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White matter alterations in the dorsal attention network contribute to a high risk of unsafe driving in healthy older people

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Abstract

Aim: Healthy older drivers may be at high risk of fatal traffic accidents. Our recent study showed that volumetric alterations in gray matter in the brain regions within the dorsal attention network (DAN) were strongly related to the risk of unsafe driving in healthy older people. However, the relationship between white matter (WM) structural connectivity and driving ability in healthy older people is still unclear.

Methods: We used diffusion tensor imaging to examine the association between microstructural alterations in the DAN and the risk of unsafe driving among healthy older people. We enrolled 32 healthy older individuals aged over 65 years and screened unsafe drivers using an on-road driving test. We then determined the pattern of WM aberrations in unsafe drivers using tract-based spatial statistics.

Results: The analysis demonstrated that unsafe drivers had significantly higher axial diffusivity values in nine WM clusters compared with safe drivers. These results were primarily observed bilaterally in the dorsal superior longitudinal fasciculus, which is involved in the DAN. Furthermore, correlation analyses showed that higher axial diffusivity values in the superior longitudinal fasciculus were associated with lower Trail Making Test A scores within unsafe drivers. This result suggests that functionally, WM microstructural alterations in the DAN are associated with attention problems, which may contribute to the risk of unsafe driving among healthy older people.

Conclusion: Our findings may elucidate the neurobiological mechanisms underlying the increased risk of unsafe driving in healthy older people, potentially facilitating the development of new interventions to prevent fatal accidents.

KEYWORDS
diffusion tensor imaging, distracted driving, healthy older people, microstructural changes, tract-based spatial statistics (TBSS)

Jinichi Hirano and Bun Yamagata contributed equally to this work.

INTRODUCTION

In developed countries, the number of older drivers is rapidly increasing as the population ages. This poses significant challenges for public health, as older drivers have a relatively higher risk of causing fatal traffic accidents.[1,2] The higher crash rates among older drivers may be related to age-related medical conditions, such as dementia, stroke, Parkinson's disease, and other neuro-degenerative disorders.[3] In fact, many studies have shown that these conditions can lead to a decline in driving ability.[4,5] Despite the large number of health conditions that can adversely affect driving ability, the percentage of older drivers who are considered healthy still represents the largest segment. Surprisingly, the latest National Police Agency report covering annual traffic accidents in Japan showed that cognitively healthy older people caused nearly half of all fatal accidents involving older drivers.[6] However, no standardized screening method to identify older drivers who are cognitively normal but carry a high risk of causing fatal traffic accidents has been established.[7] Although on-road driving tests are recognized as the gold standard for measuring driving ability, they are costly, making it impractical to administer such tests to all older drivers.[8] Therefore, an objective evaluation of driving ability in healthy older people based on biological markers of unsafe driving is needed. Such assessments could use neuropsychological tests or neurobiological markers identified using brain magnetic resonance imaging (MRI) data.

Previous studies using neuropsychological tests have shown that the Maze Navigation Time Test and the Trail-Making Test (TMT) are useful for screening driving ability on the basis of their positive correlation with on-road driving evaluations.[9,10] However, these previous studies lacked objectivity in terms of assessments of driving ability. Specifically, on-road driving ability was measured using the scores provided by driving instructors, making these studies vulnerable to interrater variability and inconsistent defini-tions of rating scores.[11] To overcome these problems, we developed a new method for objectively evaluating on-road driving ability in healthy older people based on vehicle behavior. Furthermore, to clarify the neuropsychological functions associ-ated with unsafe driving, we built a reliable classification model utilizing a machine-learning approach to dissociate unsafe drivers from safe drivers. In a previous study, our model had an accuracy of 84.8% based on neuropsychological assessments.[7] In this model, the results of an attentional function task had the greatest contribution to the classification, indicating that attentional dysfunction is strongly associated with the risk of unsafe driving in healthy older people.

