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Original article

Early diagnosis of subjective and mild cognitive impairment by MRI diffusion tensor imaging

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Abstract

This study aimed to evaluate the utility of diffusion tensor imaging (DTI) via MRI in the early diagnosis of subjective cognitive impairment (SCI) and mild cognitive impairment (MCI). A total of 173 individuals (68 males and 105 females) who visited our memory clinic or underwent brain screening between August and December 2024 were enrolled. Fractional anisotropy (FA) and mean diffusivity (MD) values were measured in the prefrontal cortex and hippocampal regions, and comparisons were made across four groups: cognitively normal (n = 19), SCI (n = 15), MCI (n = 47), and dementia (n = 78). As a result, a positive age correlation was found for prefrontal MD values and a negative age correlation for frontal MD values in the healthy brain group. Significant differences were found among the four groups in the prefrontal cortex, especially in the MCI group, which differed significantly from the healthy and dementia groups. On the other hand, no significant differences were found in FA values. These findings suggest that MD values in the prefrontal cortex may serve as potential imaging biomarkers for the early detection of SCI and MCI. Additionally, visualization of white matter tracts using tractography proved helpful as a supplementary tool in illustrating structural changes associated with disease progression. Future large-scale longitudinal studies are warranted to further explore the clinical application of DTI in the early diagnosis and prevention of dementia.

KEY WORDS: diffusion tensor imaging (DTI); fractional anisotropy (FA); mean diffusivity (MD); subjective cognitive impairment (SCI); mild cognitive impairment (MCI) anti-aging; white matter integrity

Introduction

With the rapid aging of society, the prevalence of dementia is increasing year by year, posing a serious challenge to both medical care and long-term support systems. According to estimates by Japan's Ministry of Health, Labor and Welfare, by 2025, approximately one in five individuals aged 65 and older is expected to have dementia. This underscores the growing importance of both prevention and early diagnosis. In recent years, attention has been directed toward the prodromal stages of dementia, particularly subjective cognitive impairment (SCI) and mild cognitive impairment (MCI).

SCI is defined as a condition in which individuals perceive a decline in memory or cognitive abilities, despite normal performance on standard neuropsychological assessments. In contrast, MCI is characterized by objectively measurable cognitive impairment with preserved activities of daily living (ADL), and is considered to carry a high risk of progression to dementia. Both conditions are seen as *potentially reversible* stages before the onset of full-blown dementia, making timely diagnosis and intervention critically important for prevention.

Traditionally, the diagnosis of SCI and MCI has relied on clinical symptom assessment, neuropsychological testing, and structural Magnetic Resonance Imaging (MRI) to detect brain atrophy. However, these methods often have limitations in sensitivity and specificity, prompting the need for more precise techniques to evaluate neurodegeneration. One such promising method is diffusion tensor imaging (DTI), an advanced MRI technique capable of visualizing the brain's microstructural integrity [1,2].

Diffusion tensor imaging (DTI) is a technique used to evaluate the microstructure and directional coherence

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(diffusion anisotropy) of white matter fibers by measuring the diffusion properties of water molecules. Tractography enables the non-invasive visualization of white matter pathways, facilitating the detection of structural alterations in neural networks associated with memory and executive function. Quantitative indices such as fractional anisotropy (FA) and mean diffusivity (MD) are commonly used as biomarkers to assess these microstructural changes. FA reflects the directional coherence and integrity of white matter fibers, while MD represents the overall magnitude of water diffusion—both are considered to correlate with the degree of pathology and the progression of neurodegeneration.

In this study, we analyzed 173 individuals who visited a memory clinic or underwent brain health screening from August to December 2024. Using MRI DTI, we measured FA and MD values in the prefrontal cortex and hippocampal regions and categorized participants into four groups: cognitively normal (CN), SCI, MCI, and dementia. The primary aim was to investigate whether microstructural changes in the prefrontal cortex and hippocampus, as detected by DTI, could serve as early biomarkers in the prodromal stages of dementia.

The findings from this study may provide fundamental evidence supporting the use of DTI as a supplementary imaging modality to conventional diagnostic approaches. From an anti-aging medicine perspective, DTI may also offer quantitative visualization of age-related white matter degeneration, contributing to future preventive strategies.

Subjects and methods

This study included a total of 173 individuals (68 males, mean age 73.9 ± 12.6 years; 105 females, mean age 79.8 ± 9.4 years) who visited our memory clinic or underwent brain health screening between August and December 2024.

