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The association of diffusion tensor MRI measures of normal appearing white matter and cognition

Yi Lin Ng [a], Chuen Seng Tan [a], Marco Egle [b], Bibek Gyanwali [c], Daniel J. Tozer [b], Hugh S. Markus [b], Christopher Chen [c,d], Saima Hilal [a,c,d,*]

[a] Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore
[b] Department of Clinical Neurosciences, Stroke Research Group, University of Cambridge, Cambridge, United Kingdom
[c] Memory Aging and Cognition Centre, National University Health System, Singapore
[d] Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

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ABSTRACT

Objective: Median and peak height of fractional anisotropy (FA) and mean diffusivity (MD) are diffusion tensor imaging (DTI) markers used to quantify white matter microstructure changes. We examine the association of DTI histogram-derived measures in global normal appearing white matter (NAWM) and cognitive decline in patients with normal cognition and cognitive impairment no dementia from a memory clinic in Singapore.

Methods: A total of 252 patients (mean age: 71.1 ± 7.6 years, 53.2% women) were included. All patients underwent clinical assessments, a brain MRI scan at baseline, and neuropsychological assessments annually for 2 years. DTI scans were processed to obtain MD and FA histogram-derived measures. The National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network harmonization neuropsychological battery were used to assess cognitive function. Linear regression models with generalised estimating equation (GEE) and logistic regression models were used to examine the association between DTI histogram measures and cognitive decline.

Results: When compared to baseline, MD and FA measures at Year 2 were associated with an accelerated worsening in global cognition (all p for interaction <0.001; Year 0 vs 2, MD median: -0.29 (95%CI: -0.49, -0.09) vs -0.45 (95%CI: -0.65,-0.25); MD peak height: 0.22 (95%CI: 0.07, 0.37) vs 0.37 (95%CI: 0.21, 0.53); FA median: 0.11 (95%CI: -0.05, 0.26) vs 0.22 (95%CI: 0.07, 0.37); FA peak height: -0.14 (95%CI: -0.28, 0.00) vs -0.24 (95% CI: -0.38, -0.10);). Similar findings were observed for executive function and visuomotor speed while only MD measures predicted worsening in memory domain.

Interpretation: This study shows that DTI histogram measures are associated with accelerated cognitive decline suggesting the utility of DTI as a pre-clinical marker in predicting the worsening of cognition in clinical trials.

1. Introduction

Memory clinic patients at risk for dementia often present with visible lesions, characteristic of late-stage brain injury [1]. Vascular lesions measured using conventional magnetic resonance imaging (MRI) markers include white matter hyperintensities (WMH), lacunes and microbleeds [2,3] which are recognized as an important contributor to vascular cognitive impairment (VCI) [4,5] and increase the probability of developing clinical symptoms of dementia, including Alzheimer's disease pathology [6]. VCI is associated with modifiable cardiovascular risk factors, suggesting that VCI could be preventable [7]. Hence it is important to assess vascular imaging measures and their potential role as biomarkers.

It is difficult to directly assess brain vascular pathology, particularly small vessel disease (SVD), in vivo [8]. Therefore, surrogate measures such as diffusion tensor imaging (DTI) have been utilised. DTI reveals disruption within brain networks by quantifying subtle changes in white matter (WM) microstructure [9] and is particularly sensitive to WM damage in small vessel disease [10]. Normal appearing white matter (NAWM) microstructure could be investigated using DTI, with WMH

* Corresponding author at: Saw Swee Hock School of Public Health, National University of Singapore, Tahir Foundation Building (MD1), 12 Science Drive 2, #10-03U, Singapore 117549, Singapore.
E-mail address: saimahilal@nus.edu.sg (S. Hilal).

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displaying reduced NAWM integrity, depending on the proximity to WM lesions [11,12]. There are several quantitative DTI markers. Median and peak height of fractional anisotropy (FA) and mean diffusivity (MD) are DTI markers derived from histogram analysis of the NAWM, with FA and MD measuring the directionality and magnitude of diffusion of water molecules in tissue respectively [13]. Axial diffusivity (AD) and radial diffusivity (RD) are also DTI markers correlated with axonal and myelin damage [14]. MD and FA were found to be correlated to age-related cognitive decline, [15] and are more sensitive to WM damage than WMH lesions load [16]. A greater understanding regarding the association between NAWM and cognitive decline is required.

Previous single and multi-center cross-sectional studies have reported associations between DTI measures and impaired cognitive function, not only in regions of WM abnormalities but also in NAWM regions, in populations such as mild cognitive impairment (MCI) patients and community-based cohorts [17–19]. DTI measures have also shown to be strongly associated with vascular-related cognitive deficits such as executive function and processing speed both cross-sectionally and longitudinally, [20] supporting their use as pre-clinical markers in SVD. Additionally, even in shorter periods of 1–3 years, changes in DTI have been detected in SVD patients, [21,22] further reinforcing the potential utility of DTI measures even in smaller sample sizes as previously shown in the OPtimising mulTImodal MRI markers for use as surrogate markers in trials of Vascular Cognitive Impairment due to cerebrAl small vesseL disease (OPTIMAL) study [23]

Despite these findings, there is limited longitudinal data analyzing the association of DTI measures in NAWM with individual cognitive trajectories [20]. The study aims to fill this gap by examining the association between baseline DTI measures assessing NAWM tissue integrity and cognition in memory clinic patients consisting of normal cognition and cognitive impairment in longitudinal analysis. The focus on longitudinal analysis over a two-year follow-up period distinguishes this study from previous research. We hypothesize that baseline DTI measures predicts for cognitive decline, over two years of follow-up in a memory clinic cohort.

2. Materials and methods

2.1. Study setting and sample

This study involved patients from a memory clinic study conducted at the National University Hospital, Singapore. Details of study methodology have been described elsewhere [24]. Briefly, elderly patients were recruited into the cohort if they had one of the following diagnoses at baseline: 1) No Cognitive Impairment (NCI): patients with no functional loss and cognitive impairment on the formal neuropsychological testing; 2) Cognitive Impairment No Dementia (CIND): patients with no loss of daily functions and no neuroimaging evidence of cerebral infarction but impairment in at least one cognitive domain on formal neuropsychological testing; 3) Vascular CIND (VCIND): patients with neuroimaging evidence of cerebral infarction, a history of ischemic stroke within past 6–24 months and evidence of impairment on neuropsychological tests; 4) Dementia: patients who fulfilled the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria for dementia.

From 12 August 2010 till 27 December 2016, a total of 554 patients were recruited into the memory clinic cohort (Fig. 1). For this study, we excluded patients with dementia at baseline ($n = 211$). Of these 343 NCI and (V)CIND patients, 265 had available DTI data, after excluding patients with incomplete MRI data ($n = 78$). A further eight patients who had poor quality DTI images at baseline and five patients with missing neuropsychological data were excluded, leaving a final sample size of 252 patients for analysis.

Ethical approval was obtained from the National Healthcare Group Domain-Specific Review Board and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained in the preferred language of the patients.