To our knowledge, no previous studies have investigated how brain structural alterations affect on-road driving ability. Thus, based on our previous study, we hypothesized that structural abnormalities in brain regions involved in attentional functions might be associated with the risk of unsafe driving among healthy older drivers. Previously, we exploratively built a classification model that could dissociate unsafe drivers from safe drivers with an accuracy of 87.5% using gray matter volume data.[12] Our analysis of the features that contributed to this model showed that gray matter volume in the frontal eye field and inferior parietal lobule (IPL) were strongly associated with a high risk of unsafe driving among healthy older people.[12] Since the frontal eye field and IPL constitute the dorsal attention network (DAN), this finding suggested that the DAN is more strongly involved in the risk of unsafe driving in healthy older people than other attention-related networks, such as the ventral attention network (VAN) and the default mode network (DMN). Moreover, previous diffusion tensor imaging (DTI) studies have shown that attentional dysfunction in older people was associated with white matter (WM) micro-structural alterations.[13,14] Thus, it may be possible to assess the risk of unsafe driving in healthy older people according to WM microstructural alterations in the DAN. However, to the best of our knowledge, no studies have used DTI to directly examine the relationship between WM microstructure and the risk of unsafe driving in healthy older people.

In the present study, we hypothesized that WM microstructural alterations in the DAN would be associated with the risk of unsafe driving among healthy older people. To test this hypothesis, we used a whole-brain, voxel-wise DTI approach to characterize WM microstructural properties associated with a high risk of unsafe driving among healthy older people.

METHODS

Participants

The present study included 32 healthy individuals aged over 65 years. They were recruited from the local community through online advertisements at the University of Tokyo and the Musashisakai Driving School (Tokyo, Japan). All participants were diagnosed as "cognitively normal" based on the Alzheimer's Disease Neuroimaging Initiative (ADNI) diagnostic classification: (1) Mini-Mental State Examination (MMSE) score between 24 and 30; (2), Clinical Dementia Rating (CDR) score of 0; and (3) normal memory function measured by education-adjusted scores on the Logical Memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale-Revised (WMS-R).[15] No participants had been diagnosed with psychiatric or neurological conditions. They all had a valid driver's license and were actively driving at the time of the study. After receiving an extensive description of the study, all participants provided written informed consent prior to enrollment. The study protocol was approved by the ethics committees of the University of Tokyo and Keio University and prepared in accordance with the ethical standards of the Declaration of Helsinki. All of the participants first took an on-road driving test at the Musashisakai Driving School, and then travelled to Keio University Hospital where they underwent cognitive assessments and an MRI scan.

Measurements

Cognitive assessment

We administered the Raven's Colored Progressive Matrices (RCPM) test to all participants as an estimate of general cognitive function. We then further evaluated memory and visuospatial function using the Rey Auditory Verbal Learning Test (RAVLT), the Rey–Osterrieth Complex Figure Test (ROCFT), the Clock Drawing Test (CDT), and the Everyday Memory Checklist (EMC); attentional/executive function using the Stroop Test (ST), the Trail Making Test (TMT) A and B, and the Dysexecutive Questionnaire (DEX); and subjective driving ability using the Driving Behavior Questionnaire (DBQ).[16] We assessed handedness using the Edinburgh Handedness Inventory.[17] The CDT was scored using a five-point system adopted from the cognitive assessment component.[18] Clinical neuropsychologists (M. Y. and K. K.) administered all cognitive assessments in an environment with adequate lighting and reduced noise conditions.

On-road driving test and classification of safe and unsafe drivers

To evaluate on-road driving ability on the basis of vehicle behaviors, we administered an on-road driving test using an instrumented automatic vehicle with a data recorder and charge-coupled device (CCD) cameras.[19] During the on-road driving test, we were able to collect vehicle information, including the speed, acceleration, position, and location. Based on this vehicle information, we classified all participants as unsafe or safe drivers.[7,12] Specifically, we evaluated participant driving ability at intersections with a stop sign, because older drivers most frequently cause traffic accidents at intersections without traffic lights.[20] The on-road driving tests were conducted at the Musashisakai Driving School in suburban Tokyo. All participants drove the instrumented vehicle on the same course in a city area located near the driving school for 30 min. To ensure participant safety, a driving instructor accompanied participants in the car while they drove the vehicle.