Participants were classified into four groups based on clinical diagnosis and results from neuropsychological assessments, including the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and Revised Hasegawa's Dementia Scale: HDS-R (***Table 1***):

- **Cognitively Normal (CN) Group:** 19 subjects with no clinical symptoms or cognitive impairment (mean age: 63.4 ± 14.8 years)
- **Subjective Cognitive Impairment (SCI) Group:** 15 subjects with subjective memory complaints but normal test results (mean age: 72.6 ± 9.9 years)
- **Mild Cognitive Impairment (MCI) Group:** 49 subjects with mild but measurable cognitive impairment while retaining daily function (mean age: 80.3 ± 10.2 years)
- **Dementia Group:** 90 subjects diagnosed with dementia based on clinical criteria (mean age: 79.8 ± 8.2 years)

MRI examinations were performed using a 1.5 Tesla ECHERLON Smart Zero Helium V9.0B system (Fujifilm Corporation, Tokyo, Japan). Image analysis was conducted using SYNAPSE VINCENT core V7.0, Fujifilm's proprietary platform.

Diffusion tensor imaging (DTI) was acquired with the following parameters:

- Diffusion weighting (b-value): 1,000 s/mm^2
- Number of diffusion directions: 30
- Slice thickness: 3.0 mm (no interslice gap)
- Scan duration: approximately 10 minutes

From the obtained DTI data, tractography was performed to visualize white matter fiber tracts and evaluate structural connectivity. Major fiber bundles including the superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, cingulum, and hippocampal–callosal connections were reconstructed (***Fig. 1***).

Regions of interest (ROIs) were defined in two brain areas associated with cognitive function:

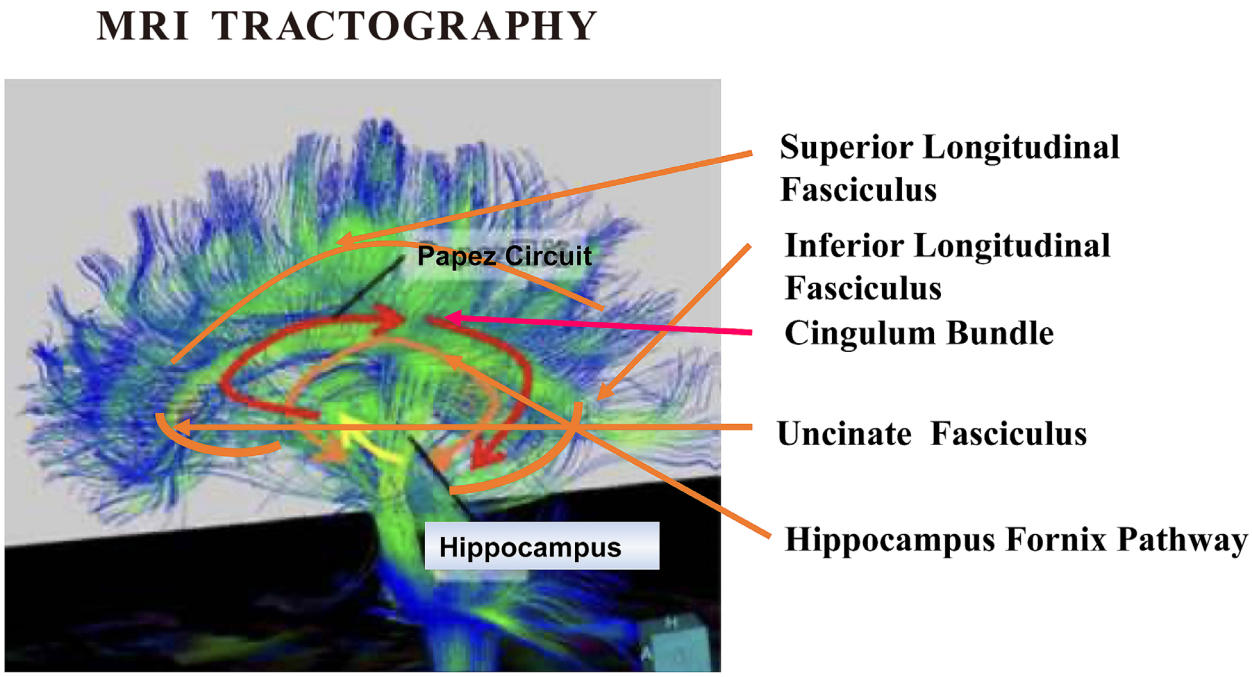
- Prefrontal cortex
- Bilateral hippocampus
- From each ROI, the following diffusion metrics were extracted:
- FA is an indicator of the anisotropy of the diffusion of water molecules in DTI, ranging from 0 to 1, and the closer it is to 1, the stronger the nerve fibers in the tissue are bundled in a certain direction. FA reflects the directionality and integrity of nerve fibers, while the latter reflects the magnitude of diffusion, suggesting the degree of progression of the disease and the degree of neurodegeneration.
- MD indicates the average magnitude of the diffusion of water molecules, reflecting changes in tissue edema and cell density. For example, in cerebral infarction, the MD at the site of infarction is elevated. FA and MD values were averaged across each ROI based on the reconstructed fiber tracts.

Table 1. Subject profile.

