Diffusion tensor imaging and cognitive function in older adults with no dementia

K. Kantarci, MD, MSc
M.L. Senjem, MS
R. Avula, PhD
B. Zhang, MD
A.R. Samikoglu, MS
S.D. Weigand, MS
S.A. Przybelski, BS
H.A. Edmonson, PhD
P. Vemuri, PhD
D.S. Knopman, MD
B.F. Boeve, MD
R.J. Ivnik, PhD
G.E. Smith, PhD
R.C. Petersen, MD, PhD
C.R. Jack, Jr., MD

Address correspondence and reprint requests to Dr. Kejal Kantarci, Mayo Clinic, 200 First Street SW, Rochester, MN 55905
kantarci.kejal@mayo.edu

ABSTRACT

Objective: To determine the patterns of diffusivity associated with cognitive domain functions in older adults without dementia.

Methods: We studied older adults without dementia ($n = 220$) who underwent neuropsychometric testing and a diffusion tensor imaging (DTI) examination at 3 T in a cross-sectional study. Memory, language, attention/executive function, and visual-spatial processing domains were assessed within 4 months of the MRI examination. A fluid-attenuated inversion recovery-based DTI sequence that enabled uncontaminated cortical diffusion measurements was performed. Associations between cortical mean diffusivity (MD) and cognitive function were tested using voxel-based regression analysis. Association between tract diffusivity and cognitive function was tested with regions of interest drawn on color-coded fractional anisotropy (FA) maps.

Results: Memory function was associated with the medial temporal lobe cortical MD on voxel-based analysis ($p < 0.001$, corrected for multiple comparisons), and inferior longitudinal fasciculus and posterior and anterior cingulum FA on tract-based analysis ($p < 0.001$). Language function was associated with the left temporal lobe cortical MD ($p < 0.001$, corrected for multiple comparisons), inferior longitudinal fasciculus, fornix, and posterior cingulum FA ($p < 0.05$). Attention and executive function was associated with the posterior and anterior cingulum FA, and visual-spatial function was associated with posterior cingulum FA ($p < 0.01$).

Conclusion: Specific cognitive domain functions are associated with distinct patterns of cortical and white matter diffusivity in elderly with no dementia. Posterior cingulum tract FA was associated with all 4 cognitive domain functions, in agreement with the hypothesis that the posterior cingulate cortex is the main connectivity hub for cognitive brain networks. Microstructural changes identified on DTI may be associated with neurodegenerative pathologies underlying cognitive changes in older adults without dementia. *Neurology*® 2011;77:26-34

GLOSSARY

ADRC = Alzheimer's Disease Research Center; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FLAIR** = fluid-attenuated inversion recovery; **FWE** = family-wise error; **GM** = gray matter; **MCI** = mild cognitive impairment; **MCSA** = Mayo Clinic Study of Aging; **MD** = mean diffusivity; **MOANS** = Mayo Older American Normative Studies; **MTL** = medial temporal lobe; **ROI** = region of interest; **TE** = echo time; **TI** = inversion time; **TR** = repetition time; **WAIS-R** = Wechsler Adult Intelligence Scale-Revised; **WM** = white matter.

Involvement of the brain with neurodegenerative dementia pathologies is insidious, starting many years before the clinical diagnosis of dementia.¹ People who develop dementia later in life may present with prodromal symptoms, clinically operationalized as mild cognitive impairment (MCI).² The continuum of early pathologic involvement from presymptomatic to MCI represents an ideal window for preventive and early therapeutic interventions in dementia. Imaging biomarkers associated with cognitive function in older adults without dementia may

Editorial, page 14

Supplemental data at
www.neurology.org

Scan this code with your smartphone to access this feature

From the Department of Radiology (K.K., M.L.S., R.A., B.Z., A.R.S. H.A.E., P.V., C.R.J.), Department of Health Sciences Research, Division of Biostatistics (S.D.W., S.A.P.), Department of Neurology (D.S.K., B.F.B., R.C.P.), and Department of Psychiatry and Psychology (R.J.I., G.E.S.), Mayo Clinic, Rochester, MN; and Department of Radiology (B.Z.), Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Study funding: Supported by the NIH (K23 AG030935, P50 AG16574/P1, R01 AG11378, U01 AG 06786). Support for several investigators was provided by the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation and the NIH Construction Grant (C06 RR018898).

Disclosure: Author disclosures are provided at the end of the article.

be valuable in detecting involvement of the brain with the neurodegenerative dementia pathologies early in the disease course.