MRI acquisition

All MRI data were acquired using a 3.0 Tesla MRI scanner (MAGNETOM Verio; Siemens Healthineers) equipped with an eight-channel head coil. Diffusion-weighted images (DWI) were collected using an echo-planar imaging (EPI) spin echo sequence with $b0$-images and 30 directions of diffusion gradients (in-plane resolution, 2.0×2.0 mm; 2-mm slice thickness with no gap; repetition time, 15.0 s; echo time, 91 ms; b-value, 1000 s/mm^2; matrix size, 114×114; phase encoding, anterior-to-posterior; 75 transversal slices; number of excitations, 1).

Preprocessing

First, DWI data were denoised using the "dwidenoise" tool from the MRtrix3 package (http://www.mrtrix.org).[21–23] The data were then corrected for Gibbs ringing artifacts using the "mrdegibbs" tool from MRtrix3,[23] corrected for eddy currents and head motion using the "dwifslpreproc" tool from MRtrix3,[24] and corrected for B1 field inhomogeneity using the "dwibiascorrect" tool with the "-ants" option from MRtrix3.[25] Next, we generated a whole brain mask for each image using the "dwi2mask" tool from MRtrix3.[26] Finally, fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) maps were calculated using the DTIFIT tool implemented in FMRIB Software Library (FSL; version 6).[27]

Tract-based spatial statistics

The FA images from all participants were registered to a template created by averaging the FA images (FMRIB-58) in Montreal Neurological Institute (MNI) space using the FNIRT tool from FSL. After registration, all of the FA images were averaged to generate a mean FA image. Then, the mean FA image was thinned to create a mean FA skeleton of WM tracts, and an FA value of 0.2 was used as a threshold to distinguish WM from gray matter.[28] Next, the FA images for each subject were projected onto the mean FA skeleton. In a similar manner, other DTI parameters, including MD, RD, and AD, were projected onto the mean FA skeleton. Differences in DTI parameters between unsafe and safe drivers were analyzed in a voxel-wise fashion using the Randomise function in FSL with 5000 permutations and age and sex as covariates.[29] Statistical significance was set at a family-wise error rate ($\alpha = 0.05$)-corrected threshold-free cluster enhancement (TFCE) of $p < 0.05$, with a minimum cluster size of 10 voxels.[30]

Correlation of DTI parameters in the superior longitudinal fasciculus with TMT A scores among unsafe drivers

We examined correlations between microstructural alterations in the superior longitudinal fasciculus (SLF) and visuospatial attentional function in unsafe drivers, because the SLF was the main WM tract where the group differences were observed in the tract-based spatial statistics (TBSS) analyses. Specifically, we analyzed the correlation between the DTI parameters of the SLF and total scores of the TMT A.[31] In this analysis, we first identified the right/left SLF in the TBSS skeleton based on the Johns Hopkins University WM tractography atlas.[32] Subsequently, the voxels within the SLF that showed significant differences between unsafe and safe drivers in the TBSS analysis were defined as regions of interest. The mean DTI parameters of the regions of interest were

TABLE 1 Demographics and cognitive measures

	Subscale	Safe drivers	Unsafe drivers	F or T	p Value
n		21	11		
Demographic data					
Sex male/female		20/1	10/1		0.631
Age (years)		74.9 ± 3.7	77.9 ± 4.1	2.02	0.052
Handedness		89.4 ± 34.3	100 ± 0.0	0.99	0.330
Education (years)		14.4 ± 2.1	14.5 ± 1.9	0.10	0.925
Driving experience (years)		51.0 ± 6.9	47.0 ± 14.5	0.83	0.424
Neuropsychological tests					
MMSE total		27.5 ± 2.2	27.8 ± 1.5	0.38	0.708
Logical memory section of the WMS-R				0.54	0.586
	Immediate recall	19.4 ± 5.1	17.2 ± 7.4		
	Delayed recall	15.1 ± 5.4	12.8 ± 6.2		
RCPM		29.3 ± 2.9	31.0 ± 2.9	1.53	0.135
RAVLT				1.58	0.183
	Immediate recall, 1st trial	5.2 ± 1.8	4.2 ± 1.5		
	Immediate recall, 2nd trial	7.2 ± 1.9	7.2 ± 2.0		
	Immediate recall, 3rd trial	8.8 ± 2.4	8.5 ± 1.8		
	Immediate recall, 4th trial	9.8 ± 2.6	10.0 ± 2.0		
	Immediate recall, 5th trial	10.8 ± 2.3	10.5 ± 2.3		
	Interference	4.6 ± 1.5	4.3 ± 1.8		
	Delayed recall	8.8 ± 3.1	6.7 ± 3.5		
	Recognition correct	14.0 ± 0.9	13.2 ± 3.9		
	Recognition false positive	1.1 ± 1.8	0.6 ± 1.1		
	Recognition false negative	1.0 ± 0.9	1.8 ± 3.9		
ROCFT				1.98	0.156
	Copy	35.0 ± 1.3	35.5 ± 0.8		
	Delayed recall	20.0 ± 5.0	23.9 ± 5.0		
ST	Completion time			0.64	0.598
	Part I (s)	17.1 ± 2.7	18.1 ± 3.8		
	Part II (s)	20.0 ± 3.8	21.8 ± 4.6		
	Part III (s)	28.8 ± 11.2	29.3 ± 6.3		
	Number of errors			0.32	0.813
	Part I	0.1 ± 0.3	0.1 ± 0.3		
	Part II	0.2 ± 0.5	0.3 ± 0.4		
	Part III	1.2 ± 1.4	0.7 ± 1.1		
TMT				0.55	0.585
	A	100.7 ± 33.9	97.3 ± 20.2		
	B	158.9 ± 79.2	133.8 ± 55.9		

