Differences in early and late mild cognitive impairment tractography using a diffusion tensor MRI

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Diffusion tensor MRI tractography is an imaging tool that can provide information of in-vivo neuronal fiber tracts to assess progress for Alzheimer's disease (AD). In an effort to detect early AD progression, we focused on distinguishing subgroups within mild cognitive impairment (MCI): early MCI and late MCI. Tractography was applied not only to white matter regions but also neighboring gray matter regions known to be affected by AD. Nerve fibers touching the hippocampus, thalamus, and amygdala in both hemispheres were extracted to quantify limbic system fiber connectivity. Two fiber extraction algorithms, fiber assignment by continuous tracking and the Runge Kutta approach, were applied to an AD imaging database. We computed the number of fibers touching regions of interest as the imaging feature. The imaging feature could distinguish between the MCI subgroups. It was also significantly correlated with a known genetic marker for AD, the apolipoprotein E epsilon 4 allele. The number of fibers might be a useful imaging biomarker to complement conventional region of interest-based biomarkers for AD research. *NeuroReport* **25:1393–1398 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Diffusion tensor MRI tractography is a powerful imaging technique that can provide information of in-vivo neuronal fiber tracts [1]. The method has several limitations including (a) inability to distinguish between efferent and afferent connections, (b) inability to model complex fiber orientations, and (c) capacity to account for only major fiber tracts because of limited voxel resolution [2]. Diffusion MRI tractography provides valuable information to quantify in-vivo fiber information with the limitations considered. Tractography, a method to extract neuronal fiber tract information using diffusion tensor MRI, can assess Alzheimer's disease (AD) progression. For instance, white matter tracts in the corpus callosum showed significant change as patients progressed from normal control to mild cognitive impairment (MCI), and finally to AD [3]. The focus of this study was MCI, an intermediate stage between normal aging and AD. In an effort to detect early AD progression, this study distinguished between two MCI subgroups: early MCI and late MCI. Diffusion tensor MRI is inherently vector-valued at every voxel, but many studies extract scalar values, such as mean diffusion or fractional anisotropy. Here, we used the full tensor, which enabled us to follow neuronal fibers. Fiber information can be measured using two approaches. One is based on whole-brain connectivity, where the degree of connectivity among many cortical and subcortical regions of interest (ROIs) is entered as a matrix element [4]. The connectivity value between ROIs is typically defined as a value proportional to the number of fibers touching two distinct ROIs. Another fiber information measurement method is to focus on specific ROIs. Some studies test hypotheses that require fiber information only from certain ROIs, and thus the full connectivity matrix is unnecessary. With fewer ROIs to deal with, the multiple-comparison problem is easier to handle [5]. Existing tractography studies have mainly focused on white matter tract-related ROIs as diffusion imaging was primarily used to quantify white matter fibers. Neuronal fibers do extend to neighboring gray matter regions, and thus it is possible to apply tractography to these regions as well. This study focused on known limbic system ROIs for both white matter and gray matter differentially affected by AD [6]. These included hippocampus, parahippocampal gyrus, thalamus, and amygdala. These ROIs are parts of the limbic system and they are close enough to white matter tracts that measureable neuronal fibers exist. Many tractography algorithms are available. We used fiber assignment by continuous tracking (FACT), a well-known tract propagation algorithm [7,8]. Another tract propagation algorithm known as Runge Kutta (RK) was applied as well [9]. Tract propagation algorithms produce the number and length of fibers touching ROIs. Some studies considered fiber lengths and others considered fiber number as imaging-derived features for hypothesis

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testing [10,11]. To distinguish between early and late MCI patients, we adopted fiber numbers touching limbic ROIs described above as imaging-derived features. The effectiveness of our imaging-derived feature, fiber number by group, was tested using a clinically proven biomarker for AD, the apolipoprotein E (ApoE) epsilon 4 allele [12]. We observed a significant correlation between fiber number and the presence of e4 ApoE. Many studies have distinguished among normal aging, MCI, and AD [1]. In an effort to apply recent promising AD cures, it is desirable to detect not only MCI as a whole but also MCI subgroups so that therapeutic measures can be applied early. We could not find any existing research that (a) extracted fibers numbers touching hippocampus, parahippocampal gyrus, thalamus, and amygdala ROIs, and (b) using the fiber numbers to distinguish between early and late MCI. The diffusion MRIs used in this study came from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [13].