	SCI	CN	MCI	D	SCI vs CN	SCI vs MCI	SCI vs D	MCI vs CN	MCI vs D	CN vs D
n	15	19	49	90	–	–	–	–	–	–
age	72.6 ± 9.9	63.4 ± 14.8	80.3 ± 10.2	79.8 ± 8.2	< 0.01	< 0.01	< 0.01	< 0.0001	0.82	< 0.0001
Sex (M : F)	6 : 9	12 : 7	15 : 35	36 : 54	–	–	–	–	–	–
CDR	0.04 ± 0.14	0	0.49 ± 0.17	1.51 ± 1.14	0.89	0.06	< 0.0001	< 0.05	< 0.0001	< 0.0001
HDS-R	29.9 ± 0.2	29.8 ± 0.4	25.4 ± 2.4	16.6 ± 5.9	0.95	< 0.01	< 0.0001	< 0.001	< 0.0001	< 0.0001
MMSE	29.8 ± 0.4	29.9 ± 0.4	26.8 ± 1.9	18.9 ± 6.1	0.95	< 0.05	< 0.0001	< 0.01	< 0.0001	< 0.0001

Results are expressed as mean ± standard deviation. ANOVA with contrast. SCI, subjective cognitive impairment; CN, cognitively normal; MCI, mild cognitive impairment; D, dementia; CDR, Clinical Dementia Rating; HDS-R, Revised Hasegawa's Dementia Scale; MMSE, Mini-Mental State Examination; ANOVA, one way analysis of variance.

"Visualization of Cognitive-Related White Matter Tracts Using Diffusion Tensor Tractography"



Connectivity Table (Origin–Termination):

Connectivity Table (Origin–Termination):		
Tract	Origin	Termination
Superior Longitudinal Fasciculus	Prefrontal Lobe	Parietal Lobe
Inferior Longitudinal Fasciculus	Occipital Lobe	Temporal Lobe
Cingulum Bundle	Cingulate Gyrus	Entorhinal Cortex
Uncinate Fasciculus	Frontal Lobe	Temporal Pole
Hippocampus–Fornix Pathway	Hippocampus	Mammillary Bodies

Fig. 1. **MRI Diffusion Tensor Tractography.**

To compare diffusion metrics across the four diagnostic groups (CN, SCI, MCI, and dementia), one-way analysis of variance (ANOVA) was conducted. Analysis of covariance (ANCOVA) with age as a covariate was also performed, comparing groups using least squares means contrasts (Bonferroni correction), and Student t-test was used to examine the association with FA and MD values. All statistical analyses were performed using JMP software (Version 10.0, SAS Japan Corp.). For all tests, the significance level was set at $p < 0.05$.

Results

1. Correlation with age in the CN group

In the CN group, FA values in the prefrontal cortex showed a significant negative correlation with age ($y = 0.2447 - 0.0006x$, $r = 0.46$, $p < 0.05$), while MD values showed a significant positive correlation ($y = 664.8 + 5.4x$, $r = 0.59$, $p < 0.01$. ***Fig. 2-a, b***). These findings suggest that with increasing age, the structural integrity of the prefrontal cortex declines and water diffusivity increases.

In contrast, FA and MD values in the bilateral hippocampus showed no significant correlation with age (*Fig. 2-c, d, e, f*).

2. Group comparisons of FA and MD values

A total of 173 participants were classified into four groups: CN, SCI, MCI, and dementia. Group comparisons were made for FA and MD values in the prefrontal cortex and hippocampi.

(1) FA values in the prefrontal cortex.

ANOVA did not reveal any significant differences in prefrontal cortex FA values among the four groups (*Table 2*). ANCOVA, with age as a co-variate, was performed using least squares mean contrasts (Bonferroni correction), and the differences among groups were not significant (*Table 3*).

(2) MD values in the prefrontal cortex ($\times 10^{-3}$ mm^2/s).

ANOVA revealed significant differences between the four groups, specifically between the CN group and the