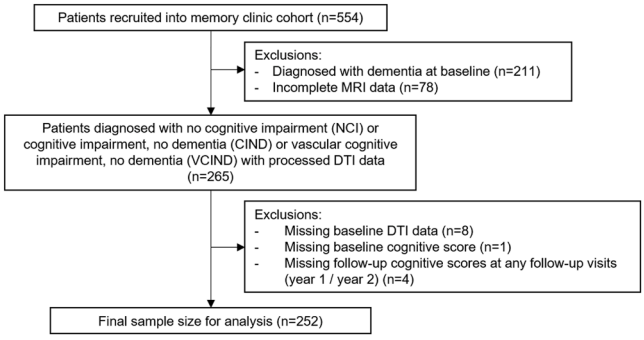

Fig. 1. Flowchart of study participants.

2.2. Image acquisition and assessment of brain vascular lesions

MRI scans were acquired at 3T Siemens Magnetom Trio Tim Scanner system. MRI protocol included T1-weighted, T2-weighted, Fluid-attenuated Inversion Recovery (FLAIR), susceptibility weighted imaging (SWI) and DTI sequences for each participant. Baseline MRI scans were visually graded by experienced researchers (BG and SH) who were blinded to the patients' clinical history. Vascular lesions of cerebral small vessel disease were graded according to STRIVE (Standards for Reporting Vascular Changes on Neuroimaging) criteria. WMH were defined based on their hyperintensity in periventricular or deep WM regions on FLAIR images and categorised using the Fazekas scale (none, punctate (mild), beginning of confluence (moderate) or confluent areas (severe) areas) [25]. As the sample size of patients without WMH was very small (less than five), WMH was dichotomised into either 'none-mild' or 'moderate-severe'. Lacunes were defined as hypointense lesions (3–15 mm diameter) with hyperintense rims on FLAIR images [26]. Cerebral microbleeds were defined as hypointense lesions ($\leq$10 mm diameter) with blooming effect on SWI [26]

2.2.1. Brain volume and WMH volume

Image preprocessing and the tissue classification algorithm have been described elsewhere. Briefly, a k-nearest-neighbor technique was used to classify voxels into cerebrospinal fluid, gray matter and NAWM and volumes were calculated from these measurements [27]. WMH volumes were detected using an adapted threshold technique [28]. Total brain volume was calculated as a sum of gray matter and WM volumes. The processing of WMH segmentation underwent a rigorous process, involving a standardized image analysis workflow which has shown good accuracy and reproducibility [29]

2.2.2. Processing of DTI

DTI scans were obtained using a diffusion-weighted echo-planar imaging sequence (61 non-collinear diffusion gradient directions at $b = 1150$ s/mm^2, seven volumes of $b = 0$ s/mm^2, repetition time (TR)/time to echo (TE)=6800/85 ms, 48 contiguous slices, and voxel size=3.1 $\times$ 3.1 $\times$ 3.0 mm^3). High-resolution T1-weighted structural MRI was acquired using magnetization-prepared rapid gradient echo (MPRAGE) sequence (192 continuous sagittal slices, TR/TE/TI=2300/1.9/900 ms, flip angle=9°, isotropic voxel size=1.0 mm^3). NAWM histogram measures (i.e., MD median and peak height, FA median and peak height), were computed. The DTI analysis pipeline has been described previously [19]. Briefly, the eddy correct software from the FMRIB's Diffusion Toolbox, (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT) was employed for DTI preprocessing. MD and FA maps were created with 'DTIFIT'. FLAIR to T1-weighted and T1-weighted to b0 registrations were performed and the affine transformation matrices were concatenated to produce a FLAIR-to-DTI transformation. Tissue Probability Maps were registered into DTI space using these transformations. Hard segmentations were

applied to generate maps of tissue classes, achieved by voxel-wise comparison of the gray matter, WM and cerebrospinal fluid Tissue Probability Maps, with each voxel being assigned to the highest probability tissue class. To identify NAWM, T1-weighed structural images and T2-weighed FLAIR images were registered to the b0 image using 12 parameter affine registration with a normalised mutual information cost function. These transformations were applied to WMH lesion masks. NAWM in DTI was classified as non-lesion voxels where the probability of WM was greater than gray matter or cerebrospinal fluid [16]. Histogram analysis was conducted on the MD and FA maps in NAWM regions. Summary histogram measures were derived from normalized histograms with 1000 bins (bin width: $0.004 mm^2 s^{-1} \times 10^{-3}$; range: 0–4 $mm^2 s^{-1} \times 10^{-3}$) [30]. The DTI histogram-derived measures were standardised to their mean and standard deviation (SD) for each DTI measure.

2.3. Assessment of cognitive function

Cognitive function was assessed annually using a formal neuropsychological test battery (National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network battery) that has been locally validated, [31] to characterize cognitive impairment. The complete battery assesses six cognitive domains in a 60-minute protocol: (1) Attention – Digit span forward and backward; (2) Executive function – Verbal fluency, Colour trail test A and B; (3) Language – 15-item modified Boston naming test; (4) Memory – Rey complex figure test and Hopkins verbal learning test: Immediate/delayed recall and recognition; (5) Visuospatial function – Rey complex figure test: Copy; and (6) Visuomotor speed – Symbol digit modalities test.

The raw scores were standardized to the mean and SD of the control group (patients with NCI at baseline) for each score. The z-scores of each individual test were averaged within the cognitive domains and then standardized using the composite mean and SD of the control group. The standardized global cognition score was then computed by averaging across the six cognitive domains z-scores and standardizing using the mean and SD of the control group. For each follow-up visit, scores were similarly computed by standardizing within the domains and subsequently standardizing global cognitive z-scores using the means and SDs of the control group at baseline [32]

2.4. Demographic characteristics

Demographic profiles were obtained through a standardized questionnaire while the vascular risk profiles were collected from clinical assessment and medical records. Data collected included information on age, sex, ethnicity, and total number of years in education. Ethnicity was binarised into Chinese and others, as the majority of the study population was Chinese. Cardiovascular risk factors included having a past medical history of hypertension, hyperlipidemia and/or diabetes mellitus and smoking history (non-smoker and ever-smoker).

2.5. Statistical analysis

Descriptive statistics was used to summarize the characteristics of patients at baseline. For continuous variables, mean and SD were provided. For categorical variables, count and percentage were presented.

To examine the association between DTI histogram-derived measures and cognitive decline, a linear regression model with generalised estimating equations (GEE) was used to account for correlation between repeated cognitive measurements across the three time points, with unstructured correlation specified [33]. GEE was performed for global cognition and the six cognitive domains as outcomes in all patients. The coefficient estimates and their corresponding 95% confidence intervals (CIs) were reported.

To determine the frequency of patients with cognitive decline in each cognitive outcome, we calculated the change in z-score for each patient from Year 2 and Year 0. If the change in score was negative, cognitive decline was considered present else cognitive decline was considered absent. The mean and SD for change in z-score were provided for the study population and for a subset of patients with negative change in z-scores in each cognitive outcome.

To further determine the association between baseline DTI measures and cognitive decline, we applied the logistic regression model and reported the odds ratios (ORs) and corresponding 95% CIs. Cognitive decline was coded as 1 if there was a decrease in cognitive scores from baseline to Year 2, else 0.

For global cognitive scores, p-values of less than 0.05 were considered statistically significant. To account for family-wise error rate for the cognitive domains that made up the global cognition score and the combination of measures (median and peak height) for each DTI measure, the Bonferroni correction was applied. P-values of less than $0.05/(6 \times 2) \approx 0.0042$ were deemed as statistically significant.