Materials and methods

Participants and MRI images

Diffusion tensor MRI volumes were obtained from the ADNI database [13]. Each patient received diffusion MRI with a 3 T GE scanner (General Electric, Milwaukee, Wisconsin, USA), a 90° flip angle, a $256 \times 256 \times 59$ image matrix, and a $1.37 \times 1.37 \times 2.7\ \text{mm}^3$ voxel resolution. Forty-one diffusion volumes were obtained with $b = 1000\ \text{s/mm}^2$ and five with $b = 0\ \text{s/mm}^2$. The ADNI team implemented an up-to-date diffusion imaging protocol producing better than average voxel dimensions and gradient diffusion direction number. A typical diffusion MRI study might have $2 \times 2 \times 2\ \text{mm}^3$ voxels with 30 gradient directions. MCI can be associated with non-AD-type dementias such as vascular or Lewy body dementia, which we excluded in this study [14]. We focused on MCI, which is an early stage of AD known as 'MCI due to AD.' The ADNI database further subdivided the MCI group into early and late MCI. We selected 23 early MCI cases and 23 late MCI cases if they were clinically classified as follows: (a) early MCI – individuals with a memory complaint who experienced very mild cognitive decline with a clinical dementia rating of 0.5, Mini-Mental State Examination score between 24 and 30, and objective memory loss as shown on scores on delayed recall of one paragraph from the Wechsler Memory Scale Logical Memory II (adjusted for age and education; ≥ 16 years: 9–11; 8–15 years: 5–9; 0–7 years: 3–6). (b) Late MCI – the same criterion for early MCI except for greater loss of objective memory measured by delayed recall of Wechsler Memory Scale Logical Memory II (adjusted by age and education; ≥ 16 years: ≤ 8; 8–15 years: ≤ 4; 0–7 years: ≤ 2) and a few patients with a clinical dementia rating of 1. Early MCI patients were 75.34 ± 6.6 (mean $\pm$ SD) years old, with a 12/11 (M/F) sex ratio. Late MCI patients were 75.7 ± 6.4 (mean $\pm$ SD) years old, with a 16/7(M/F) sex ratio. There were no significant differences ($P > 0.05$) between groups in age or sex ratio. Details on patients can be found in the supplement (Supplemental digital content 1, *http://links.lww.com/WNR/A303*).

Image preprocessing and ROIs

Each diffusion volume was corrected for participant motion and eddy current artifacts by affine registration to the first b0 volume using an in-house image registration software based on a mutual information similarity measure [15]. Diffusion tensor orientations were corrected by the rotation induced by these registration transforms. Many existing AD tractography studies have focused on white matter ROIs, namely, uncinated fasciculus and its neighbors [1]. This is because diffusion tensor MRI was primarily used to quantify white matter neuronal fibers. Neuronal fibers mainly exist in white matter regions, but they do extend to neighboring white matter regions. Many limbic system ROIs are known to be affected by AD progression [6]. Here, we focus on hippocampus, parahippocampal gyrus, thalamus, and amygdala, which are all parts of the limbic system and close enough to white matter that measureable neuronal fibers exist. These ROIs have been well studied using other imaging-derived features, such as ROI volume and cortical thickness [16]. This study considered fiber information from the above-mentioned ROIs. ROIs can be specified manually or by automatic methods. We used an automatic method to propagate ROIs from a predefined atlas onto our b0 volume. A well-known atlas with 90 labeled ROIs is available [17]. We applied in-house image registration software to register the atlas with the b0 volume in an affine manner using mutual information [15]. Once the atlas was registered onto our b0 volume, we transferred the atlas ROI information onto the b0 volume.