TABLE 1 (Continued)

	Subscale	Safe drivers	Unsafe drivers	F or T	p Value
CDT				0.77	0.388
	Copy	5.0 ± 0.0	5.0 ± 0.0		
	Free-drawn	4.9 ± 0.3	4.7 ± 0.4		
DEX*		10.5 ± 7.3	17.2 ± 9.4	2.15	0.040
EMC*		6.7 ± 3.8	10.8 ± 3.8	2.82	0.008
DBQ		69.5 ± 14.5	73.2 ± 15.2	0.65	0.518

Abbreviations: CDT, Clock Drawing Test; DBQ, Driving Behavior Questionnaire; DEX, Dysexecutive Questionnaire; EMC, Everyday Memory Checklist; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; RCPM, Raven's Colored Progressive Matrices; ROCFT, Rey–Osterrieth Complex Figure Test; SD, standard deviation; ST, Stroop Test; TMT, Trail Making Test; WMS-R, Logical Memory II subscale of the Wechsler Memory Scale–Revised.

*Statistical significance between groups.

then extracted from each participant and plotted against the corresponding TMT A scores.

Statistical analysis

For the clinical data, we adopted a two-tailed t-test, χ^2 test, or multivariate analysis of variance for the group comparisons between safe drivers and unsafe drivers. We used IBM SPSS Statistics 25 software for Mac OS (IBM) for the statistical analysis. We used a liberal statistical threshold of $p < 0.05$.

RESULTS

Demographics and cognitive measures

We classified 21 participants as safe drivers and 11 participants as unsafe drivers (Table 1). There were significant differences between the groups in terms of the DEX and the EMC scores. There were no differences in the sex ratio, age, duration of education, driving experience, or handedness between the groups.

TBSS

TBSS demonstrated that unsafe drivers had significantly higher AD values in nine WM clusters compared with safe drivers (TFCE-corrected $p < 0.05$; Figure 1; Table 2). These results were primarily observed bilaterally in the SLF. Specifically, the nine clusters contained a total of 1804 voxels, of which 384 voxels were placed in the right SLF and 286 voxels were located in the left SLF. Other clusters with significantly higher AD were bilaterally distributed in the anterior thalamic radiation (ATR), inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus. No clusters exhibited significant group differences in FA, RD, or MD (TFCE-corrected $p < 0.05$).

Correlation between AD values in the SLF and TMT A scores among unsafe drivers

We found significant positive correlations between AD values in the SLF and TMT A scores within unsafe drivers (left: $R^2 = 0.62$, $p = 0.0037$; right: $R^2 = 0.50$, $p = 0.015$) (Figure 2).

DISCUSSION

The aim of the present study was to characterize WM microstructural properties associated with a high risk of unsafe driving among healthy older people using a whole-brain, voxel-wised DTI approach. We found that unsafe drivers had significantly higher AD values in nine WM clusters compared with safe drivers. These results were primarily observed bilaterally in the SLF. In contrast, we found no group differences in other DTI parameters, such as FA, RD, and MD. Furthermore, correlation analyses showed that AD values in the SLF were positively correlated with TMT A scores.