Three models were built for each combination of DTI histogram-derived measures and cognition scores. Model I was a univariable analysis unadjusted for any confounders. For Model II, we adjusted for demographic characteristics (age, sex, ethnicity, education, and baseline diagnosis) and cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, and smoking history). In Model III, we further adjusted the model for MRI markers of cerebrovascular disease (WMH, lacunes, cerebral microbleeds, and total brain volume). For the GEE analysis, all three models included adjustment for follow-up time. An additional analysis was conducted that included the interaction between follow-up time and each DTI measure to assess whether the effects of DTI measures were the same across time. For the interaction analysis, interaction P-values of less than 0.05 were considered statistically significant. Using Model III, cognitive trajectories over time were presented visually by plotting the estimated marginal means of the cognition score at baseline, year 1 and year 2 with the baseline DTI measure specified at ±1 SD and at the mean.

To calculate the ratio of the absolute mean difference in the cognitive z-scores between Year 2 and Year 0 of baseline DTI measures with significant time interaction, delta method was used. The ratios and their corresponding 95% CIs were reported. Similarly, ratios with P-values of less than 0.05 were considered statistically significant.

All statistical analyses were performed using STATA (Stata Version17, StataCorp, College Station, TX).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the 252 patients analyzed is presented in Table 1a. The mean age of the study population was 71.1 (SD: ±7.6) years with 53.2% women. Most of the study participants were Chinese (87.3%). A total of 92 patients (36.5%) were diagnosed with NCI, 109 (43.3%) as CIND and 51 (20.2%) as VCIND. 134 (53.2%) patients had none or mild WMH. The mean and SD of cognitive scores for patients over time and the frequency of cognitive decline in global cognition and the respective cognitive domains is presented in Table 1b. At the end of two years follow-up, 127 patients (50%) were observed to have a cognitive decline in visuospatial function, followed by 122 patients (48%) with a cognitive decline in attention. For those with negative change in z-scores, on average, the greatest decline in z-scores were observed to be in language (mean:−2.27, SD:1.20), followed by visuospatial function (mean:−0.86, SD:0.65) and executive function (mean:−0.85, SD:0.71).

3.2. Longitudinal association between baseline DTI measures and cognitive scores

Significant interaction between time and baseline DTI measures (MD and FA) for global cognition, attention, executive function and visuomotor speed were observed for all models (all $p < 0.046$) (Table 2,

Table 1a
Baseline characteristics of study population.

Covariates	All (n = 252)
Age (mean,sd)	71.1 (7.6)
Gender (n,%)	
Male	118 (46.8)
Female	134 (53.2)
Race (n,%)	
Chinese	220 (87.3)
Others	32 (12.7)
Total years of education (mean,sd)	8.4 (5.0)
History of hypertension (n,%)	167 (66.3)
History of hyperlipidemia (n,%)	191 (75.8)
History of diabetes (n,%)	73 (29.0)
Smoking history (n,%)	
Non-smoker	191 (75.8)
Current or former smoker	61 (24.2)
Baseline Diagnosis (n,%)	
NCI	92 (36.5)
CIND	109 (43.3)
VCIND	51 (20.2)
White matter hyperintensities (n,%)	
None-to-mild	134 (53.2)
Moderate-to-severe	118 (46.8)
Number of lacunes present (mean,sd)	0.4 (1.1)
Number of cerebral microbleeds present (mean,sd)	1.7 (6.6)
DTI measures (mean,sd)	
MD median, x10^{-3} (mm^2s^{-1})	0.87 (0.06)
MD peak height, x10^{-2}	1.20 (0.22)
FA median (mm^2s^{-1})	0.19 (0.02)
FA peak height, x10^{-2}	0.52 (0.07)
Total brain volume, ml (mean,sd)	902.5 (98.5)

Table 1b
Summary statistics of cognitive outcomes by Year.

Cognitive z-scores	Year 0	Year 1	Year 2	Change in z-score (Year 2 - Year 0)	Decline Count*, n(%)	Change in z-score (Year 2 - Year 0)[a]
Global	−1.01 (1.52)	−0.86 (1.57)	−0.89 (1.67)	0.12 (0.68)	94 (37)	−0.55 (0.49)
Attention	−0.3 (1.10)	−0.28 (1.07)	−0.32 (1.17)	−0.02 (0.80)	122 (48)	−0.66 (0.49)
Executive function	−1.16 (1.68)	−1.06 (1.75)	−1.01 (1.85)	0.15 (0.96)	90 (36)	−0.85 (0.71)
Memory	−0.92 (1.32)	−0.58 (1.45)	−0.63 (1.58)	0.29 (0.75)	86 (34)	−0.48 (0.46)
Language	−0.57 (1.65)	−0.46 (1.59)	−0.43 (1.66)	0.14 (1.44)	36 (14)	−2.27 (1.20)
Visuomotor speed	−0.63 (1.08)	−0.58 (1.08)	−0.66 (1.07)	−0.02 (0.48)	104 (41)	−0.44 (0.36)
Visuospatial function	−0.62 (1.46)	−0.64 (1.48)	−0.67 (1.47)	−0.05 (1.07)	127 (50)	−0.86 (0.65)

Values are presented as mean (SD) unless otherwise stated.
* Includes only patients with negative change scores between Year 2 and Year 0.

Table 3). For memory, significant interaction between time was observed only with MD measures (p <0.006) and FA median (p <0.018) while significant time interaction was observed only with FA peak height for language in all models (p = 0.013).

3.2.1. Longitudinal association between baseline MD measures and cognitive scores

For global cognition, the effects of MD measures (median and peak height) were more pronounced in Year 1 and Year 2 (p <0.001), although the measures had significant associations in all three time points (Table 2). Similarly, within specific cognitive domains with significant interaction (i.e., all domains except language and visuospatial function) and after Bonferroni correction for each time-point, MD median and peak height had more pronounced negative and positive effects at Year 1 and Year 2 for executive function, memory and visuomotor speed in all models (p <0.004).

The effect of MD measures was homogeneous and significant for visuospatial function in all models. MD median was negatively associated (β = −0.39; 95%CI (−0.61, −0.17)) while MD peak height was positively associated with visuospatial function (β = 0.26; 95%CI (0.09,0.43)).

3.2.2. Longitudinal association between FA measures and cognitive scores

For global cognition, the effects of FA measures (median and peak height) were more pronounced in Year 1 and Year 2 (p <0.002), with significant associations only in later periods, excluding the effect of FA median in Year 2 in Model III (Table 3). Within the specific cognitive domains with significant interactions and after Bonferroni correction for each time-point, both FA measures were associated with pronounced effects in Year 1 and Year 2 in executive function ($p \leq 0.004$). Only FA peak height had more pronounced negative effects at Year 1 and Year 2 for visuomotor speed in all models ($p \leq 0.004$).

Among the homogenous effects of FA measures on specific cognitive domains, these effects were only significant for visuospatial function in all models, similar to MD measures. FA median was positively associated (β = 0.30, 95%CI (0.13,0.46)) while FA peak height was negatively associated with visuospatial function (β = −0.26, 95%CI (−0.42, −0.10)) (Model III).