Tractography and number of fibers

Fiber information was computed using the FACT algorithm and RK approach implemented using the Diffusion Toolkit [18]. The FACT algorithm propagated a line from the center of a seed voxel along the direction of the dominant vector, determined by the largest eigenvector of the tensor until the line exited to the next voxel. The starting point of the next voxel was the intercept of the previous voxel. Tracking was terminated when the algorithm entered a region where an abrupt change in fiber direction (i.e. angle threshold more than 35°) was detected. The FACT algorithm propagated a line from one voxel to another, whereas the RK approach could fit a higher order polynomial curve (i.e. second-order higher polynomial) to intended voxel locations. The RK approach used trial steps at interval midpoints to cancel out lower-order error terms. We adopted the second-order RK approach using the same termination criterion as the FACT algorithm. In this study, every voxel was considered a seed voxel and we retained only fibers that

touched the predefined ROIs. Two main features were derived from the tractography: fiber number and length. Number of fibers touching the ROIs was adopted as the imaging-derived feature. Individuals with large cerebral volume (i.e. larger brains) tend to have more neuronal fibers than individuals with average cerebral volume. The number of fibers was normalized using each patient's cerebral volume. Number of fibers was normalized by the ratio between the patient's cerebral volume and the average cerebral volume for all patients. This was to avoid normalizing by a large value (i.e. cerebral volume in mm^3) and to normalize using a value varying around one. The cerebral volume of each patient was obtained by using the affine registration results between the predefined atlas and each patient's b0 volume. Each patient's cerebral volume was computed as a multiplication of the determinant of the affine registration transform and the cerebral volume of the predefined atlas.

Results

Difference between early MCI and late MCI groups

We measured the number of fibers touching specified ROIs for early and late MCI patients using two tract propagation algorithms. Fiber number was normalized using each patient's cerebral volume as described before. We observed significant differences [$P=0.02$ (FACT), $P=0.04$ (RK)] between fiber numbers in early and late MCI groups (Table 1). Both tract propagation algorithms showed fewer numbers of fibers touching ROIs for late MCI compared with early MCI groups. This is expected, as during AD progression, fiber number and length are expected to reduce compared with normal aging. The RK approach yielded fewer fibers than the FACT algorithm by group. This was partly because optimal tuning parameters, including termination angle, are different for each tract propagation algorithm [19]. This study did not attempt to derive an optimal tract propagation algorithm setting and thus adopted two commonly used tract propagation settings. We found significant differences between early and late MCI groups on the basis of fiber number and observed consistent significant differences using these well-validated tract propagation algorithms. A representative sample of selected ROIs and extracted fibers are shown in Figs 1 and 2. Transferred ROIs from the predefined atlas seemed to align well with the b0 volume in the supplementary (Supplemental digital content 1, *http://links.lww.com/WNR/A303*). Overall, there was good agreement between fibers extracted using FACT (Fig. 1) and the RK approach (Fig. 2). Known fiber connections in the corpus callosum seemed prominent, as shown in Figs 1 and 2 subplots.

Table 1 Number of fibers detected for early and late MCI groups

	Mean (SD)	
	Early MCI ($n=23$)	Late MCI group ($n=23$)
Number of fibers (FACT)	7714 (931)	6940 (1331)
P-value	0.02 (<0.05)	
Number of fibers (RK)	5538 (568)	4993 (1109)
P-value	0.04 (<0.05)	

FACT, fiber assignment by continuous tracking; MCI, mild cognitive impairment; RK, Runge Kutta.