A potential imaging biomarker for neurodegenerative dementia pathologies is diffusion tensor imaging (DTI), which provides information on the integrity of tissue microstructure. Mean diffusivity (MD) increases with the degeneration of microstructural barriers such as myelin and cell membranes, and the directionality of diffusion measured with fractional anisotropy (FA) decreases with degeneration of the white matter (WM) tracts.³

We investigated correlations between diffusivity measurements and specific cognitive domain functions in older adults without dementia who were either cognitively normal or diagnosed with MCI. Our objective was to determine whether regional alterations in tissue microstructure detected with DTI would be a valuable imaging marker for memory, language, attention/executive function, and visual-spatial processing domain functions. The rationale for including both cognitively normal and MCI cases was to identify the microstructural changes associated with cognitive function in a group that represents the widest range of cognitive functioning from normal to MCI, who are the focus of preventive and early therapeutic interventions in dementia.

METHODS Recruitment of subjects. Subjects were recruited from the Mayo Clinic Alzheimer's Disease Research Center (ADRC), a dementia clinic-based cohort, and Mayo Clinic Study of Aging (MCSA), a population-based cohort.⁴ A total of 220 older subjects without dementia (149 MCI and 71 cognitively normal subjects) participated in the MRI/DTI study during the period June 2007 through 2009. Characteristics of the study subjects are listed in table 1. Individuals participating in the ADRC and MCSA studies undergo approximately annual clinical examinations, MRI, routine laboratory tests, and neuropsychological tests. At the completion of the evaluation, a consensus committee meeting is held involving the behavioral neurologists, neuropsychologists, and nurses who evaluated the subjects to assign a clinical diagnosis to the participant.

The operational definition of MCI was based on clinical judgment through a careful history from the patient and preferably a collateral source without reference to MRI using the criteria for the broad definition of MCI.⁵ The distribution of MCI subtypes was as follows: 67/149 amnesic MCI single domain, 49/149 amnesic MCI multiple domain, 23/149 nonamnesic MCI single domain, 10/149 nonamnesic MCI multiple domain. Patients with structural abnormalities, psychiatric diseases, or treatments that would have an effect on cognitive function were excluded. The cognitively normal group did not have any neurologic or psychiatric conditions, did not have a cognitive

Table 1 Patient characteristics ^a	
Characteristics	Values
No. of subjects	220
No. (%) women	85 (38.6)
No. (%) APOE ε4 carriers	76 (41)
No. (%) patients with MCI	149 (67.7)
Age, y, median (minimum, maximum)	79 (52, 95)
Education, y, median (minimum, maximum)	13 (7, 20)
Short Test of Mental Status (minimum, maximum)	32 (19, 38)
CDR Sum of Boxes (minimum, maximum)	0.5 (0.0, 5.0)
Cognitive domain MOANS scores, median (minimum, maximum)	
Memory	8.3 (2.3, 18.0)
Attention/executive	9.5 (3.0, 17.0)
Visual-spatial	10.5 (3.5, 18.0)
Language	10.5 (2.5, 15.5)

Abbreviations: CDR = Clinical Dementia Rating; MCI = mild cognitive impairment; MOANS = Mayo Older American Normative Studies.

^a Missing data note: APOE genotyping was not performed on 37 subjects; Short Test of Mental Status was not available for 4 subjects; CDR Sum of Boxes was not available for 2 subjects; memory domain function was not available for 5 subjects; attention/executive domain function was not available for 12 subjects; visual-spatial domain function was not available for 8 subjects; language domain function was not available for 5 subjects.

complaint, had normal neurologic and neurocognitive examination results, and were not taking psychoactive medications in doses that would affect cognition.

Standard protocol approvals, registrations, and patient consents. This study was approved by the Mayo Clinic Institutional Review Board, and informed consent for participation was obtained from every subject or an appropriate surrogate.

Neuropsychological testing. Cognitive testing was completed within 4 months of the MRI scans. Memory was evaluated by free recall retention scores computed after a 30-minute delay for the Wechsler Memory Scale–Revised Logical Memory and Visual Reproduction subtests and the Rey Auditory Verbal Learning Test. Language tests measured naming to confrontation (i.e., the Boston Naming Test)⁶ and category fluency (i.e., naming animals, fruits, and vegetables).⁷ The attention/executive measures included the Trail Making Test part B and the Wechsler Adult Intelligence Scale–Revised (WAIS-R) Digit Symbol subtest. Visual-spatial processing was examined by the WAIS-R Picture Completion and Block Design subtests. All tests were administered by experienced psychometrists and supervised by clinical neuropsychologists (R.J.I. and G.E.S.). All raw scores were converted to Mayo Older American Normative Studies (MOANS) age-adjusted scaled scores that are normally distributed and that have a mean of 10 and SD of 3 in cognitively healthy subjects on whom each test was normed.^{7–9} In each cognitive domain, a mean MOANS age-corrected scaled score was computed for every participant. The patients' mean MOANS scores within a certain domain did not strictly define

their MCI category although cognitive tests were used to inform the clinical consensus diagnosis.