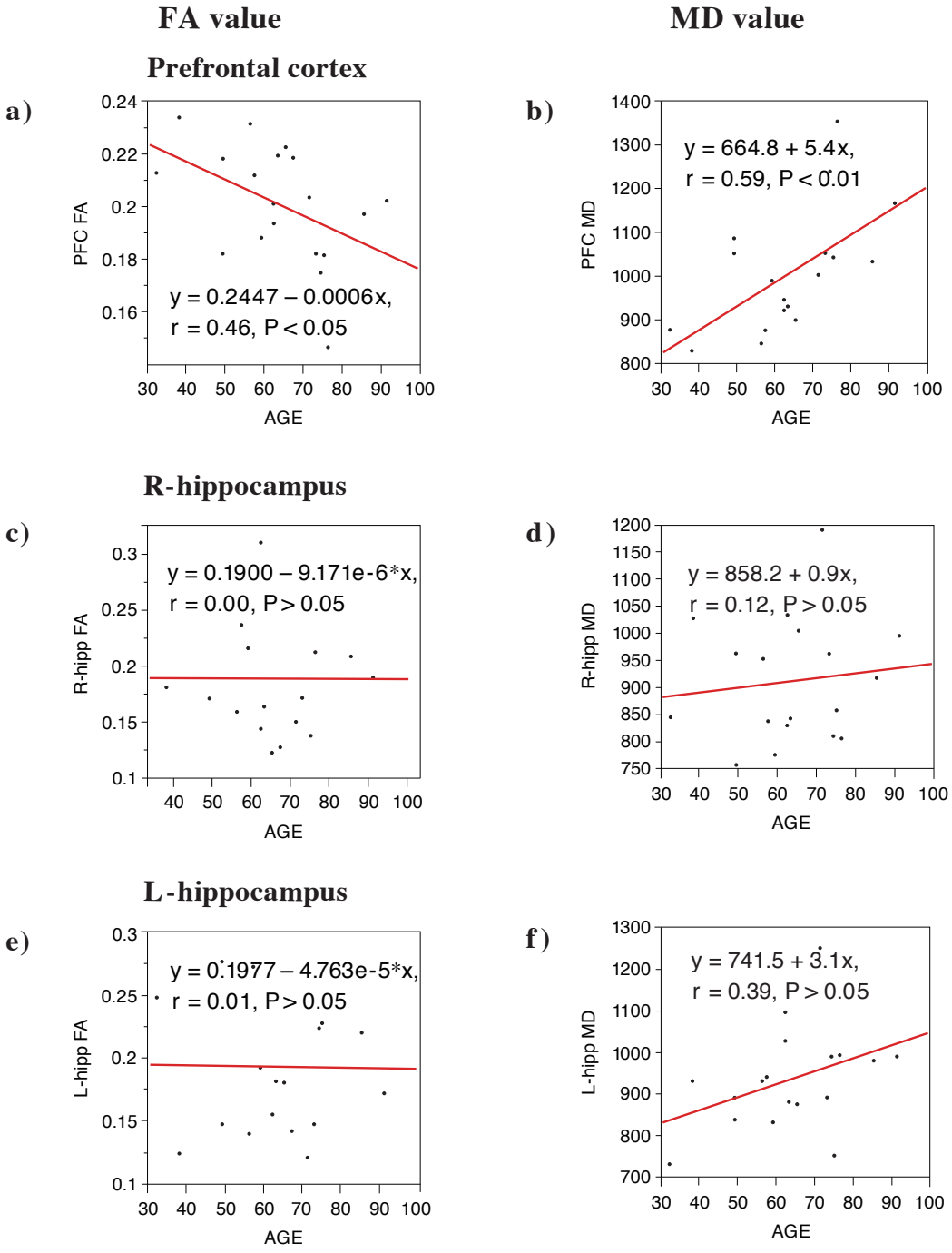


Fig. 2. **Age-related changes in FA and MD values of the MRI Diffusion Tensor Tractography in the cognitively normal group.**

FA, fractional anisotropy; MD, mean diffusivity.

Table 2. Comparison of FA values: ANOVA.

	SCI	CN	MCI	D	SCI vs CN	SCI vs MCI	SCI vs D	MCI vs CN	MCI vs D	CN vs D
n	15	19	47	78	–	–	–	–	–	–
PFC	0.2013 ± 0.041	0.2001 ± 0.022	0.1997 ± 0.044	0.2016 ± 0.062	0.97	0.95	0.95	0.91	0.84	0.99
RH	0.1787 ± 0.068	0.1892 ± 0.052	0.2179 ± 0.089	0.2035 ± 0.088	0.72	0.12	0.29	0.21	0.35	0.36
LH	0.1865 ± 0.049	0.1947 ± 0.053	0.2052 ± 0.077	0.2173 ± 0.1180	0.81	0.51	0.26	0.69	0.5	0.5

Results are expressed as mean ± standard deviation. SCI, subjective cognitive impairment; CN, cognitively normal; MCI, mild cognitive impairment; D, dementia; FA, fractional anisotropy; PFC, prefrontal cortex; RH, right hippocampus; LH, left hippocampus; ANOVA, one way analysis of variance.

Table 3. Comparison of FA values: ANCOVA.

	SCI	CN	MCI	D	SCI vs CN	SCI vs MCI	SCI vs D	MCI vs CN	MCI vs D	CN vs D
n	15	19	47	78	–	–	–	–	–	–
PFC	0.2006 ± 0.014	0.2013 ± 0.013	0.1980 ± 0.008	0.2024 ± 0.006	0.94	0.84	0.94	0.77	0.65	0.99
RH	0.1787 ± 0.020	0.1892 ± 0.021	0.2269 ± 0.012	0.1979 ± 0.095	0.71	0.06	0.43	0.14	0.06	0.74
LH	0.187 ± 0.025	0.1947 ± 0.025	0.2139 ± 0.014	0.2117 ± 0.0811	0.85	0.32	0.34	0.44	0.9	0.47

Results are expressed as mean ± standard deviation. SCI, subjective cognitive impairment; CN, cognitively normal; MCI, mild cognitive impairment; D, dementia; FA, fractional anisotropy; PFC, prefrontal cortex; RH, right hippocampus; LH, left hippocampus; ANCOVA, analysis of co-variance adjusted by age.