Fiber number and apolipoprotein E

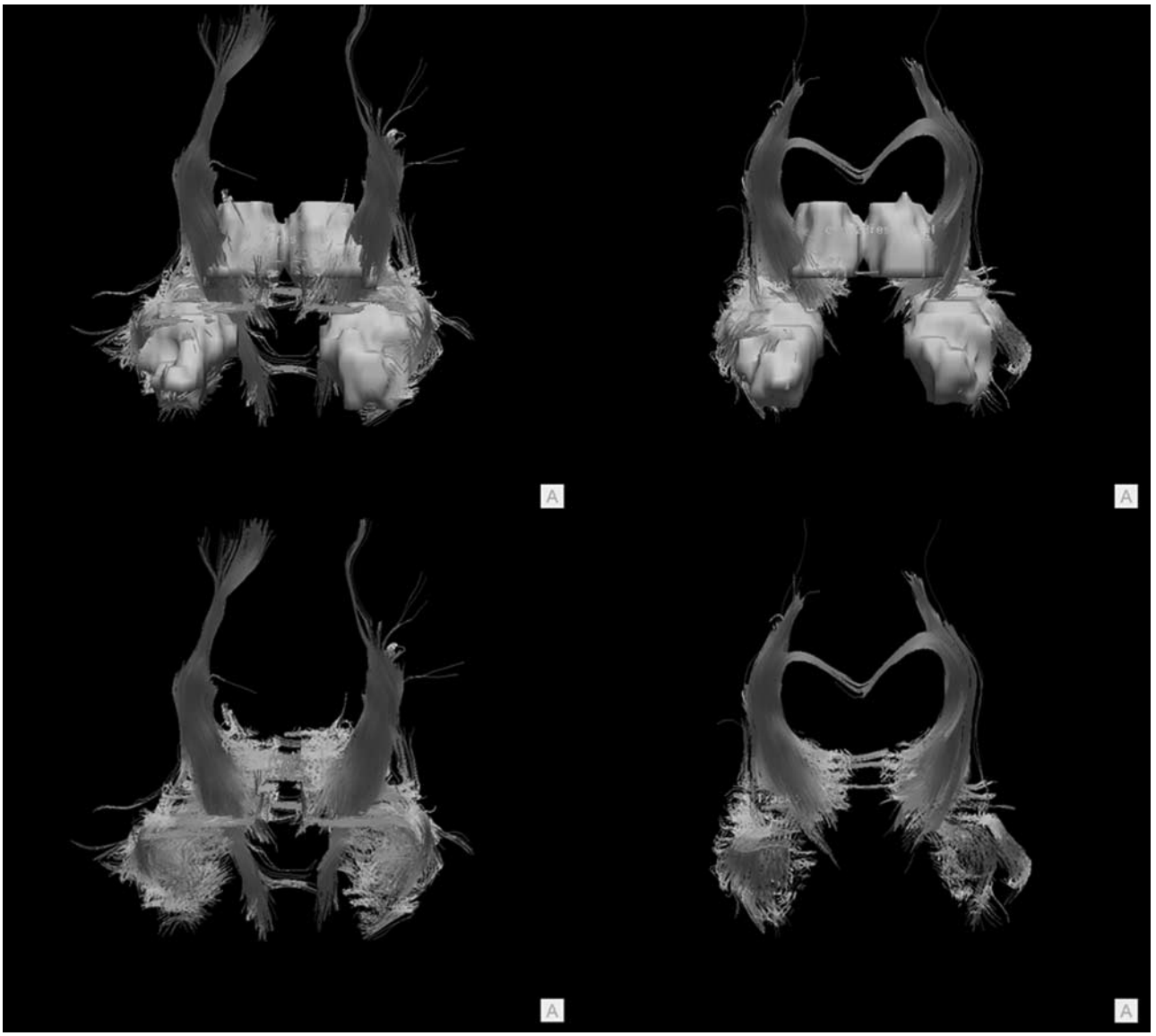
Number of fibers touching ROIs distinguished between early and late MCI groups. A good image-derived feature should be capable of describing other important clinical variables as well. We explored the correlation between the number of fibers and the ApoE e4 allele. ApoE was chosen as it is a known AD genetic biomarker [12]. We stripped grouping information of early and late MCI from all patients and divided them into two groups: (a) homozygous and (b) heterozygous or no e4 allele. A Spearman's correlation with ApoE e4 allele and fiber number was computed. Spearman's correlation instead of the regular Pearson's correlation was adopted as number of fibers were correlated with a categorical measurement, presence or absence of a specific allele. Significant correlations using FACT-derived fiber number ($r=-0.31$, $P=0.04$) and RK-derived fiber number ($r=-0.34$, $P=0.02$) were obtained. Thus, fiber number was significantly negatively correlated with the e4 allele (both Ps <0.05). This is consistent with evidence showing that the e4 allele is correlated with AD progression, which is also correlated negatively with fiber number.