MRI acquisition. MRI examinations were performed at 3 Tesla using an 8-channel phased array coil (GE, Milwaukee, WI) and parallel imaging with an acceleration factor of 2. A 3-dimensional high-resolution magnetization-prepared rapid gradient echo acquisition with repetition time (TR)/echo time (TE)/inversion time (TI) = 7/3/900 msec, flip angle 8 degrees, in-plane resolution of 1.0 mm, and a slice thickness of 1.2 mm was performed for anatomic segmentation and labeling. DTI was performed with an echoplanar imaging fluid-attenuated inversion recovery (FLAIR) sequence with TR/TI/TE = 8,800/2,200/60 msec, 21 diffusion-sensitive gradient directions ($b = 1,000$ msec/mm²), an in-plane resolution of 2.96 mm, and a slice thickness of 3.3 mm. MD is significantly higher in CSF than the brain tissue. We avoided the partial volume averaging of cortical tissue with the higher diffusivity CSF signal by suppressing it with FLAIR DTI.¹⁰ Unlike the more standard T2-based DTI sequences, this FLAIR-based approach enabled reliable measures of cortical MD.

DTI analysis. Twenty-one diffusion-weighted images were registered to the non-diffusion-weighted FLAIR b0 volume with affine registration using 12 degrees of freedom to correct for eddy-current induced distortions. Maps of MD, FA, and color-coded FA were generated using the DTIStudio software. T1-weighted MRI volume of each subject was warped to his or her own FLAIR b0 image using an in-house modified version of the high dimensional warping toolbox in SPM5. Each subject's MRI scan was then spatially normalized to the custom template generated from 200 subjects with AD and 200 normal elderly subjects¹¹ using the unified segmentation model of SPM5 and segmented into gray matter (GM), WM, and CSF. The resulting deformation was applied to the FLAIR b0 images in native space in order to warp the segmented native FLAIR b0 images to the customized template. Voxel-based association between GM MD and cognitive function was assessed in SPM5. Statistical maps were displayed at a significance value of $p < 0.05$ and corrected for multiple comparisons using family-wise error (FWE) with a cluster size threshold of 20 voxels including age, gender, and education as covariables.

WM tract-based analysis of MD and FA was performed by manual placement of regions of interest (ROIs) on the color-coded FA maps using Analyze software (Mayo Clinic, Rochester, MN) by a radiologist (B.Z.) who was blinded to the clinical diagnosis. Anatomic landmarks were used when placing the ROIs, which were transferred to the FLAIR b0 images to ensure CSF spaces and WM hyperintensities were avoided. We analyzed the FA of the major WM tracts including the corticopontine tracts, inferior longitudinal fasciculus, superior longitudinal fasciculus, fornix, anterior and posterior cingulum tracts, and corpus callosum. The locations of many of these ROIs have been illustrated¹² (figure e-1 on the *Neurology*[®] Web site at www.neurology.org). Intrarater reliability for the manual ROI measurements was excellent with a within-subject coefficient of variation ranging from 0.02 to 0.06 across different ROIs. Correlations between tract-based FA and cognitive domain MOANS scores were tested with partial Spearman rank-order correlation controlling for age, gender, and education.

Voxel-based morphometry. Patterns of cortical atrophy were assessed with voxel-based morphometry in SPM5. All images were normalized to a customized template and segmented using customized tissue probability maps. GM images were modulated and smoothed at 8 mm full width at half maximum. Statistical maps of the regression with cognitive domain

MOANS scores were displayed at a significance value of $p < 0.05$, corrected for multiple comparisons using FWE with a cluster size threshold of 20 voxels including age, gender, and education as covariables.

RESULTS Diffusivity and memory domain function.

Associations between memory domain function and cortical diffusivity were confined to the hippocampus, parahippocampal gyrus, and amygdala in both hemispheres on voxel-based analysis in the whole group of subjects. Higher cortical MD (figure 1) and atrophy (figure e-2) in the medial temporal lobes (MTL) were associated with greater impairment in the memory domain ($p < 0.05$; FWE corrected) (figure 1). WM tract-based analysis showed that greater impairment in the memory domain was associated with lower FA in the inferior longitudinal fasciculus ($p < 0.001$), anterior cingulum ($p < 0.002$), and posterior cingulum ($p < 0.001$) tracts in the whole group of subjects after controlling for age, gender, and education (table 2).

