Two series of linear regression analyses examined the relationship between regions exhibiting significant group differences in FA or MD and level of impairment on the MoCA. The first series of regression analyses did not include covariates into the analysis. The second series included both age and years of education entered as the first step, and FA or MD of the significant region as the second step of the hierarchical linear regression models.

Results

Demographic information for the participants is listed in Table 1. No significant differences were observed between groups for age, sex, or years of education. Additionally, the groups did not significantly differ in total white matter volume. Total MoCA scores ranged from 22–30 points. The probable MCI group exhibited significantly worse performance on the visuospatial/executive function, ($t(42) = -3.28$, $p = .002$), language, ($t(42) = -2.89$, $p = .01$), abstraction, ($t(42) = -2.09$, $p = .04$), and delayed recall, ($t(42) = -6.11$, $p < .001$), subtests of the MoCA.

Mean Diffusivity

The probable MCI group initially exhibited significantly higher MD in the fusiform white matter, ($F(1, 42) = 4.35$, $p = .04$), but this did not survive FDR correction. Additionally, significantly higher MD was observed in the temporal lobe white matter of the probable MCI group, ($F(1, 42) = 7.52$, $p = .01$). This result remained significant after FDR correction.

Over the entire sample, temporal lobe MD was significantly related to total MoCA score. Specifically, higher MD of the temporal lobe was associated with lower total MoCA score, ($F(1, 42) = 7.96$, $p = .007$, $\beta = -.399$). This association remained significant with age and years of education included as the first step of the hierarchical regression model, ($F(1, 42) = 6.981$, $p = .01$, $\beta = -.323$).

Fractional Anisotropy

The probable MCI group demonstrated significantly lower FA compared to the healthy group in the cuneus, ($F(1, 42) = 10.70$, $p = .002$), fusiform, ($F(1, 42) = 13.85$, $p = .001$), lingual ($F(1, 42) = 4.32$, $p = .04$), pericalcarine, ($F(1, 42) = 10.40$, $p = .002$), temporal, ($F(1, 42) = 5.78$, $p = .02$), and occipital, ($F(1, 42) = 9.16$, $p = .004$), white matter. Of these results, the cuneus, fusiform, pericalcarine and occipital lobe white matter differences remained significant after the FDR correction was applied.

Simple linear regressions revealed that across the sample, lower FA of the fusiform, ($F(1, 42) = 6.91$, $p = .01$, $\beta = .376$), pericalcarine, ($F(1, 42) = 5.02$, $p = .03$, $\beta = .327$), and occipital lobe, ($F(1, 42) = 4.92$, $p = .03$, $\beta = .324$), were significantly related to lower total MoCA score. When age and years of education were factored in as a first step in the regression, the fusiform, ($F(1, 42) = 2.92$, $p = .04$, $\beta = .322$), remained significantly related to total MoCA score.

Raw means and standard deviations for the MANOVA analyses are reported in Table 2. Regression results are reported in Tables 3 and 4.

Discussion

The aim of the present study was to examine microstructural differences in brain regions associated with visual processing between cognitively healthy older adults and those with probable MCI. The cuneus, fusiform, pericalcarine, occipital lobe and temporal lobe differed significantly between groups. The direction of differences is consistent with reduced microstructural integrity of white matter in visual processing brain regions in the probable MCI group, as evidenced by significantly lower FA and higher MD. At the lobar level, only the temporal and occipital lobes exhibited significant differences between groups. This pattern including the temporal lobe could be expected based on reported changes in the microstructural integrity of the temporal lobe and temporal lobe structures in MCI. Linear regression analyses revealed that FA or MD of regions and lobes with significant group differences were also related to total MoCA score. Higher temporal lobe MD and lower fusiform, pericalcarine, and occipital lobe FA were significantly related to lower total MoCA score. However, only temporal lobe MD and fusiform FA retained a significant relationship with total MoCA score independent of age and years of education.

As hypothesized, there were a greater number of significant group differences in FA of selected regions and lobes. Only one MD result remained significant after FDR correction. These decreases in FA might be attributed to a number of factors, including loss of neuronal integrity, decreased myelination, and decreased fiber coherence (Alexander et al., 2007; Le Bihan et al., 2001). It should be noted that the present study did not assess white matter

volume as a contributor to changes in FA. As this study only included healthy older adults, we did not expect large white matter changes in this sample. Furthermore, total white matter volume did not significantly differ by group.

These results are in agreement with previous studies of MCI in identifying lower FA in the brain. Our results extend the work of previous studies by focusing on diffusion abnormalities among individuals with probable MCI. Specifically, our results contribute to the identification of a pattern of microstructural changes in posterior regions of the brain in older adults who demonstrate impairment on a cognitive screening measure. These results will add to the existing literature that has primarily focused on larger-scale changes, such as atrophy, and changes specific to regions in the temporal lobes.