The SLF is an extensive WM tract that mainly connects the frontal and parietal lobes, and is anatomically divided into three segments: dorsal, ventral, and posterior.[33] In detail, the dorsal SLF links the IPL to the superior frontal gyrus (SFG), the ventral SLF originates from the supramarginal gyrus and terminates in the inferior frontal gyrus, and the posterior SLF connects the middle temporal gyrus to the angular gyrus.[34] Functionally, each segment of the SLF has been shown to be involved in different cognitive functions. Specifically, the dorsal SLF is involved in visuospatial attention,[35,36] the ventral SLF is responsible for verbal working memory and auditory language comprehension,[37,38] and the posterior SLF is related to prosodic processing and social cognition.[39,40] In general, it is technically infeasible to determine the segments of the SLF that exhibit the strongest WM microstructural alterations between groups. Thus, we were unable to perform this type of analysis in the present study. However, we assumed that the dorsal SLF was the main WM segment that was disrupted for the following two reasons. First, anatomically, most
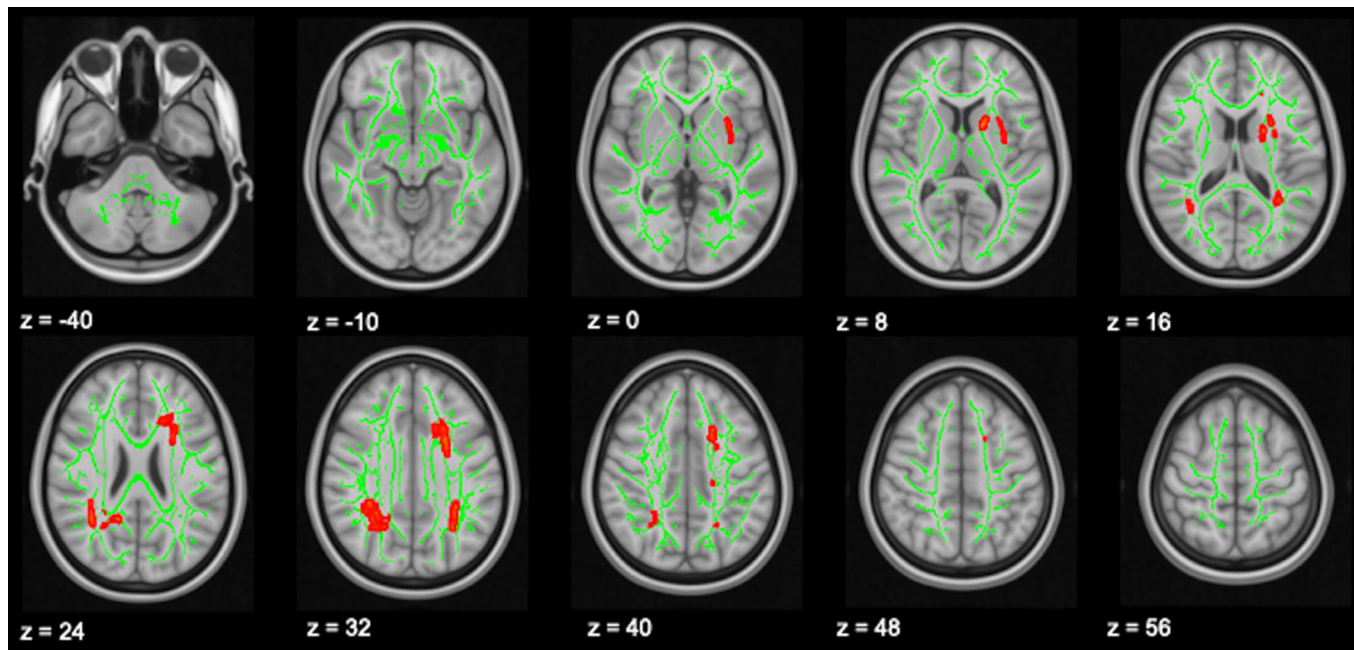
FIGURE 1 Voxels showing significant higher axial diffusivity (AD) values in unsafe drivers compared with safe drivers (threshold-free cluster enhancement [TFCE]-corrected $p < 0.05$). An AD increase in unsafe drivers relative to safe drivers is shown in red. The whole-brain skeleton is shown in green. The results are mapped onto a standard T1 Montreal Neurological Institute (MNI) 152 template. Images are presented using the right/left radiological convention with MNI z coordinates in millimeters.