Unlike MD measures, memory had no significant associations across all time points in Model III for FA median, although the interaction was significant. Attention and language were not associated with FA and MD measures (Tables 2, 3).

3.2.3. Baseline DTI measures and cognitive trajectories

The effects of each DTI histogram-derived measure on different cognitive trajectories of all patients are shown in Fig. 2. Global cognition and executive function were visualized as these two cognitive outcomes had significant findings for all DTI measures on the time-varying effect on cognition (Tables 2, 3). As illustrated, executive function trajectory is consistent with the global cognition trajectory in both MD and FA measures, suggesting executive dysfunction to be the main driver for the global cognitive score. The main effects of time are positive, hence the group with the worse DTI profile would present a flat line.

3.2.4. The odds of cognitive decline from baseline DTI measures

DTI measures were not found to be associated with global cognition decline from Model III; see Appendix Table 1. Significant associations with cognitive decline were only found within the cognitive domain, specifically in visuomotor speed, after Bonferroni correction, in FA median (OR = 0.58, 95%CI (0.41,0.84)) (Model III).

An additional analysis on the cognitive outcomes stratified by baseline diagnosis (NCI, CIND and VCIND) was performed in Model III and have found significant interaction (p <0.05) between baseline diagnosis and baseline DTI measures for attention (p < 0.024) and memory (p = 0.037). (Supplementary Table 2) For attention, all baseline DTI measures had significant interaction with baseline diagnosis. However, no significant associations with any baseline diagnosis were observed after Bonferroni correction. Global cognition and other cognitive domains (executive function, language, visuomotor speed, visuospatial function) did not have any significant interaction with baseline diagnosis for all baseline DTI measures.

3.2.5. Ratio of absolute mean difference in cognitive scores between Year 2 and Year 0

For cognitive outcomes with significant time interaction, the ratio in the absolute mean difference in cognitive outcomes for Year 2 and Year 0 of baseline DTI measures was only significant for MD measures in global z-scores, executive function, memory and visuomotor speed (all p <0.05) (Model III) (Table 4).

Table 2
Association of baseline MD measures with cognitive scores over time.

MD Measures	Model I[a] β (95% CI)	*p*	Model II[b] β (95% CI)	*p*	Model III[c] β (95% CI)	*p*
Outcome: Global cognition z-score						
MD median[d]	−0.59 (−0.74,−0.43)	<0.001	−0.35 (−0.52,−0.18)	<0.001	−0.38 (−0.56,−0.19)	<0.001
Baseline[e]	−0.51 (−0.67,−0.35)	<0.001	−0.26 (−0.44,−0.09)	0.003	−0.29 (−0.49,−0.09)	0.004
Year 1[e]	−0.65 (−0.80,−0.50)	<0.001	−0.41 (−0.57,−0.24)	<0.001	−0.44 (−0.62,−0.25)	<0.001
Year 2[e]	−0.67 (−0.84,−0.49)	<0.001	−0.42 (−0.60,−0.24)	<0.001	−0.45 (−0.65,−0.25)	<0.001
p for interaction	<0.001		<0.001		<0.001	
MD peak height[d]	0.47 (0.33,0.60)	<0.001	0.31 (0.17,0.45)	<0.001	0.31 (0.16,0.46)	<0.001
Baseline[e]	0.39 (0.25,0.54)	<0.001	0.22 (0.08,0.37)	0.002	0.22 (0.07,0.37)	0.005
Year 1[e]	0.54 (0.40,0.68)	<0.001	0.37 (0.23,0.52)	<0.001	0.37 (0.22,0.52)	<0.001
Year 2[e]	0.54 (0.38,0.71)	<0.001	0.37 (0.22,0.53)	<0.001	0.37 (0.21,0.53)	<0.001
p for interaction	<0.001		<0.001		<0.001	
Cognitive domains						
Outcome: Attention						
MD median[d]	0.12 (−0.25,0.01)	0.066	−0.03 (−0.18,0.12)	0.671	−0.09 (−0.26,0.07)	0.269
Baseline[e]	−0.03 (−0.18,0.12)	0.703	0.06 (−0.10,0.23)	0.471	0.00 (−0.19,0.18)	0.987
Year 1[e]	−0.15 (−0.29,−0.01)	0.033	−0.06 (−0.23,0.10)	0.470	−0.12 (−0.30,0.05)	0.160
Year 2[e]	−0.20 (−0.35,−0.05)	0.008	−0.11 (−0.28,0.05)	0.182	−0.17 (−0.35,0.01)	0.062
p for interaction	0.003		0.003		0.004	
MD peak height[d]	0.11 (−0.02,0.24)	0.099	0.08 (−0.07,0.24)	0.295	0.12 (−0.05,0.29)	0.157
Baseline[e]	0.03 (−0.10,0.17)	0.638	0.01 (−0.15,0.17)	0.915	0.05 (−0.12,0.22)	0.597
Year 1[e]	0.15 (0.01,0.29)	0.032	0.13 (−0.04,0.30)	0.147	0.16 (−0.01,0.34)	0.070
Year 2[e]	0.15 (−0.01,0.30)	0.059	0.12 (−0.06,0.30)	0.177	0.16 (−0.03,0.35)	0.102
p for interaction	0.034		0.034		0.036	
Outcome: Executive function						
MD median[d]	−0.69 (−0.85,−0.53)	<0.001	−0.40 (−0.60,−0.20)	<0.001	−0.42 (−0.64,−0.20)	<0.001
Baseline[e]	−0.59 (−0.75,−0.43)	<0.001	−0.30 (−0.51,−0.08)	0.006	−0.31 (−0.54,−0.09)	0.007
Year 1[e]	−0.75 (−0.92,−0.58)	<0.001	−0.46 (−0.66,−0.26)	<0.001	−0.48 (−0.70,−0.25)	<0.001
Year 2[e]	−0.77 (−0.96,−0.57)	<0.001	−0.47 (−0.69,−0.26)	<0.001	−0.49 (−0.73,−0.26)	<0.001
p for interaction	0.003		0.003		0.003	
MD peak height[d]	0.54 (0.39,0.69)	<0.001	0.31 (0.14,0.48)	<0.001	0.30 (0.11,0.48)	0.002
Baseline[e]	0.45 (0.30,0.60)	<0.001	0.21 (0.04,0.39)	0.018	0.20 (0.01,0.39)	0.036
Year 1[e]	0.58 (0.42,0.74)	<0.001	0.35 (0.17,0.53)	<0.001	0.34 (0.15,0.53)	<0.001
Year 2[e]	0.61 (0.43,0.79)	<0.001	0.38 (0.19,0.58)	<0.001	0.37 (0.17,0.57)	<0.001
p for interaction	0.004		0.004		0.004	
Outcome: Memory						
MD median[d]	−0.50 (−0.62,−0.37)	<0.001	−0.29 (−0.45,−0.14)	<0.001	−0.24 (−0.42,−0.06)	0.010
Baseline[e]	−0.49 (−0.62,−0.35)	<0.001	−0.22 (−0.38,−0.06)	0.006	−0.17 (−0.36,0.02)	0.074
Year 1[e]	−0.59 (−0.73,−0.45)	<0.001	−0.33 (−0.48,−0.17)	<0.001	−0.27 (−0.46,−0.09)	0.003
Year 2[e]	−0.64 (−0.81,−0.47)	<0.001	−0.38 (−0.55,−0.21)	<0.001	−0.32 (−0.52,−0.12)	0.002
p for interaction	0.003		0.003		0.005	
MD peak height[d]	0.41 (0.28,0.54)	<0.001	0.26 (0.12,0.40)	<0.001	0.21 (0.06,0.36)	0.007
Baseline[e]	0.39 (0.26,0.53)	<0.001	0.18 (0.04,0.33)	0.014	0.13 (−0.02,0.29)	0.094
Year 1[e]	0.52 (0.38,0.66)	<0.001	0.31 (0.16,0.46)	<0.001	0.26 (0.10,0.42)	0.001
Year 2[e]	0.55 (0.37,0.72)	<0.001	0.34 (0.17,0.50)	<0.001	0.28 (0.11,0.45)	0.001
p for interaction	0.001		0.001		0.001	
Outcome: Language						
MD median[d]	−0.26 (−0.41,−0.11)	0.001	−0.17 (−0.37,0.04)	0.114	−0.21 (−0.45,0.02)	0.071
p for interaction	0.190		0.190		0.188	
MD peak height[d]	0.22 (0.08,0.36)	0.003	0.22 (0.04,0.40)	0.016	0.25 (0.06,0.43)	0.010
p for interaction	0.210		0.210		0.208	
Outcome: Visuomotor speed						
MD median[d]	−0.44 (−0.55,−0.33)	<0.001	−0.22 (−0.33,−0.11)	<0.001	−0.24 (−0.36,−0.12)	<0.001
Baseline[e]	−0.36 (−0.49,−0.24)	<0.001	−0.15 (−0.26,−0.03)	0.011	−0.16 (−0.29,−0.04)	0.012
Year 1[e]	−0.45 (−0.56,−0.33)	<0.001	−0.23 (−0.34,−0.12)	<0.001	−0.25 (−0.37,−0.12)	<0.001
Year 2[e]	−0.48 (−0.59,−0.37)	<0.001	−0.26 (−0.38,−0.15)	<0.001	−0.28 (−0.40,−0.16)	<0.001
p for interaction	<0.001		<0.001		<0.001	
MD peak height[d]	0.35 (0.24,0.46)	<0.001	0.17 (0.07,0.27)	0.001	0.16 (0.06 (0.27)	0.003
Baseline[e]	0.27 (0.16,0.39)	<0.001	0.09 (−0.02,0.19)	0.100	0.08 (−0.03,0.20)	0.139
Year 1[e]	0.36 (0.25,0.47)	<0.001	0.17 (0.07,0.27)	0.001	0.17 (0.06,0.28)	0.002
Year 2[e]	0.40 (0.29,0.51)	<0.001	0.21 (0.11,0.32)	<0.001	0.21 (0.10,0.32)	<0.001
p for interaction	<0.001		<0.001		<0.001	
Outcome: Visuospatial function						
MD median[d]	−0.44 (−0.59,−0.30)	<0.001	−0.37 (−0.57,−0.17)	<0.001	−0.39 (−0.61,−0.17)	<0.001
p for interaction	0.944		0.944		0.971	
MD peak height[d]	0.34 (0.21,0.46)	<0.001	0.28 (0.11,0.44)	0.001	0.26 (0.09,0.43)	0.003
p for interaction	0.878		0.878		0.875	