MCI/dementia group, and between the SCI group and the dementia group ($p < 0.01$, ***Table 4***). In addition, ANCOVA with age as a co-variate revealed significant differences between the SCI group and the dementia group ($p < 0.05$, ***Table 5***).

These results suggest that the prefrontal cortex and MD values tend to increase with the progression of the disease, and the changes were particularly noticeable during the transition from the healthy state to MCI/dementia and from SCI to dementia.

(3) FA values in the hippocampus.

Comparison of hippocampal FA values among the four groups was as follows.

ANOVA showed no significant differences in prefrontal cortex FA values among the four groups (***Table 2***). ANCOVA also showed no significant differences among the groups (***Table 3***).

(4) MD Values in the hippocampus ($\times 10^{-3}$ mm²/s)

The hippocampal MD values (left and right, $\times 10^{-3}$ mm²/s) were as follows.

There were no significant differences in hippocampal MD values among the four groups in the SCI and MCI groups, but ANCOVA showed a significant difference in the left hippocampus between the CN group and the dementia group ($p < 0.05$, ***Table 5***).

These results suggest that the MD value of the left hippocampus shows a tendency to increase with the progression of the disease, and the change was particularly remarkable in the transition stage from a healthy state to dementia.

3. Tractography findings

The structural image of the white matter nerve pathway using tractography visually confirmed age and disease related reductions and disconnections of nerve fibers in the prefrontal region (***Fig. 3***). In the CN group, the connecting pathways running from the frontal lobe to the cingulate gyrus and anterior cingulate cortex were clear, but in the SCI (***Fig. 4***), MCI (***Fig. 5***), and dementia groups (***Fig. 6***), these connections tended to be unclear or fragmented. As the disease progressed from SCI to MCI to Alzheimer's disease, there was an increase in the loss and disconnection of nerve fibers, and visualization defects were observed in the prefrontal cortex, precuneus, posterior cingulate gyrus, and relevant association tracts. These visual changes tended to coincide with the quantitative increase in MD values.

Thus, it was suggested that the MD value ofof the prefrontal cortex may be a highly sensitive indicator for detecting neurodegeneration at an early stage in the SCI and MCI stages. On the other hand, the FA value did not show a significant difference between groups in this study, highlighting the need to consider its limitations as an evaluation indicator.

Hippocampal MD values were not significantly different among the four groups in the SCI and MCI groups, but there was a significant difference between the CN group and the dementia group in the left hippocampus.

These results suggest that MD values in the left hippocampus show an increasing trend with disease progression, especially during the transition stage from normal state to dementia.

Table 4. Comparison of MD values: ANOVA.

	SCI	CN	MCI	D	SCI vs CN	SCI vs MCI	SCI vs D	MCI vs CN	MCI vs D	CN vs D
n	15	18	39	75	–	–	–	–	–	–
PFC	1028.9 ± 269.4	1008.3 ± 139.4	1140.8 ± 296.8	1198.1 ± 181.8	0.79	0.11	< 0.01	< 0.05	0.2	< 0.01
RH	935.6 ± 145.8	914.0 ± 113.4	1296.5 ± 1642.4	1170.1 ± 303.3	0.94	0.17	0.35	0.13	0.47	0.27
LH	979.8 ± 176.5	937.2 ± 121.8	1030.5 ± 233.6	1147.6 ± 323.5	0.97	0.93	0.13	0.62	0.31	< 0.05

Results are expressed as mean ± standard deviation. SCI, subjective cognitive impairment; CN, cognitively normal; MCI, mild cognitive impairment; D, dementia; MD, mean diffusivity; PFC, prefrontal cortex; RH, right hippocampus; LH, left hippocampus; ANOVA, one way analysis of variance.

Table 5. Comparison of MD values: ANCOVA.

	SCI	CN	MCI	D	SCI vs CN	SCI vs MCI	SCI vs D	MCI vs CN	MCI vs D	CN vs D
m	15	18	39	75	–	–	–	–	–	–
PFC	1028.9 ± 63.6	1008.3 ± 65.3	1119.8 ± 38.6	1201.1 ± 28.6	0.87	0.44	< 0.05	0.57	0.08	0.08
RH	935.6 ± 230.5	914.0 ± 236.7	1290.9 ± 141.8	1171.4 ± 104.2	0.85	0.16	0.3	0.12	0.48	0.22
LH	979.8 ± 70.4	937.2 ± 72.2	1037.2 ± 43.4	1139.6 ± 32.3	0.74	0.57	0.05	0.36	0.05	< 0.05

Results are expressed as mean ± standard deviation. SCI, subjective cognitive impairment; CN, cognitively normal; MCI, mild cognitive impairment; D, dementia; MD, mean diffusivity; PFC, prefrontal cortex; RH, right hippocampus; LH, left hippocampus; ANCOVA, analysis of co-variance adjusted by age.