Discussion

Diffusion tensor MRI tractography is currently the only method to reconstruct the in-vivo fiber pathway, but it comes with the following known confounds [2]. The method cannot model complex fiber orientations because of limited angular resolution. Use of high-angular resolution diffusion imaging allows for such complex modeling within a voxel, but high-angular resolution diffusion imaging involves longer scan times compared with diffusion MRI. The method can only model major fiber tracts because of limited voxel resolution. At a typical voxel resolution of $2\times2\times2\ mm^3$, there are 10^5 axons and thus only major fibers survive the tractography analysis and information from minor fibers is lost. Tractography results vary significantly depending on many user-definable parameters of the software or algorithm used and thus users should fully explore those parameters. Tractography results in compelling images to visualize fiber information, but it lacks validation. There is no gold standard to validate tractography results for human brains.

ApoE is a known AD genetic biomarker with three major isoforms: e2, e3, and e4 [12]. The risk of AD is associated primarily with the presence of the ApoE e4 allele. The strength of association with AD is higher when e4 is homozygous compared with heterozygous. Our imaging

Fig. 1

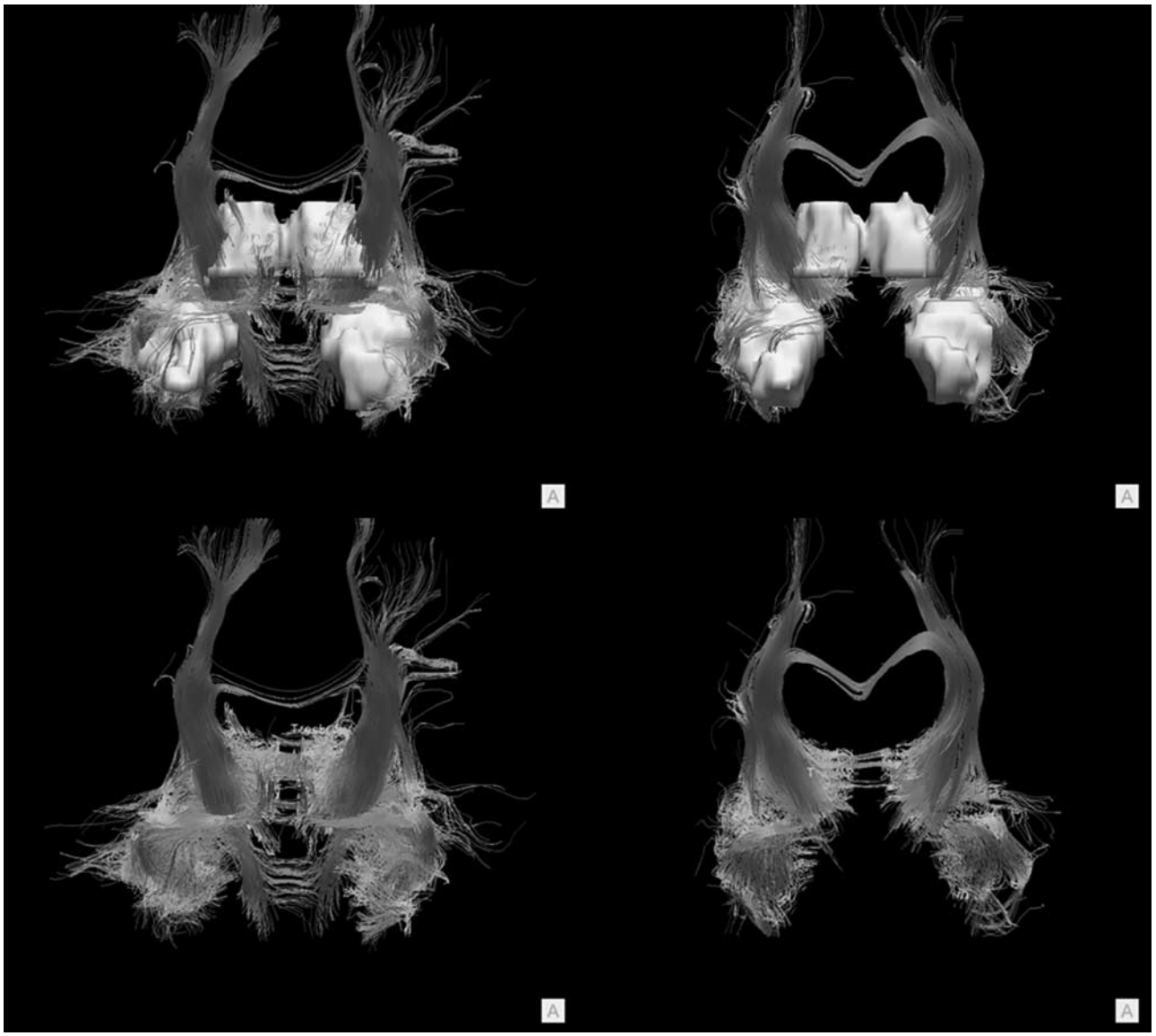


Neuronal fibers of the selected ROIs for typical early and late MCI patients using FACT. Top left: visualization of fibers touching ROIs for a typical early MCI patient. Bottom left: visualization of fibers without ROIs for a typical early MCI patient. Top right: visualization of fibers touching ROIs for a typical late MCI patient. Bottom right: visualization of fibers without ROIs for a typical late MCI patient. Subfigures in the second row are shown to better display associated fibers. FACT, fiber assignment by continuous tracking; MCI, mild cognitive impairment; ROI, region of interest.