[a] Model I: adjusted for follow-up time.
[b] Model II: adjusted for Model I + demographic factors (age, sex, race, baseline diagnosis, education) and cardiovascular risk factors (smoking status, hypertension, hyperlipidemia, diabetes).
[c] Model III: adjusted for Model II + risk factors for cerebrovascular disease (white matter hyperintensities, number of lacunes, number of cerebral microbleeds, total brain volume).
[d] The beta-coefficients for baseline DTI measures in GEE analysis without the interaction terms between DTI measures and time in the model.

[e] The beta-coefficients for baseline DTI measures at each time point (Baseline, Year 1, Year 2) with the interaction terms (DTI measure and time) in the model.

For global z-scores, the magnitude of decrease in mean difference in MD median was 54% more than baseline at year 2, while for MD peak height, the magnitude of increase in mean difference at Year 2 was 68% more than baseline for the same change.

In the cognitive domains, for executive function, the magnitude of decrease in mean difference in MD median was 58% more than baseline at Year 2, while for MD peak height, the magnitude of increase in mean difference at Year 2 was 84% more than baseline for the same change. For memory, the magnitude of decrease in mean difference in MD median was 87% more than baseline at Year 2, while for MD peak height, the magnitude of increase in mean difference at Year 2 is 113% more than baseline for the same change. Finally, for visuomotor speed, the magnitude of decrease in mean difference in MD median was 72% more than baseline at Year 2, while for MD peak height, the magnitude of increase in mean difference at Year 2 is 150% more than baseline for the same change.

4. Discussion

In this current study, NAWM microstructure using baseline DTI histogram-derived measures were significantly associated with worse cognition over time. Generally, the associations of MD and FA measures with cognitive score over time became more pronounced in global cognition, executive function and visuomotor speed, suggesting an accelerated worsening of cognition as time progresses even when time has no effect on cognition. Only MD measures predicted worsening of cognition in memory over time. All DTI measures were associated with visuospatial function, with the effect remaining the same over a 2-year follow-up.

Previous studies have shown that DTI measures are altered in MCI and dementia [34–36]. MCI subjects had lower peak height and higher median on the MD histogram, while having higher peak height and lower median on the FA histogram [36]. These findings suggest that DTI histogram-derived measures could be used to predict cognitive decline progression in patients with suspected MCI. Although disruption of global WM integrity from normal aging contributes to cognitive decline, [37]. WM injury is often presumed to be vascular due to their correlation to ischemia, increasing the likelihood of cognitive impairment [38]. It has also been previously shown that brain amyloid β and SVD are independent processes in CIND individuals [39]. NAWM have been strongly associated with cognitive decline in visuomotor speed and executive function in our study, but the relationship of NAWM with visuomotor speed is not well-understood. A recent study has found significant changes in NAWM with mobility, where a decrease in NAWM FA volume correlated to a slower gait, contributed by SVD [40]. Ischemic damage may have the greatest impact in visuomotor speed domain but further research is warranted.

Cognitive domains known to be affected in VCI included executive function, processing speed and delayed recall of word lists and visual content [41]. A study had showed that executive dysfunction was more prominent in early onset of VCI without loss of memory [42]. In our study, NAWM microstructure was similarly associated with cognitive deficit in executive function and visuospatial function while cognitive deficit in memory was associated to a lesser extent (only MD measures). This suggests that DTI measures might be a sensitive marker for vascular damage, with ischemic changes causing NAWM tract abnormalities including increased diffusivity magnitude and possible loss of myelin. Network disruption in NAWM could be driven by ischemic processes in multiple cognitive domains prior to the development of visible vascular lesions. Even though there were a greater proportion of NCI and CIND than VCIND in our study population, similar associations of DTI with executive function and visuospatial function were also found in those with SVD in other studies [43,44]. However, similar domains are also affected by WM atrophy, [45] which were not adjusted for in our current study.