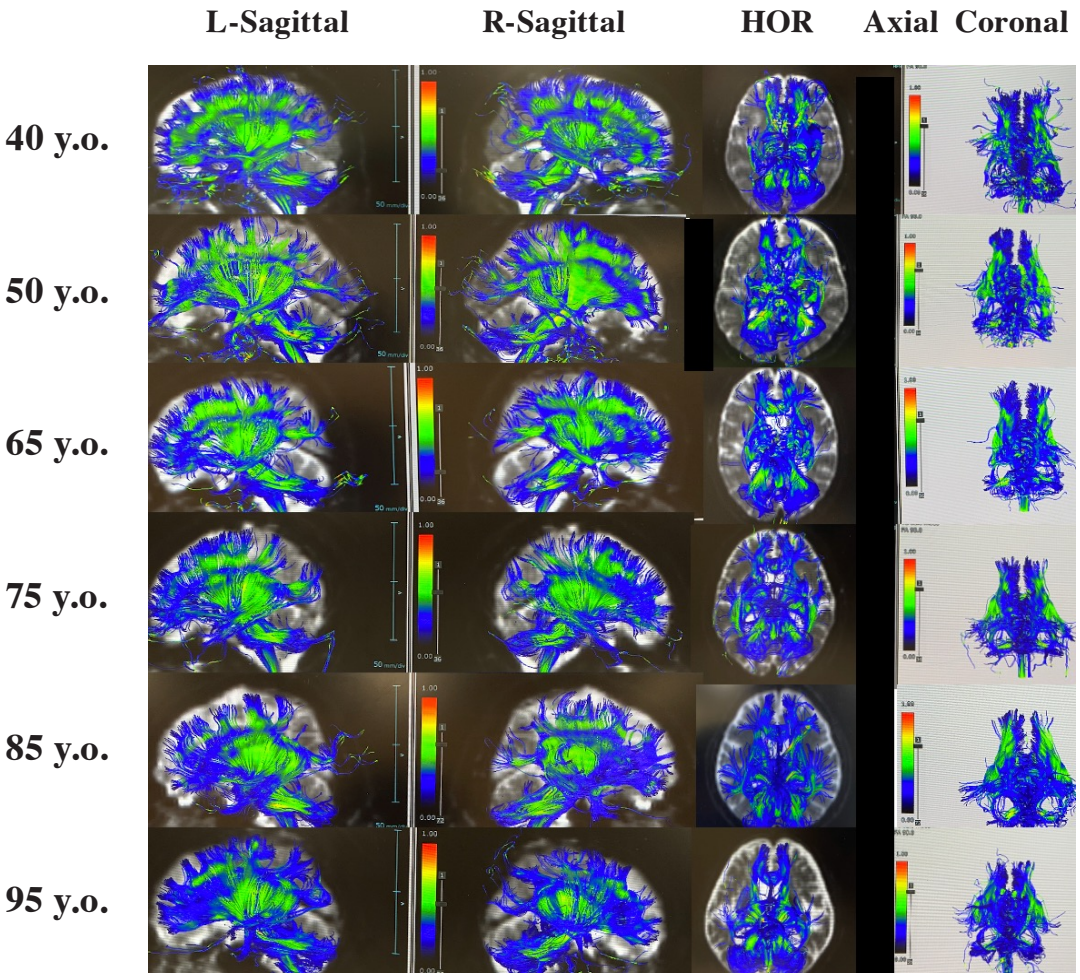


Fig. 3. **MRI Diffusion Tensor Tractography in the cognitively normal group.**
Age-related disconnection and shortening of nerve fibers delineation in the superior longitudinal fasciculus and posterior cingulate gyrus in the cognitively normal group. HOR, horizontal.