TABLE 2 Clusters with significant higher AD values in unsafe drivers (TFCE-corrected $p < 0.05$)

Cluster ID	Tract(s)	p	T_{max}	voxels	X	Y	z
1	R anterior thalamic radiation, cingulate gyrus, hippocampus, forceps major, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus	0.033	5.05	705	24	−55	29
2	L anterior thalamic radiation, cingulate gyrus, forceps minor, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, uncinate fasciculus	0.036	4.78	565	−21	15	35
3	L anterior thalamic radiation, cingulate gyrus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus	0.047	3.13	147	−32	−47	31
4	L anterior thalamic radiation, inferior fronto-occipital fasciculus	0.045	3.75	125	−20	3	15
5	L superior longitudinal fasciculus	0.045	4.01	83	−33	−4	6
6	L inferior fronto-occipital fasciculus, superior longitudinal fasciculus, uncinate fasciculus	0.047	3.53	74	−32	4	1
7	L anterior thalamic radiation, cingulate gyrus, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, uncinate fasciculus	0.047	3.29	53	−27	12	12
8	L anterior thalamic radiation, inferior fronto-occipital fasciculus, superior longitudinal fasciculus	0.048	4.32	36	−33	−50	15
9	L corticospinal tract	0.050	3.01	16	−17	−21	35

Abbreviations: AD, axial diffusivity; TFCE, threshold-free cluster enhancement; T_{max}, maximum T statistic within the cluster at X Y Z MNI coordinates in millimeters; R, right; L, left.

of the voxels showing WM microstructural alterations were located around the SFG and IPL, which constitute the dorsal SLF. Second, functionally, the findings of our correlation analyses showed that higher AD values were associated with worse scores on the TMT-A task in the unsafe drivers group. Thus, we assumed that the microstructure of the dorsal SLF was the most strongly affected based on its functional role in visuospatial attention.

Intriguingly, a recent brain imaging study combining functional MRI and network tractography showed that the dorsal SLF plays major roles in the DAN.[41] In general, the DAN is involved in the goal-directed control of perceptual processing (i.e., top-down attention).[42–44] Top-down attention improves the detection of targets such as road signs by prioritizing goal-relevant information in the visual cortex prior to the appearance of the target.[45] For older
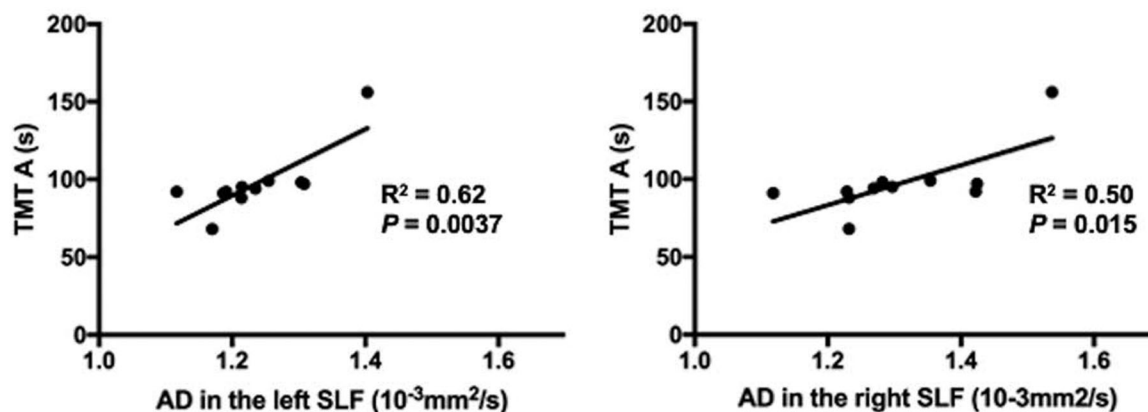
FIGURE 2 Scatter plots of axial diffusivity (AD) values in the superior longitudinal fasciculus (SLF) against Trail Making Test (TMT) A scores in unsafe drivers. AD values in the SLF were significantly and positively correlated with TMT A scores. Statistical significance threshold: $p < 0.05$ for the left and right SLF (Bonferroni correction).