The underlying pathology of DTI measures is not fully understood, but pathology studies have supported MD and FA measures as well as AD and RD to reflect breakdown in WM microstructure [46]. The discrepancy in the associations between both measures (MD and FA) with memory and visuomotor speed found in our study suggests that the pathophysiology measured by MD and FA could be different, with similar findings in other studies as well [47]. Our finding on memory lends strength to the smaller studies which found only MD to be primarily related to memory [48,49]. One study on interstitial cerebral edema had proposed that MD measures, which reflect diffuse changes, could be reversible after treatment, while FA measures were considered irreversible [50]. More research is needed on understanding the pathophysiology of MD measures, as it could reveal important targets that could potentially be reversible. Overall, our data suggests utility of DTI histogram-derived measures as a pre-clinical marker to predict the worsening of cognition, where ischemic changes is likely responsible for NAWM damage in MCI.

Our study has several strengths. Firstly, longitudinal analyses allowed us to associate cognitive scores over time with baseline measurement of NAWM microstructure suggesting changes in NAWM potentially contributes to the worsening of cognition. Secondly, the use of a locally validated neuropsychological test battery provided comprehensive information in multiple cognitive domains. Thirdly, as DTI measures are statistically calculated from diffusion MRI images, its non-invasive and automated nature are major advantages of this technique. DTI histogram-derived measures have shown to be reproducible, with low variability on repeated imaging [51]. Whole brain histogram analysis also lends strength in quantifying total disease burden. Lastly, the use of GEE in our analysis to account for repeated measurements of cognition scores, as well as adjustment for various confounders including demographics, cardiovascular risk factors and MRI markers of cerebrovascular disease.

A main limitation of histogram analysis is the loss of topographic information. Regional information can be recovered if the histogram calculation is led by segmentation using anatomic landmarks [13]. In regards to methodological limitations, the findings of this study are restricted to elderly individuals with (V)CIND or NCI in memory clinic settings and may not be generalizable to older people in the general population. Though our study population consisted of individuals with cerebrovascular disease, we were unable to perform analysis separately for small and large vessel disease. This would be of interest for future studies to further delineate the effects of DTI on cognitive decline. There may have been selection bias introduced, whereby there might have been an underestimation of effects on cognition due to restricting analysis to NCI and CIND and excluding those with dementia. DTI measures should be interpreted as an indirect approximation to WM microstructural status [52]. Markers should not be used independently, where more than one modality might improve prediction of future dementia. Future studies should include the analysis of other DTI measures and tract specific analysis to further determine their relationship with cognitive decline.

For potential clinical applications, individuals with cerebral SVD would benefit greatly from the information on DTI measures, to predict severe sporadic SVD progression, which would likely lead to an eventual conversion to dementia [23]. In conclusion, this study has demonstrated the potential utility of summary statistics from DTI histogram analysis to detect subtle ischemic changes of NAWM. Our findings provide evidence that baseline DTI measures are associated with cognitive decline, suggesting the potential use of DTI as a pre-clinical marker in predicting the worsening of cognition in clinical trials.

Table 3
Association of baseline FA measures with cognitive scores over time.

FA Measures	Model I[a] β (95% CI)	*p*	Model II[b] β (95% CI)	*p*	Model III[c] β (95% CI)	*p*
Outcome: Global cognition z-score						
FA median[d]	0.45 (0.31,0.59)	<0.001	0.19 (0.05,0.32)	0.006	0.19 (0.04,0.33)	0.012
Baseline[e]	0.38 (0.22,0.53)	<0.001	0.11 (−0.03,0.25)	0.124	0.11 (−0.05,0.26)	0.169
Year 1[e]	0.52 (0.38,0.67)	<0.001	0.26 (0.12,0.40)	<0.001	0.26 (0.11,0.41)	0.001
Year 2[e]	0.49 (0.32,0.65)	<0.001	0.22 (0.08,0.37)	0.002	0.22 (0.07,0.37)	0.005
p for interaction	<0.001		<0.001		<0.001	
FA peak height[d]	−0.52 (−0.67,−0.37)	<0.001	−0.21 (−0.34,−0.08)	0.001	−0.22 (−0.35,−0.09)	0.001
Baseline[e]	−0.45 (−0.60,−0.29)	<0.001	−0.13 (−0.26,0.00)	0.052	−0.14 (−0.28,0.00)	0.054
Year 1[e]	−0.60 (−0.76,−0.45)	<0.001	−0.29 (−0.42,−0.16)	<0.001	−0.30 (−0.44,−0.16)	<0.001
Year 2[e]	−0.55 (−0.71,−0.39)	<0.001	−0.24 (−0.37,−0.10)	0.001	−0.24 (−0.38,−0.10)	0.001
p for interaction	<0.001		<0.001		<0.001	
Cognitive domains						
Outcome: Attention						
FA median[d]	0.09 (−0.03,0.20)	0.141	0.01 (−0.11,0.13)	0.814	0.04 (−0.08,0.16)	0.536
Baseline[e]	0.01 (−0.12,0.15)	0.857	−0.06 (−0.19,0.07)	0.367	−0.04 (−0.18,0.10)	0.610
Year 1[e]	0.15 (0.03,0.27)	0.017	0.07 (−0.05,0.20)	0.263	0.10 (−0.03,0.23)	0.127
Year 2[e]	0.10 (−0.04,0.24)	0.160	0.03 (−0.11,0.17)	0.692	0.05 (−0.10,0.20)	0.497
p for interaction	0.044		0.044		0.045	
FA peak height[d]	−0.13 (−0.25,−0.01)	0.039	−0.01 (−0.14,0.11)	0.825	−0.03 (−0.16,0.10)	0.614
Baseline[e]	−0.05 (−0.18,0.09)	0.481	0.06 (−0.07,0.20)	0.351	0.04 (−0.10,0.19)	0.541
Year 1[e]	−0.17 (−0.30,−0.05)	0.005	−0.06 (−0.19,0.07)	0.358	−0.08 (−0.22,0.05)	0.228
Year 2[e]	−0.16 (−0.31,−0.01)	0.037	−0.05 (−0.19,0.10)	0.538	−0.06 (−0.21,0.09)	0.414
p for interaction	0.027		0.027		0.029	
Outcome: Executive function						
FA median[d]	0.55 (0.39,0.71)	<0.001	0.25 (0.08,0.42)	0.005	0.24 (0.06,0.42)	0.009
Baseline[e]	0.48 (0.32,0.63)	<0.001	0.17 (−0.01,0.35)	0.058	0.16 (−0.02,0.35)	0.088
Year 1[e]	0.60 (0.43,0.77)	<0.001	0.30 (0.11,0.48)	0.002	0.29 (0.09, 0.48)	0.004
Year 2[e]	0.60 (0.41,0.79)	<0.001	0.30 (0.11,0.49)	0.002	0.29 (0.09,0.49)	0.004
p for interaction	0.026		0.026		0.025	
FA peak height[d]	−0.61 (−0.77,−0.46)	<0.001	−0.28 (−0.44,−0.12)	0.001	−0.29 (−0.46,−0.12)	0.001
Baseline[e]	−0.53 (−0.69,−0.37)	<0.001	−0.20 (−0.37,−0.03)	0.020	−0.21 (−0.38,−0.03)	0.019
Year 1[e]	−0.68 (−0.85,−0.50)	<0.001	−0.34 (−0.52,−0.17)	<0.001	−0.35 (−0.54,−0.16)	<0.001
Year 2[e]	−0.66 (−0.83,−0.48)	<0.001	−0.32 (−0.50,−0.15)	<0.001	−0.33 (−0.51,−0.15)	<0.001
p for interaction	0.013		0.013		0.013	
Outcome: Memory						
FA median[d]	0.36 (0.20,0.52)	<0.001	0.12 (−0.01,0.25)	0.062	0.09 (−0.05,0.23)	0.221
Baseline[e]	0.34 (0.20,0.48)	<0.001	0.06 (−0.08,0.19)	0.394	0.02 (−0.12,0.17)	0.744
Year 1[e]	0.45 (0.31,0.60)	<0.001	0.17 (0.04,0.30)	0.011	0.14 (−0.01,0.28)	0.062
Year 2[e]	0.45 (0.28,0.62)	<0.001	0.17 (0.02,0.32)	0.024	0.13 (−0.03,0.29)	0.101
p for interaction	0.014		0.014		0.017	
FA peak height[d]	−0.40 (−0.56,−0.23)	<0.001	−0.14 (−0.26,−0.03)	0.017	−0.13 (−0.26,−0.01)	0.037
p for interaction	0.068		0.068		0.081	
Outcome: Language						
FA median[d]	0.14 (−0.01,0.29)	0.066	0.01 (−0.15,0.16)	0.938	0.02 (−0.14,0.18)	0.784
p for interaction	0.191		0.191		0.188	
FA peak height[d]	−0.22 (−0.37,−0.07)	0.005	−0.06 (−0.22,0.11)	0.480	−0.08 (−0.25,0.09)	0.349
Baseline[e]	−0.12 (−0.29,0.05)	0.155	0.03 (−0.14,0.21)	0.700	0.01 (−0.18,0.20)	0.908
Year 1[e]	−0.35 (−0.53,−0.17)	<0.001	−0.19 (−0.39,0.00)	0.046	−0.22 (−0.42,−0.02)	0.030
Year 2[e]	−0.19 (−0.38,0.00)	0.050	−0.04 (−0.24,0.16)	0.718	−0.06 (−0.26,0.14)	0.550
p for interaction	0.013		0.013		0.013	
Outcome: Visuomotor speed						
FA median[d]	0.32 (0.21,0.44)	<0.001	0.11 (0.01,0.21)	0.025	0.10 (0.00,0.21)	0.050
Baseline[e]	0.25 (0.13,0.37)	<0.001	0.03 (−0.08,0.14)	0.568	0.02 (−0.10,0.14)	0.694
Year 1[e]	0.35 (0.23,0.46)	<0.001	0.13 (0.04,0.23)	0.007	0.12 (0.02,0.23)	0.017
Year 2[e]	0.36 (0.25,0.48)	<0.001	0.15 (0.05,0.25)	0.004	0.14 (0.03,0.25)	0.010
p for interaction	<0.001		<0.001		<0.001	
FA peak height[d]	−0.38 (−0.48,−0.27)	<0.001	−0.12 (−0.21,−0.03)	0.007	−0.12 (−0.21,−0.03)	0.012
Baseline[e]	−0.31 (−0.42,−0.20)	<0.001	−0.05 (−0.15,0.04)	0.263	−0.05 (−0.15,0.05)	0.320
Year 1[e]	−0.39 (−0.50,−0.29)	<0.001	−0.14 (−0.22,−0.05)	0.002	−0.13 (−0.22,−0.04)	0.004
Year 2[e]	−0.41 (−0.51,−0.31)	<0.001	−0.15 (−0.25,−0.06)	0.002	−0.15 (−0.25,−0.05)	0.002
p for interaction	0.001		0.001		<0.001	
Outcome: Visuospatial function						
FA median[d]	0.40 (0.26,0.53)	<0.001	0.30 (0.14,0.46)	<0.001	0.30 (0.13,0.46)	<0.001
p for interaction	0.932		0.932		0.893	
FA peak height[d]	−0.43 (−0.57,−0.28)	<0.001	−0.26 (−0.42,−0.11)	0.001	−0.26 (−0.42,−0.10)	0.001
p for interaction	0.548		0.548		0.499	