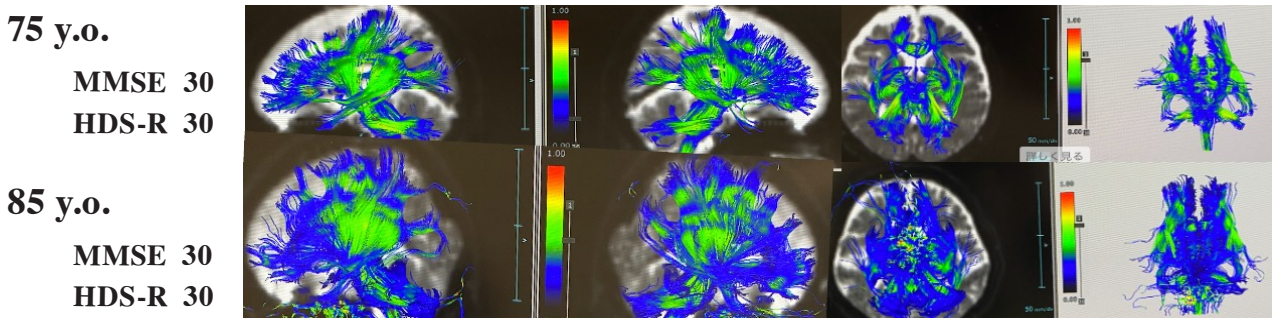


Fig. 4. **MRI Diffusion Tensor Tractography in the SCI group.**

In the SCI group, there are more discontinuities and shortening in the delineation of nerve fibers in the prefrontal cortex than in the cognitively normal group. SCI, subjective cognitive impairment; MMSE, mini mental state examination; HDS-R, Revised Hasegawa's Dementia Scale.

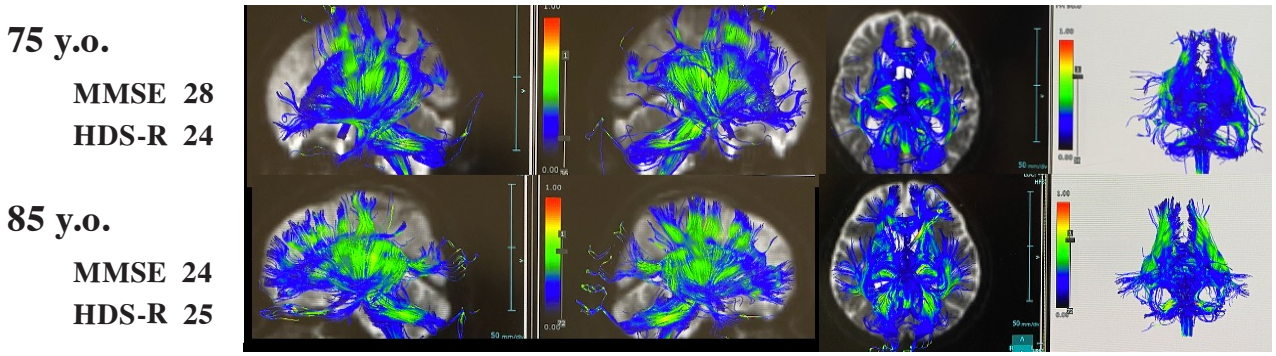


Fig. 5. **MRI Diffusion Tensor Tractography in the MCI group.**

In the MCI group, there are more discontinuities and shortening in the delineation of nerve fibers in the prefrontal cortex than in the SCI group. There is a loss of nerve fibers, especially in the prefrontal cortex and precuneus. MCI, mild cognitive impairment; SCI, subjective cognitive impairment; MMSE, mini mental state examination; HDS-R, Revised Hasegawa's Dementia Scale.

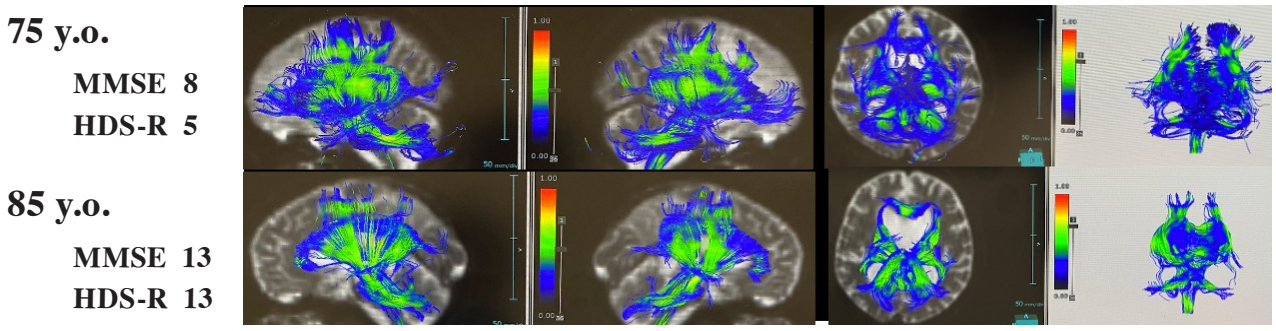


Fig. 6. **MRI Diffusion Tensor Tractography in patients with Alzheimer's disease**

In patients with Alzheimer's disease, there are more discontinuities and shortening of nerve fiber delineation than in the MCI group, with marked deficits in nerve fiber delineation in the prefrontal,precuneus regions and occipital lobe. MCI, mild cognitive impairment; MMSE, mini mental state examination; HDS-R, Revised Hasegawa's Dementia Scale.

Discussion

In this study, we aimed to assess the early diagnosis of SCI and MCI by evaluating white matter microstructure using MRI DTI. We focused on changes in FA and MD values in the prefrontal cortex and hippocampus and compared these indices among four groups: CN, SCI, MCI, and dementia.