Diffusivity and language domain function. Left temporal lobe cortical diffusivity was associated with the language domain function. Higher cortical MD (figure 2) in the left temporal pole and amygdala, fusiform gyrus, and posterior inferior temporal gyrus correlated with the impairment in language domain function ($p < 0.05$; FWE corrected). Similarly, cortical atrophy correlated with the impairment in language domain function in the left temporal pole, fusiform gyrus, and amygdala ($p < 0.05$; FWE corrected), but not in the posterior inferior temporal gyrus (figure e-3). Lower FA in the inferior longitudinal fasciculus ($p < 0.01$) and posterior cingulum tracts ($p = 0.02$) correlated with greater impairment in the language domain in the whole group of subjects after controlling for age, gender, and education. Whereas there was a left-sided association between the temporal cortical MD and language function, inferior longitudinal fasciculus FA correlated with language function bilaterally ($p < 0.01$).

Diffusivity and attention/executive domain function.

We did not identify any associations between the attention/executive domain function and cortical diffusivity or atrophy. However, a significant correlation was present between attention/executive domain function and anterior cingulum ($p < 0.001$), posterior cingulum ($p < 0.001$), and inferior longitudinal fasciculus FA ($p = 0.04$) in the whole group of subjects. Lower FA in these tracts correlated with greater impairment in the attention/executive domain after controlling for age, gender, and education.

Diffusivity and visual-spatial processing domain function.

We did not identify any associations between the visual-spatial processing domain function and

Figure 1 Memory and cortical diffusivity

Voxel-based analysis of cortical diffusivity using SPM5 shows the correlation between cortical mean diffusivity (MD) and memory domain function in red and yellow (family-wise error correction $p < 0.05$) adjusted for age, gender, and education. Surface render projections show that higher MD is associated with lower memory domain Mayo Older American Normative Studies scores in the medial temporal lobe (denoted by red pixels). Cerebellum and brainstem are removed from the midline projections in order to display the medial temporal lobes. The cross-sections demonstrate the significant associations in the hippocampus, parahippocampal gyrus, and amygdala (denoted by yellow pixels).

cortical diffusivity or atrophy. Lower FA in the posterior cingulum tract ($p = 0.001$) and the fornix ($p = 0.03$) correlated with greater impairment in the visual-spatial processing domain function after controlling for age, gender, and education. In addition, there was a trend of association between impairment in the visual-spatial processing domain function and decreased FA in the dorsal component of superior longitudinal fasciculus ($p = 0.05$).

There were no associations between individual domain functions and cortical MD and tract-based FA measurements when MCI and cognitively normal groups were tested separately ($p > 0.05$) (figure 3).

DISCUSSION Voxel-based analysis of cortical diffusivity and atrophy revealed a significant association between increased MD and GM loss in the MTL and decreased memory function in older adults without dementia. Hippocampus, parahippocampal gyrus, and amygdala are the key structures for memory function, typically involved with the pathology of AD earlier than other regions of the brain. Cortical MD increases with the loss of normal tissue microstructure such as disruption of neuronal cell membranes that restrict random motion of water molecules. DTI studies have consistently found elevated MD in the hippocampus and decreased FA in the main limbic pathways connecting to the hippocampus in MCI,^{13–24} and recently hippocampal MD predicted cognitive decline in healthy elderly people.²⁵ Early neurodegenerative changes, most commonly associated with AD in older adults without dementia, may be responsible for the elevated diffusivity in cortical regions that is associated with memory function.

Tract-based FA is a measure of directionality of diffusion, which decreases with the loss of myelin

Table 2 Spearman partial correlation (p value) between WM tract FA and cognitive domain Z score^a

ROI	Cognitive domain			
	Memory	Language	Attention	Visual-spatial
Inferior longitudinal fasciculus	0.26 (<0.001) ^b	0.22 (0.002) ^b	0.15 (0.04) ^b	0.09 (0.19)
Fornix	0.09 (0.22)	0.14 (0.05)	0.03 (0.63)	0.15 (0.03) ^b
Posterior cingulum	0.25 (<0.001) ^b	0.16 (0.02) ^b	0.26 (<0.001) ^b	0.22 (0.001) ^b
Superior longitudinal fasciculus	0.09 (0.18)	0.02 (0.72)	0.10 (0.14)	0.13 (0.05)
Corticopontine tract	0.07 (0.30)	−0.03 (0.65)	−0.03 (0.71)	0.10 (0.17)
Corpus callosum	−0.01 (0.87)	0.02 (0.78)	0.02 (0.74)	0.09 (0.18)
Anterior cingulum	0.21 (0.002) ^b	0.11 (0.11)	0.23 (<0.001) ^b	0.08 (0.23)

Abbreviations: FA = fractional anisotropy; ROI = region of interest; WM = white matter.

^a Partial correlations control for age, sex, and education.

^b Significant.