Previous research has not conclusively identified why posterior regions of the brain, and specific regions of the occipital lobe in particular, may be impacted by MCI. However, studies have demonstrated a vulnerability of the occipital lobe to vascular risk factors. Whereas normal aging is commonly associated with an anterior pattern of brain aging (Head et al., 2004; Sullivan & Pfefferbaum, 2006), vascular risk factors are associated with the simultaneous proliferation of white matter damage into posterior regions (Raz, Rodrigue, Kennedy & Acker, 2007) and impaired cognition (Artero et al., 2004). Interactions between hypertension and age have also been found to differentially and significantly impact FA of the temporal and occipital lobes (Kennedy & Raz, 2009). Decreased CBF, another vascular risk factor, has previously been identified in the occipital lobe and precuneus region in individuals with MCI (Binnewijzend et al., 2013). These relationships remain conjecture at this point and future studies will need to identify the specific relationship between vascular factors and white matter microstructure of the posterior brain regions.

Groups in the present study were based on performance on a screening measure rather than clinical observation and comprehensive testing. This grouping method may have limited observed differences in microstructural integrity of specific brain regions. Nevertheless, we were able to find significant group differences in several brain regions despite using a screening measure in place of a more comprehensive assessment. Employing the MoCA with a <26 cutoff for MCI was originally shown to have a sensitivity of 90% and specificity of 87% to detecting MCI (Nasreddine et al., 2005) and the measure is a commonly utilized clinical tool for rendering a diagnosis of MCI. Sensitivity of the MoCA to identify MCI has been cross-validated through other studies with comparable results (Luis, Keegan, & Mullan, 2009; Smith, Gildeh, & Holmes, 2007). The existence of significant group differences in the present study demonstrates that the cutoff point of <26 is sensitive to group differences in white matter microstructure. Additionally, a previous study (Paul et al., 2011) from our group that analyzes participants from the same subset as our study revealed that when individuals were divided based on MoCA score, the groups also significantly differed on two other common screening measures, the Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975) and the Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, Tierney, Mohr, & Chase, 1998). These results provide evidence supporting that individuals scoring <26 on the MoCA also perform more poorly on other cognitive measures. Furthermore, all participants displayed independence in daily functioning on IADLs. This independence indicates that while those in the probable

MCI group demonstrated some cognitive difficulties on the MoCA, it was not severe enough to indicate dementia. Although more in-depth clinical testing would be needed to confirm a diagnosis of MCI per the current guidelines, the MoCA provides a brief screening measure that demonstrates considerable sensitivity to the identification of possible MCI.

There are several important limitations of this study. Although the MoCA is considered a sensitive screening measure, it is important to note the possibility of false positives for MCI. As previously stated, the prevalence of MCI for individuals over the age of 65 is generally 15–20% (Lopez et al., 2003; Petersen et al., 2010; Plassman et al., 2008). Prevalence of MCI based on MoCA score in the present study was almost 57%, a rate higher than expected in a general population. Furthermore, our sample was young (mean age under 65 years), a condition where lower prevalence rates would be expected. Consequently, it is likely that some individuals who are cognitively intact were identified as "probable MCI." As the results demonstrated significant group differences, the significant microstructural changes observed in the present study would be magnified further had these individuals been classified as cognitively healthy. It is also possible that these microstructural changes may be present in some individuals who are otherwise classified as cognitively healthy. Alternatively, our sample was not a pure community sample, as these individuals self-selected into a study to assess cognition in older adults. As such, it is possible that our sample includes a higher than expected number of individuals with MCI as a function of a recruitment bias. A final limitation to consider is that the MoCA does not allow for speculation as to the types of cognitive profiles of individuals in the probable MCI group. In the present study, groups significantly differed on subtests of visuospatial/executive functioning, language, abstraction and delayed memory indicating the possibility of mixed MCI subtypes. However, a more comprehensive neuropsychological battery would be needed to accurately assess these subtypes.

Future DTI studies of visual processing brain regions in MCI might look at regions associated with higher-order visual processing. We limited regions of interest to four main posterior areas, the pericalcarine (V1) and three visual association areas (cuneus, fusiform gyrus and lingual gyrus) that are involved relatively early on in the visual processing pathways. Analyzing brain regions that lie along the entire dorsal and ventral visual processing pathways would provide a more comprehensive conclusion of group differences. Additionally, employing diffusion imaging with more directions would improve analysis of regions with fiber crossings. Finally, longitudinal studies are necessary to determine whether neuroimaging methods such as DTI offer predictive value in defining risk for conversion to MCI. Although DTI studies are costly and often limit sample sizes due to time, size restrictions, and MRI contraindications, the information provided through analysis of the data is invaluable in identifying changes in brain microstructure.