[a] Model I: adjusted for follow-up time.
[b] Model II: adjusted for Model I + demographic factors (age, sex, race, baseline diagnosis, education) and cardiovascular risk factors (smoking status, hypertension, hyperlipidemia, diabetes).
[c] Model III: adjusted for Model II + risk factors for cerebrovascular disease (white matter hyperintensities, number of lacunes, number of cerebral microbleeds, total brain volume).
[d] The beta-coefficients for baseline DTI measures in GEE analysis without the interaction terms between DTI measures and time in the model.

[e] The beta-coefficients for baseline DTI measures at each time point (Baseline, Year 1, Year 2) with the interaction terms (DTI measure and time) in the model.

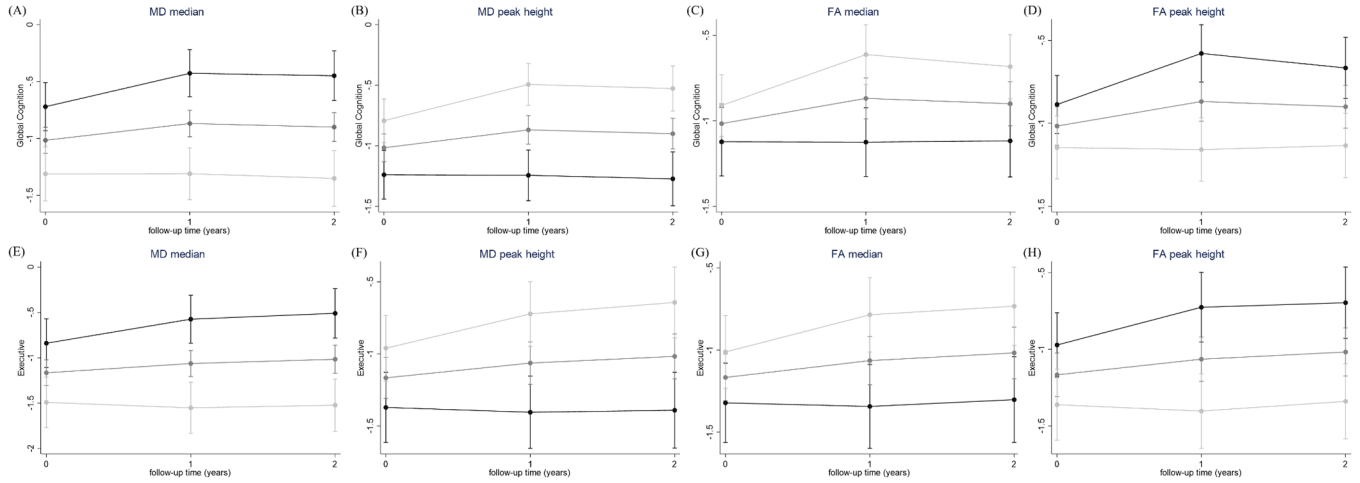

Fig. 2. DTI Histogram-derived measures and cognitive trajectories. Estimated marginal means of Global cognition z scores (A-D) and executive function z scores (E-H) of all patients from baseline to Year 2 follow-up are shown. Cognitive trajectories were plotted for patients at mean-1SD (black line), mean (gray line) and mean+1SD (light gray line) after adjustment for demographics, cardiovascular risk factors, MRI markers for cerebrovascular disease and interaction term (DTI measure with follow-up time). 95% confidence interval are represented as vertical lines.