Voxel-based analysis of the cortical diffusivity using SPM5 shows the correlation between cortical mean diffusivity (MD) and language domain function in red and yellow (family-wise error correction $p < 0.05$) adjusted for age, gender, and education. Surface render projections show that higher MD is associated with lower language domain Mayo Older American Normative Studies scores in the left temporal lobe (denoted by red pixels). Cerebellum and brainstem are removed from the midline projection in order to display the left medial temporal lobe. The cross-sections demonstrate significant associations in the left temporal pole, amygdala, fusiform gyrus, and posterior inferior temporal gyrus (denoted by yellow pixels). There was no association between hippocampal diffusivity and language domain function.

and axonal membranes that restrict the movement of water molecules along the WM tracts. In the current study, decreased FA in tracts connecting to MTL, such as the inferior longitudinal fasciculus and the cingulum tracts, significantly correlated with decreased memory function, indicating that memory function in older adults without dementia depends on both the integrity of MTL structures and their connectivity with other temporal, parietal, and frontal lobe regions. Although WM diffusion properties depend on aging throughout the adult lifespan,^{26,27} the associations we found were independent of age effects on WM diffusivity, suggesting that loss of WM integrity may be an early feature of neurodegenerative dementia pathology.²⁸

Language domain function was assessed using confrontation naming and category fluency tests that focus on word retrieval and visual naming functions. fMRI and lesion studies have long indicated that semantic processing and word retrieval is localized to left temporal pole, fusiform, middle temporal, and posterior inferior temporal gyri.^{29–31} In the current study, language function was associated with the left temporal pole, anterior fusiform, posterior middle, and inferior temporal gyri MD, which is in agreement with the typical localization of word retrieval and visual naming functions. This pattern matched

well with the pattern of association between language domain function and cortical atrophy except in the left posterior temporal lobe, where no association was identified between language domain function and cortical atrophy. Moreover, FA of the inferior longitudinal fasciculus, which connects these cortical regions, significantly correlated with the language domain function. Correlations with inferior longitudinal fasciculus, however, was not lateralized to the left temporal lobe, but involved the inferior longitudinal fasciculi in both hemispheres. There was also a weaker but significant correlation between language function and posterior cingulum tract FA. Overall, these data demonstrated that the connectivity within the temporal lobes as well as the connectivity between the temporal lobe and parietal association areas are critical for language function, a finding in agreement with a previous DTI study in early AD.³²

Attention/executive domain function is typically localized to the frontal lobes in fMRI and lesion studies.³³ In the current study, we did not identify a relationship between cortical MD, atrophy, and attention/executive domain function. However, significant associations were present between attention/executive domain function and anterior and posterior cingulum tract FA. A relationship between executive function and FA was previously identified

Figure 3 Cognitive domain function and tract-based fractional anisotropy (FA)

Scatterplots showing the relationship between cognitive domain Mayo Older American Normative Studies (MOANS) scores and FA values for 3 regions of interest. Red squares indicate cognitively normal subjects while blue triangles represent subjects with mild cognitive impairment. (A) All 4 cognitive domains vs posterior cingulum tract FA. (B) Memory and language MOANS scores vs inferior longitudinal fasciculus FA. (C) Memory and attention MOANS scores vs anterior cingulum tract FA.

in the frontal WM, extending to the parietal WM in cognitively normal adults.³⁴ Our data in part agree with this finding, showing that the connectivity along the cingulum tract in the frontal and parietal

lobes is associated with the attention/executive domain function.

Visual-spatial processing domain function did not correlate with MD or atrophy in any of the cortical

regions, but there was a significant correlation between posterior cingulum tract FA and visual-spatial processing. In addition, there was a weaker association between the fornix and superior longitudinal fasciculus FA and visual-spatial processing domain function. We measured the FA from the dorsal component of superior longitudinal fasciculus which constitutes the thickest portion of the tract that connects the caudal parietal cortex and the dorsolateral prefrontal cortex. Lesion studies in monkeys and humans suggest that this tract provides information concerning the perception of the visual space from the parietal lobe to the prefrontal cortex.³⁵ The posterior parietal association cortex is a component of the spatial-attention network through the dorsal visual stream, which may be responsible for the association between the visual-spatial processing domain function and the posterior cingulum and the superior longitudinal fasciculus tract FA.³⁶

Structural integrity of the posterior cingulum tract on DTI was associated with all 4 cognitive domain functions, in agreement with the resting state fMRI findings indicating that posterior cingulate cortex is the main connectivity hub for the major cortical networks.^{37,38} AD is the most common dementia pathology encountered in older adults without dementia, and the frequency and severity of AD pathology is associated with impaired cognitive function, even in people who do not have dementia.³⁹ Other neurodegenerative pathologies that are associated with cognitive impairment in older adults without dementia include dementia with Lewy bodies, which is usually mixed with the AD pathology, and frontotemporal lobar degeneration, which is relatively infrequent compared to AD.³⁹ Because loss of cingulum tract integrity on DTI is typically seen in early AD, we hypothesize that the presence of early AD pathology in some of our elderly adults without dementia may be driving the association between cognitive function and posterior cingulum tract integrity. We are planning to test this hypothesis with future longitudinal studies.