drivers, top-down attention compensates for age-related reductions in road hazard detection. Correspondingly, declines in top-down attention have been shown to lead to motor vehicle accidents involving older drivers.[46] WM microstructural disruptions in the dorsal SLF are thus associated with reduced top-down attention, and may be associated with the risk of unsafe driving in older drivers. However, no previous DTI studies have directly examined the relationship between on-road driving ability and WM microstructural alterations in healthy older individuals. Therefore, the present results extend the previous findings and provide the first neurobiological evidence that changes in WM microstructures involved in top-down attention are associated with a greater risk of unsafe driving in healthy older people.

In general, different DTI parameters reflect distinct aspects of WM microstructure; so investigating the DTI parameters that vary between groups could elucidate the mechanisms of WM microstructural alterations.[47] In the present study, the AD value was the most sensitive parameter that could be used to characterize group differences. Specifically, unsafe drivers had significantly higher AD values compared with safe drivers. An increased AD represents elevated water diffusivity parallel to axonal fiber tracts,[48] which reflects axonal swelling and a consequent narrowing of the space between myelin fiber bundles.[49,50] Although the underlying neuropathological mechanisms of our findings are unclear, age-related chronic ischemia could cause axonal swelling leading to increased AD values. Previous postmortem brain studies have shown that axonal edema is caused by diseases associated with chronic ischemia. Specifically, autopsy findings using electron microscopy in patients with reversible posterior leukoencephalopathy syndrome[51] and Fabry's disease[52] demonstrated hydropic swelling of axons in the cerebral deep WM. Furthermore, a recent in vitro study using mouse models showed that chronic ischemia induces axonal swelling because of water influx via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors.[53] In summary, axonal edema caused by chronic ischemia may underlie the enhanced risk of unsafe driving in healthy older people.

Using TBSS, we found that unsafe drivers had significantly higher AD values in WM tracts, including the bilateral SLF and ATR. Increased AD values in the SLF and ATR have repeatedly been shown to be associated with normal aging. For example, a TBSS study comparing 63 healthy older subjects with 80 young healthy subjects showed that the older group had increased AD values in WM tracts, including the bilateral SLF and ATR.[54] In addition, another TBSS study exploring WM structural changes in healthy older adults during a 2-year period revealed a significant increase in AD values in multiple brain regions, including the SLF and ATR, at 2 years compared with the baseline.[55] According to these observations, increased AD values in unsafe drivers may represent age-related WM microstructural alterations, suggesting that the effect of aging on WM microstructure might have been more pronounced in unsafe versus safe drivers.

LIMITATIONS

This study has several limitations. First, given the cross-sectional nature of our study design, future longitudinal studies are needed to establish the causal relationship suggested by the current results. A longitudinal design with two or more data-collection time points would allow us to more precisely assess the relationship between WM microstructural changes and the risk of unsafe driving. Second, although we evaluated on-road driving ability on the basis of vehicle behavior, we only assessed one aspect of driving ability. Examining driver behaviors when turning right at an intersection or making a lane change, for example, might yield useful results. Third, the number of participants per group was relatively small, which might have caused our study to be underpowered. In other words, due to the limited sample size, there might have been no clusters exhibiting significant group differences in FA, MD, or RD. Therefore, our findings require additional confirmation by future studies with larger samples at multiple sites.

CONCLUSION

In conclusion, we revealed for the first time that WM microstructural alterations are associated with the risk of unsafe driving in healthy older people. Specifically, unsafe drivers exhibited increased AD values mainly in the dorsal SLF, which is involved in DAN. The current findings enhance our understanding of the mechanisms underlying an increased risk of unsafe driving in healthy older people, which may facilitate the development of new interventions to prevent fatal accidents.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request to the corresponding author.

ETHICS APPROVAL STATEMENT

Research procedures involving human participants were reviewed and approved by the ethics committees of the University of Tokyo and Keio University.

PATIENT CONSENT STATEMENT

The participants provided their written informed consent to participate in this study.

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