Table 4
Ratio of absolute mean differences in cognitive scores for Year 2 to Year 0 with the same change in DTI measures and the same profile for the other covariates.

Cognitive z-scores	MD median	MD peak height	FA median	FA peak height
Global	1.54 (1.10,2.16) 0.013	1.68 (1.15,2.46) 0.007	2.03 (0.83,5.00) 0.122	1.74 (0.95,3.22) 0.075
Attention*	#	#	#	#
Executive function	1.58 (1.05,2.37) 0.029	1.84 (1.04,3.25) 0.036	1.81 (0.87,3.76) 0.113	1.62 (0.94,2.78) 0.081
Memory	1.87 (1.02,3.46) 0.044	2.13 (1.02,4.45) 0.044	#	-
Language	-	-	-	#
Visuomotor speed*	1.72 (1.12,2.64) 0.013	2.50 (1.03,6.08) 0.043	#	2.95 (0.68,12.78) 0.147
Visuospatial function	-	-	-	-

Values are presented as OR (95%CI), *p* values.
Estimates were adjusted for demographic factors (age, sex, race, baseline diagnosis, education), cardiovascular risk factors (smoking status, hypertension, hyperlipidemia, diabetes), risk factors for cerebrovascular disease (white matter hyperintensities, number of lacunes, number of cerebral microbleeds, total brain volume) and interaction term between DTI measure and follow-up.
#: For these cognitive z-score and DTI measure combinations, their DTI effects for each timepoint was non-significant (i.e., $p<0.05/12 = 0.004$ for domain-specific cognitive z-score, and $p<0.05$ for global z-score). Although some the combinations had wide 95%CIs, all had p-values > 0.05.
-: For these cognitive z-score and DTI measure combinations, their p-value for interaction were non-significant. Hence ratio is 1.

Data availability statement

Data can be obtained upon request. Requests should be directed towards the Memory, Aging and Cognition Center, which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

Declaration of Competing Interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2023.100174.

Appendix Table 1. Association of baseline DTI measures with cognitive decline

DTI Measures	Model I[a] OR (95% CI)	p	Model II[b] OR (95% CI)	p	Model III[c] OR (95% CI)	p
Outcome: Global cognition z-score						
MD median	1.58 (1.21,2.06)	0.001	1.26 (0.86,1.85)	0.239	1.33 (0.85,2.06)	0.213
MD peak height	0.62 (0.47,0.83)	0.001	0.73 (0.50,1.08)	0.120	0.70 (0.46,1.07)	0.096
FA median	0.70 (0.53,0.91)	0.008	0.86 (0.61,1.21)	0.389	0.86 (0.60,1.22)	0.392
FA peak height	1.42 (1.09,1.85)	0.009	1.12 (0.80,1.56)	0.514	1.15 (0.81,1.64)	0.442
Cognitive domains;						
Outcome: Attention						
MD median	1.33 (1.03,1.71)	0.030	1.11 (0.77,1.60)	0.578	1.09 (0.71,1.65)	0.704
MD peak height	0.86 (0.67,1.10)	0.237	1.10 (0.78,1.57)	0.580	1.14 (0.78,1.66)	0.499
FA median	0.88 (0.68,1.12)	0.301	1.06 (0.77,1.45)	0.723	1.10 (0.79,1.53)	0.583
FA peak height	1.15 (0.89,1.47)	0.277	0.97 (0.71,1.34)	0.872	0.96 (0.68,1.34)	0.801
Outcome: Executive function						
MD median	1.28 (0.98,1.65)	0.066	1.27 (0.87,1.86)	0.208	1.15 (0.75,1.78)	0.512
MD peak height	0.82 (0.63,1.07)	0.144	0.84 (0.59,1.22)	0.368	0.92 (0.62,1.36)	0.662
FA median	0.85 (0.65,1.10)	0.212	0.90 (0.65,1.25)	0.531	0.97 (0.69,1.37)	0.868
FA peak height	1.13 (0.87,1.46)	0.368	1.04 (0.75,1.44)	0.820	0.97 (0.68,1.37)	0.863
Outcome: Memory						
MD median	1.61 (1.22,2.11)	0.001	1.22 (0.82,1.81)	0.331	1.17 (0.74,1.85)	0.495
MD peak height	0.57 (0.43,0.77)	<0.001	0.63 (0.41,0.96)	0.033	0.62 (0.39,0.97)	0.037
FA median	0.70 (0.53,0.93)	0.012	0.90 (0.63,1.28)	0.553	0.93 (0.64,1.35)	0.706
FA peak height	1.46 (1.11,1.91)	0.006	1.17 (0.83,1.66)	0.366	1.16 (0.80,1.68)	0.423
Outcome: Language						
MD median	1.29 (0.91,1.81)	0.149	1.07 (0.63,1.82)	0.806	1.54 (0.81,2.92)	0.184
MD peak height	0.66 (0.45,0.97)	0.035	0.61 (0.35,1.08)	0.089	0.43 (0.22,0.83)	0.012
FA median	0.75 (0.52,1.09)	0.134	0.81 (0.50,1.31)	0.389	0.68 (0.40,1.16)	0.157
FA peak height	1.53 (1.08,2.18)	0.017	1.44 (0.92,2.25)	0.107	1.65 (1.01,2.67)	0.044
Outcome: Visuomotor speed						
MD median	1.76 (1.33,2.31)	<0.001	1.73 (1.17,2.55)	0.006	1.81 (1.17,2.81)	0.008
MD peak height	0.59 (0.44,0.78)	<0.001	0.66 (0.45,0.96)	0.030	0.67 (0.45,1.00)	0.051
FA median	0.57 (0.43,0.75)	<0.001	0.60 (0.43,0.85)	0.004	0.58 (0.41,0.84)	0.003
FA peak height	1.57 (1.20,2.05)	0.001	1.42 (1.02,1.98)	0.038	1.44 (1.02,2.06)	0.041
Outcome: Visuospatial function						
MD median	0.92 (0.72,1.18)	0.503	0.86 (0.60,1.24)	0.430	0.68 (0.45,1.03)	0.071
MD peak height	1.04 (0.81,1.33)	0.774	1.06 (0.75,1.50)	0.727	1.20 (0.83,1.74)	0.325
FA median	1.10 (0.86,1.41)	0.437	1.16 (0.85,1.58)	0.355	1.28 (0.92,1.77)	0.146
FA peak height	0.82 (0.64,1.05)	0.121	0.76 (0.55,1.04)	0.088	0.69 (0.49,0.98)	0.038

Logistic regression was performed with outcome binarised on the difference of cognition scores at Year 2 and at baseline, where a negative difference is considered an event.

[a] Model I: Unadjusted.

[b] Model II: Model I + adjusted for demographic factors (age, sex, race, baseline diagnosis, education) and cardiovascular risk factors (smoking status, hypertension, hyperlipidemia, diabetes).

[c] Model III: adjusted for Model II + risk factors for cerebrovascular disease (white matter hyperintensities, number of lacunes, number of cerebral microbleeds, total brain volume).

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