Memory and language domain functions were associated with both MD in temporal lobe cortex regions and FA in WM tracts that connect to these temporal lobe cortices. On the contrary, attention/executive and visual-spatial processing domain functions were associated only with WM tract FA in the parietal and frontal lobe regions but not the cortical MD. One explanation for this dissociation among the individual cognitive domains is that the temporal course of the WM tract degeneration may be different from the temporal course cortical degeneration that is most commonly associated with early AD pathology in patients with MCI and cognitively normal

elderly. Because the pathology of AD involves temporal lobes earlier than other regions of the brain, cognitive domains that are impaired early in the disease course of AD such as memory and language domains would be associated with the altered integrity of the temporal lobe cortices as demonstrated in the current study. Conversely, visual-spatial processing and attention/executive function may be associated with cortical integrity outside of the temporal lobe that has not yet been involved with the neurodegenerative pathology in the subjects without dementia we studied. The finding that these domain functions were only associated with WM tract FA in the parietal and frontal lobe regions suggests that the disruption of WM tract integrity may be preceding or promoting the changes in cortical microstructure associated with impairment in the visual-spatial processing and attention/executive function domains that occur later.⁴⁰ A second explanation for this dissociation among the cognitive domains may be the more focal representation of memory and language in contrast to the anatomically widespread representation of the visual-spatial processing and attention/executive function domains in the cortex, thereby identifying a regional association between cortical MD and visual-spatial processing and attention/executive function domains was not possible due to insufficient effect size on voxel-based analysis.

The current study demonstrates that specific cognitive domain functions are associated with distinct patterns of cortical and WM diffusivity in elderly without dementia. We studied a cohort of older adults without dementia who represent a wide range of cognitive functioning from normal to MCI in order to include the complete range of cognitive functioning in subjects without dementia. Although each cognitive domain was associated with a characteristic pattern of diffusion abnormalities, abnormal FA in the posterior cingulum tract was a unifying feature that spanned all cognitive domains.

AUTHOR CONTRIBUTIONS

Dr. Kantarci: drafting/revising the manuscript; study concept or design; analysis or interpretation of data; acquisition of data; statistical analysis; study supervision; obtaining funding. M.L. Senjem: analysis or interpretation of data; contribution of vital reagents/tools/patients; statistical analysis. Dr. Avula: study concept or design; analysis or interpretation of data. Dr. Zhang: drafting/revising the manuscript; analysis or interpretation of data; acquisition of data. A.R. Samikoglu: analysis or interpretation of data. S.D. Weigand: study concept or design; analysis or interpretation of data; statistical analysis. S.A. Przybelski: drafting/revising the manuscript; analysis or interpretation of data; statistical analysis. Dr. Edmonson: study concept or design; analysis or interpretation of data; acquisition of data; study supervision. Dr. Vemuri: analysis or interpretation of data. Dr. Knopman: drafting/revising the manuscript; acquisition of data. Dr. Boeve: drafting/revising the manuscript; acquisition of data. Dr. Ivnik: drafting/revising the manuscript; analysis or interpretation of data; acquisition of data. Dr. Smith: drafting/revising the manuscript; analysis or interpretation of data; study supervision. Dr. Petersen: drafting/revising the man-

uscript; obtaining funding. Dr. Jack: drafting/revising the manuscript; study concept or design; analysis or interpretation of data; acquisition of data; obtaining funding.