Our findings revealed statistically significant group differences in MD values in the prefrontal cortex, with the MCI group differing significantly from both the CN and dementia groups. In addition, left hippocampal MD values showed significant differences, particularly between the CN and dementia groups[3, 4]. In contrast, no significant differences were observed in FA values among the groups. These results suggest that MD may serve as a more sensitive marker than FA for detecting subtle neurodegenerative changes in the early stages of cognitive decline.

DTI is a non-invasive imaging modality that measures the diffusion of water molecules in brain tissue, enabling the quantitative assessment of white matter fiber structure[1, 2]. Previous studies have reported that white matter changes can be detected even in the early stages of Alzheimer's disease, potentially preceding neuropsychological test abnormalities. MD, which reflects the average diffusivity of water molecules, is particularly sensitive to pathological processes such as axonal loss, gliosis, and increased extracellular space[4]. Niwa et al. also reported that FA values in the uncinate fasciculus were significantly reduced in SCI and MCI groups compared to CN subjects[5]. In our study, the progressive increase in prefrontal MD values from SCI to dementia supports the hypothesis that changes in white matter diffusivity occur gradually along with disease progression[6].

On the other hand, FA values did not significantly differ among the groups. FA reflects the degree of anisotropy of water diffusion, influenced by factors such as fiber orientation, axonal density, and myelination. However, FA can be less sensitive to subtle changes because opposing pathological processes (*e.g.*, demyelination vs. axonal loss) may cancel each other out, resulting in minimal net change. The lack of significant FA differences in this study may indicate that white matter tract directionality remains relatively preserved in the SCI and MCI stages, with changes in diffusivity (MD) preceding changes in anisotropy. Moreover, FA is known to have greater variability depending on the measurement region and analysis method, and its sensitivity and reproducibility are often inferior to MD. These limitations must be taken into account when using FA as a diagnostic biomarker.

In the CN group, FA values in the prefrontal cortex were negatively correlated with age, while MD values showed a positive correlation (***Fig. 2-a, b***). This finding is consistent with prior studies indicating that aging is associated with decreased structural integrity and increased water diffusivity due to expansion of extracellular space[7].

In contrast, no age correlation was observed in hippocampal FA or MD values, possibly due to the hippocampus being primarily composed of gray matter, which may limit the sensitivity of DTI parameters. Additionally, hippocampal degeneration often manifests as volume loss (atrophy), with diffusion changes occurring at later stages[8].

Tractography-based visualization of white matter tracts also revealed reductions and fragmentation in fiber density in the prefrontal cortex as disease progressed. Notably, degeneration was observed in tracts such as the cingulum and superior longitudinal fasciculus, which are associated with executive and attentional functions. These visual changes correlated with the quantitative increase in MD values. Tractographic images, when combined with quantitative indices, may enhance the visual and clinical interpretability of DTI, and can serve as useful tools in patient communication and monitoring, particularly in preventive dementia care and education.

In summary, our results suggest that MD values in the prefrontal cortex may be a valuable imaging biomarker for the early detection of SCI and MCI. The significant elevation of MD in the SCI group supports the possibility that microstructural neurodegeneration may already be present even in individuals who report subjective symptoms but perform normally on cognitive tests.

Future studies are warranted to address several limitations:

- Larger sample size: The SCI group in this study included only 15 participants, and larger cohort studies are needed for validation.
- Longitudinal analysis: This cross-sectional design limits causal inference. Long-term follow-up will be necessary to determine whether DTI changes predict cognitive decline.
- Multimodal biomarker integration: Combining DTI with cerebrospinal fluid biomarkers, blood-based protein assays (*e.g.*, Aβ, tau), and amyloid PET imaging could contribute to more accurate predictive models.

Conclusion

In this study, diffusion tensor imaging (DTI) was employed to quantitatively evaluate white matter structural changes across different stages of cognitive function, including subjective cognitive impairment (SCI) and mild cognitive impairment (MCI). Among the diffusion metrics analyzed, mean diffusivity (MD) values in the prefrontal cortex showed significant differences across the four groups—CN, SCI, MCI, and dementia—highlighting the potential of MD as a useful biomarker for the early detection of SCI and MCI.

In contrast, fractional anisotropy (FA) values did not demonstrate significant group differences, indicating limitations in its sensitivity as a diagnostic indicator. Additionally, visualization of white matter tracts using tractography proved helpful as a supplementary tool in illustrating structural changes associated with disease progression.

Future research should focus on larger sample sizes and longitudinal study designs to further enhance the predictive power of DTI indices. As a non-invasive and quantitative imaging technique, DTI holds promise as a novel diagnostic aid in preventive dementia care, particularly from the perspective of anti-aging and neurodegenerative disease management.

Acknowledgements

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Conflict of interest declaration

There are no conflicts of interest regarding this study.

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