The results of the present study indicate microstructural differences between cognitively healthy older adults and older adults with probable MCI in white matter of visual processing brain regions. There were a greater number of FA than MD group differences. Identifying these patterns of alterations in older adults who are beginning to demonstrate cognitive decline may contribute to a more complete profile of changes in white matter microstructure associated with MCI.

Acknowledgments

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Table 1

Participant Characteristics

N = 44			
	Probable MCI	**Healthy**	**p**
Sex	9 M/16 F	8 M/11 F	.69
Age, years	61.6 (8.5)	59.3 (7.6)	.35
Education, years	14.8 (2.4)	16.2 (2.6)	.07
Total MoCA Score	23.8 (1.1)	27.8 (1.3)	<.001[*]
Visuospatial/Exec	3.7 (0.9)	4.5 (0.8)	.002[*]
Naming	2.9 (0.3)	2.9 (0.2)	.45
Memory	9.5 (0.8)	9.8 (0.5)	.36
Attention	5.6 (0.8)	5.7 (0.5)	.49
Language	2.4 (0.8)	2.9 (0.3)	.01[*]
Abstraction	1.8 (0.6)	2.1 (0.5)	.04[*]
Delayed Recall	1.4 (1.2)	3.6 (1.2)	<.001[*]
Orientation	6.0 (0.2)	6.0 (0.0)	.39
Total white matter volume	464681.5 (60042)	479207.8 (38849)	.36

Values are given as mean (standard deviation)

[*]
$p<0.05$

Table 2

MANOVA results of selected regions

	Mean (SD)		F-value	p-value
	Probable MCI	**Healthy**		
MD (mm²/ms)				
Cuneus	0.69 (0.03)	0.68 (0.03)	2.47	.12
Fusiform	0.71 (0.03)	0.70 (0.02)	4.35	.04
Lingual	0.75 (0.03)	0.75 (0.04)	0.001	.97
Pericalcarine	0.75 (0.04)	0.75 (0.04)	0.05	.83
Occipital lobe	0.70 (0.02)	0.70 (0.02)	0.39	.54
Temporal lobe	0.71 (0.02)	0.70 (0.02)	7.52	.01[*]
Parietal lobe	0.71 (0.02)	0.70 (0.02)	2.52	.12
Frontal lobe	0.71 (0.01)	0.70 (0.03)	2.07	.16
FA (mm²/s)				
Cuneus	0.27 (0.02)	0.29 (0.02)	10.70	.002[*]
Fusiform	0.33 (0.02)	0.35 (0.02)	13.85	.001[*]
Lingual	0.28 (0.02)	0.29 (0.02)	4.32	.04
Pericalcarine	0.29 (0.03)	0.31 (0.02)	10.40	.002[*]
Occipital lobe	0.29 (0.01)	0.30 (0.02)	9.16	.004[*]
Temporal lobe	0.34 (0.01)	0.35 (0.01)	5.78	.02
Parietal lobe	0.37 (0.02)	0.37 (0.02)	0.56	.46
Frontal lobe	0.35 (0.01)	0.35 (0.02)	2.47	.12

[*] Significant after FDR correction

Table 3

Regression outcomes for regions with significant group differences and total MoCA score

Region	β	R^2	F-value	p-value
MD				
Temporal lobe	−0.40	0.14	7.96	.01[*]
FA				
Cuneus	0.28	0.06	3.70	.06
Fusiform	0.38	0.12	6.91	.01[*]
Pericalcarine	0.33	0.09	5.02	.03[*]
Occipital lobe	0.32	0.09	4.92	.03[*]

[*]
$p<0.05$

Table 4

Hierarchical regression results for regions with significant group differences

Variable		β	Adjusted R²	R²	F	Sig. F	F-value	p-value
Total MoCA score	[1]Age	−0.15	0.04	0.04	1.90	0.16	1.90	.16
	[1]Education	0.25						
	[2]Temporal lobe MD	−0.43	0.14	0.10	5.88	0.02	3.38	.03[*]
	[2]Cuneus FA	0.25	0.08	0.04	2.95	0.09	2.31	.09
	[2]Fusiform FA	0.32	0.18	0.002	0.094	0.76	2.92	.046[*]
	[2]Pericalcarine FA	0.30	0.11	0.07	4.22	0.05	2.77	.05
	[2]Occipital lobe FA	0.29	0.10	0.06	3.90	0.06	2.66	.06

Superscript denotes the regression step number into which each variable was entered

Each DTI variable was analyzed as a separate regression analysis

[*]
$p<0.05$