DISCLOSURE

Dr. Kantarci receives research support from the NIH. M.L. Senjem has received research support from Pfizer Inc. Dr. Avula serves as a consultant for Medical Imaging Solutions. Dr. Zhang, A.R. Samikoglu, S.D. Weigand, and S.A. Przybelski report no disclosures. Dr. Edmonson is author on a patent re: Real-time shimming of polarizing field in magnetic resonance system; receives research support from the NIH (NIA, NCRR, NIBIB, NIMH), NARSAD The Brain and Behavior Research Fund; has received license fee payments for ACR phantom analysis software; and has received royalty payments from Siemens for a patent re: Real-time shimming of polarizing field in magnetic resonance system. Dr. Vemuri reports no disclosures. Dr. Knopman serves as Deputy Editor for *Neurology*[®]; has served on a data safety monitoring board for Eli Lilly and Company; has served as a consultant for Elan/Janssen AI; is an investigator in clinical trials sponsored by Elan/Janssen AI, Baxter International Inc., and Forest Laboratories, Inc.; and receives research support from the NIH. Dr. Boeve receives royalties from the publication of *Behavioral Neurology of Dementia* (Cambridge University Press, 2009); has served as a consultant for GE Healthcare; and receives research support from Cephalon, Inc., Allon Therapeutics, Inc., the NIH/NIA, and the Alzheimer's Association, and the Mangurian Foundation. Dr. Ivnik serves on the editorial boards of *The Clinical Neuropsychologist and Aging, Neuropsychology, and Cognition*; receives publishing royalties for *Clinical Interpretation of the WAIS-III and WMS-III* (Academic Press, 2003); and receives research support from the NIH/NIA. Dr. Smith serves on the editorial boards of *The Clinical Neuropsychologist* and the *Journal of International Neuropsychological Society*; serves as a consultant for Homeinstead Senior Living Inc.; and receives research support from the NIH (NCRR, NIA, NINDS) and Mayo Clinic Alzheimer's Disease Research Center. Dr. Petersen serves on scientific advisory boards for the Alzheimer's Association, the National Advisory Council on Aging (NIA), Elan/Janssen AI, Pfizer Inc (Wyeth), and GE Healthcare; receives royalties from publishing *Mild Cognitive Impairment* (Oxford University Press, 2003); serves as a consultant for Elan/Janssen AI and GE Healthcare; and receives research support from the NIH/NIA. Dr. Jack serves on scientific advisory boards for Elan/Janssen AI, Eli Lilly & Company, GE Healthcare, and Eisai Inc.; receives research support from Baxter International Inc., Allon Therapeutics, Inc., Pfizer Inc, the NIH/NIA, and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation; and holds stock/stock options in Johnson & Johnson.

Received June 14, 2010. Accepted in final form December 29, 2010.

REFERENCES

1. Morris JC, Kimberly A, Quaid K, et al. Role of biomarkers in studies of presymptomatic Alzheimer's disease. *Alzheimers Dement* 2005;1:145–151.
2. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome [erratum 1999;56:760]. *Arch Neurol* 1999;56:303–308.
3. Ulug AM, Moore DF, Bojko AS, Zimmerman RD. Clinical use of diffusion-tensor imaging for diseases causing neuronal and axonal damage. *AJNR Am J Neuroradiol* 1999;20:1044–1048.
4. Roberts RO, Geda YE, Knopman DS, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology* 2008;30:58–69.
5. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256:183–194.
6. Kaplan E, Goodglass H, Weintraub S. The Boston Naming Test, 2nd ed. Philadelphia: Lea & Febiger; 1983.

7. Lucas JA, Ivnik RJ, Smith GE, et al. Mayo's older Americans normative studies: category fluency norms. *J Clin Exp Neuropsychol* 1998;20:194–200.
8. Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC. Neuropsychological tests' norms above age 55: COWAT, BNT, MAE Token, WRAT-R Reading, AMNART, STROOP, TMT, and JLO. *Clin Neuropsychol* 1996;10:262–278.
9. Ivnik RJ, Malec JF, Smith GE, et al. Mayo's Older Americans Normative Studies: WAIS-R, WMS-R and AVLT norms for ages 56 through 97. *Clin Neuropsychol* 1992;6(suppl):1–104.
10. Kwong KK, McKinstry RC, Chien D, Crawley AP, Pearlman JD, Rosen BR. CSF-suppressed quantitative single-shot diffusion imaging. *Magn Reson Med* 1991;21:157–163.
11. Vemuri P, Whitwell JL, Kantarci K, et al. Antemortem MRI based STructural Abnormality iNDEX (STAND) scores correlate with postmortem Braak neurofibrillary tangle stage. *Neuroimage* 2008;42:559–567.
12. Kantarci K, Avula R, Senjem ML, et al. Dementia with Lewy bodies and Alzheimer disease: neurodegenerative patterns characterized by DTI. *Neurology* 2010;74:1814–1821.
13. Fellgiebel A, Muller MJ, Wille P, et al. Color-coded diffusion-tensor-imaging of posterior cingulate fiber tracts in mild cognitive impairment. *Neurobiol Aging* 2005;26:1193–1198.
14. Fellgiebel A, Dellani PR, Greverus D, Scheurich A, Stoeter P, Muller MJ. Predicting conversion to dementia in mild cognitive impairment by volumetric and diffusivity measurements of the hippocampus. *Psychiatry Res* 2006;146:283–287.
15. Kantarci K, Jack CR Jr, Xu YC, et al. Mild cognitive impairment and Alzheimer disease: regional diffusivity of water. *Radiology* 2001;219:101–107.
16. Lee DY, Fletcher E, Martinez O, et al. Regional pattern of white matter microstructural changes in normal aging, MCI, and AD. *Neurology* 2009;73:1722–1728.
17. Liu Y, Spulber G, Lehtimäki KK, et al. Diffusion tensor imaging and tract-based spatial statistics in Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging Epub* 2009.
18. 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;27:663–672.
19. Zhang Y, Schuff N, Jahng GH, et al. Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. *Neurology* 2007;68:13–19.
20. Chen TF, Chen YF, Cheng TW, Hua MS, Liu HM, Chiu MJ. Executive dysfunction and periventricular diffusion tensor changes in amnesic mild cognitive impairment and early Alzheimer's disease. *Hum Brain Mapp* 2009;30:3826–3836.
21. Grambaite R, Stenset V, Reinvang I, Walhovd KB, Fjell AM, Fladby T. White matter diffusivity predicts memory in patients with subjective and mild cognitive impairment and normal CSF total tau levels. *J Int Neuropsychol Soc* 2009;16:58–69.
22. Huang J, Friedland RP, Auchus AP. Diffusion tensor imaging of normal-appearing white matter in mild cognitive impairment and early Alzheimer disease: preliminary evidence of axonal degeneration in the temporal lobe. *AJNR Am J Neuroradiol* 2007;28:1943–1948.