feature, number of fibers, was meaningfully correlated with the presence of the ApoE e4 allele. We obtained the results by regrouping all the patients into two groups depending on the existence of a homozygous e4 allele. Our imaging feature was not only capable of distinguishing between MCI subgroups but also correlated with the presence of the ApoE e4 allele. This might imply that our imaging feature could be applied to other clinical parameters of AD. In the same vein, this might indicate that the number of fibers is a useful imaging biomarker besides the traditional ROI-based biomarkers for monitoring AD progression. The imaging feature, number of fibers, was computed over limbic system ROIs differentially affected by AD [6]. The effectiveness of our imaging feature might reaffirm these known ROIs for AD research.

There are many well-established tractography algorithms [19]. We compared results using FACT and RK, and found similar differences between early and late MCI patient groups. Other tractography algorithms might yield different extracted fiber numbers,

Fig. 2



Neuronal fibers of the selected ROIs for typical early and late MCI patients using the second-order Runge Kutta approach. Top left: visualization of fibers touching ROIs for a typical early MCI patient. Bottom left: visualization of fibers without ROIs for a typical early MCI patient. Top right: visualization of fibers touching ROIs for a typical late MCI patient. Bottom right: visualization of fibers without ROIs for a typical late MCI patient. Subfigures in the second row are shown to better display associated fibers. MCI, mild cognitive impairment; ROI, region of interest.

but the difference between the two MCI groups that we used should be similar to that observed in this study.

We considered limbic system ROIs known to be preferentially affected by AD progression not necessarily confined to white matter. Neuronal fibers extend outside white matter tracts to their neighbors, and thus the use of tractography was feasible. Number of fibers touching selected ROIs was used successfully as an imaging-derived feature to distinguish between early and late MCI patients. This feature was also correlated significantly with a known genetic biomarker for AD: the ApoE e4 allele.

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Conflicts of interest

There are no conflicts of interest.

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