23. Mielke MM, Kozauer NA, Chan KC, et al. Regionally-specific diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. *Neuroimage* 2009;46:47–55.
24. Walhovd KB, Fjell AM, Amlie I, et al. Multimodal imaging in mild cognitive impairment: Metabolism, morphometry and diffusion of the temporal-parietal memory network. *Neuroimage* 2009;45:215–223.
25. Carlesimo GA, Cherubini A, Caltagirone C, Spalletta G. Hippocampal mean diffusivity and memory in healthy elderly individuals: a cross-sectional study. *Neurology* 2010;74:194–200.
26. Bendlin BB, Fitzgerald ME, Ries ML, et al. White matter in aging and cognition: a cross-sectional study of microstructure in adults aged eighteen to eighty-three. *Dev Neuropsychol* 2010;35:257–277.
27. Westlye LT, Walhovd KB, Dale AM, et al. Life-span changes of the human brain White matter: diffusion tensor imaging (DTI) and volumetry. *Cereb Cortex* 2010;20:2055–2068.
28. Bendlin BB, Ries ML, Canu E, et al. White matter is altered with parental family history of Alzheimer's disease. *Alzheimers Dement* 2010;6:394–403.
29. Chao LL, Haxby JV, Martin A. Attribute-based neural substrates in temporal cortex for perceiving and knowing about objects. *Nat Neurosci* 1999;2:913–919.
30. Schwartz MF, Kimberg DY, Walker GM, et al. Anterior temporal involvement in semantic word retrieval: voxel-based lesion-symptom mapping evidence from aphasia. *Brain* 2009;132:3411–3427.
31. Birn RM, Kenworthy L, Case L, et al. Neural systems supporting lexical search guided by letter and semantic category cues: a self-paced overt response fMRI study of verbal fluency. *Neuroimage* 2010;49:1099–1107.
32. Fellgiebel A, Schermuly I, Gerhard A, et al. Functional relevant loss of long association fibre tracts integrity in early Alzheimer's disease. *Neuropsychologia* 2008;46:1698–1706.
33. Zakzanis KK, Mraz R, Graham SJ. An fMRI study of the Trail Making Test. *Neuropsychologia* 2005;43:1878–1886.
34. Grieve SM, Williams LM, Paul RH, Clark CR, Gordon E. Cognitive aging, executive function, and fractional anisotropy: a diffusion tensor MR imaging study. *AJNR Am J Neuroradiol* 2007;28:226–235.
35. Mesulam MM. A cortical network for directed attention and unilateral neglect. *Ann Neurol* 1981;10:309–325.
36. Benarroch E. Basic Neurosciences with Clinical Applications. Philadelphia: Elsevier; 2006.
37. Buckner RL, Sepulcre J, Talukdar T, et al. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *J Neurosci* 2009;29:1860–1873.
38. Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb Cortex* 2009;19:72–78.
39. Knopman DS, Parisi JE, Salviati A, et al. Neuropathology of cognitively normal elderly. *J Neuropathol Exp Neurol* 2003;62:1087–1095.
40. Bourgeat P, Chetelat G, Villemagne VL, et al. Beta-amyloid burden in the temporal neocortex is related to hippocampal atrophy in elderly subjects without dementia. *Neurology* 2010;74:121–127.

Meet Your ABPN-mandated Performance in Practice Requirements for Maintenance of Certification. . . and more!

The American Academy of Neurology's new online performance improvement modules:

- Walk you step-by-step through each phase of a performance improvement project
- Extend beyond MOC requirements into everyday practice
- Provide up to 20 *AMA PRA Category 1 CME credits*TM per module
- Offer an excellent value at \$199* per module—that's only \$9.95 per CME credit!

Order today at www.aan.com/view/neuropi.

**Special pricing for AAN members*