



Five-Year Lower Extremity Function is Associated with White Matter Abnormality in Older Adults

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OBJECTIVE: To explore associations between changes of lower extremity function (LEF) parameters over a 5-year period and diffusion tensor imaging (DTI) parameters of white matter tracts among community-dwelling older adults.

DESIGN: A secondary analysis on image and physical function data collected from the Multidomain Alzheimer's Preventive Trial (MAPT).

PARTICIPANTS: 208 older adults (aged 75 ± 4 years, with spontaneous memory complaint or limited instrumental daily living activity or slow gait speed, 60% female) of the MAPT-magnetic resonance imaging (MRI) ancillary study. The time interval between a participant's enrolment and MRI scan was on average 110 ± 97 days.

MEASUREMENTS: Forty-eight white matter tracts (WMTs) were measured. LEF parameters (measured after the MRI scan) were assessed as the short physical performance battery (SPPB) score, gait speed, and chair stands time over a 5-year period. Mixed-effects models were performed to explore the associations between baseline DTI values and the progression of LEF parameters. Bonferroni correction was applied for multiple comparison correction.

RESULTS: The progression of LEF was associated with 35 baseline DTI parameters from 24 WMTs. Higher baseline DTI parameter values were related to more decreases in SPPB score and gait speed, and greater increases in chair

stands time. Bilateral uncinat fasciculus was associated with all LEF parameters. Other WMTs in cingulum, cerebral and cerebellar peduncle, internal capsule, and corpus callosum also showed close connections with LEF changes.

CONCLUSIONS: Our findings show that DTI parameters of some WMTs are associated with the 5-year decline in LEF, suggesting that alterations in WMT integrity (evaluated by DTI parameters) might be used to explore potential causes of impaired mobility in older adults when no clear explanations can be found. *J Am Geriatr Soc* 00:1-8, 2021.

Keywords: older adults; lower extremity function; diffusion tensor imaging; white matter

INTRODUCTION

Decreased lower extremity function (LEF) is one of the overt characteristics during aging and it has been closely linked to disability^{1,2} and mortality.³⁻⁵ Changes of LEF are multifactorial, yet the relationship with the brain structure remains unknown. White matter lesion is one of the main brain structural changes during aging and appears to be part of the physiopathologies of mobility disorders in older adults through a possible connection with cognitive decline and other risk factors.^{6,7}

The integrities of white matter tracts (WMTs) can be evaluated by diffusion tensor imaging (DTI). Decreased white matter integrity and increased myelin damage, which are commonly found during the aging process, have been associated with increased axial (AxD), mean (MD), and radial diffusivity (RD) values as well as decreased fractional anisotropy (FA) values.^{8,9} DTI parameters of multiple WMTs have been connected to abnormal gait pattern¹⁰⁻¹⁵ and chair stands performance.¹⁶ Yet, most of the current studies on DTI of WMTs and LEF performances are cross-sectional, and the relationship between WMT integrities

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and the evolution of physical performance still remains unclear. A DTI-based estimation of over time changes in LEF will be helpful to better understand aging-related LEF decline as a function of WMT integrity. Moreover, considering that LEF, especially gait speed, is determined by complex movements which involve neuromuscular coordination, aging-related declines in physical functions are not only associated with muscle strength¹⁷ and bone status,¹⁸ but with central nervous system as well.^{19,20} It is, thus, possible that in clinical practice, when there is impaired mobility in older adults but no muscle or bone cause is found, changes in central nervous system might also be a potential explanation.

Therefore, this study aimed at examining the association between the evolution of LEF over a 5-year period and baseline DTI parameters in WMTs among community-dwelling older adults. We hypothesized that higher baseline MD, AxD, and RD levels and lower FA levels might be associated with higher impairment in LEF over time.

METHODS

This is a post hoc investigation using clinical and MRI data from the Multidomain Alzheimer's Preventive Trial-magnetic resonance imaging ancillary study (MAPT-MRI). The objectives of the parent MAPT randomized controlled clinical trial (ClinicalTrials.gov (NCT00672685)) were to explore the effects of multidomain interventions (physical and nutritional counseling and cognitive training) and omega-3 supplementation, combined or alone, on changes of cognitive functions in older adults over a 3-year period.²¹ The MAPT study, including the MRI ancillary investigations, was approved by the ethics committee in Toulouse (CPP SOOM II).

Study Population

Participants ($n = 1,679$, aged 70 years and older) were recruited in MAPT with any of the following criteria: (1) expressing spontaneous memory complaint, (2) having limitation in at least one instrumental activity of daily living, and (3) demonstrating slow gait speed (i.e., lower than 0.8 m/s). Those participants underwent cognitive and functional assessments, including measurements of LEF, at baseline, the 6th month and each year during 5 years.

The MAPT sample size of 1,679 was determined as described in Andrieu et al.²² The present study was a secondary analysis on the MAPT study and we included 208 MAPT participants (aged 75 ± 4 years), who performed the baseline MRI scans and for whom DTI parameters were available and exploitable (Figure 1).

Main Outcome Measure

The LEF was assessed using the short physical performance battery (SPPB),³ which comprises three performance-based physical tests: a 4-m walking test at usual pace, a timed 5-repetition chair stands at maximum speed, and three standing balance tests with increased difficulties.³ Each performance has a score of 0 to 4 with a higher score representing a better performance. A final SPPB score was calculated by summing the score of each performance.

Key Points

- 35 baseline diffusion tensor imaging parameters from 24 white matter tracts (WMTs) were associated with lower extremity function (LEF) changes in older adults over a 5-year period.

Why Does this Paper Matter?

Our results enrich the understanding of ageing-related LEF decline from the aspect of WMTs, suggesting that alterations in WMT integrity might be a possible explanation of impaired mobility in older adults.

We used three outcome measures for the LEF parameters: the SPPB total score (from 0 to 12, higher is better), 4-m usual gait speed (in m/s), and the 5-repetition chair stands performance (in seconds). Moreover, only data of these three outcomes assessed after the MRI scan were used in our analysis. Time intervals (TIs, in days) between the first MRI scan and SPPB measurements over the 5-year period were calculated and used as covariates.

MRI Scans and DTI Analyses

In the MAPT study, MRI scans were conducted in nine centers (Toulouse, Bordeaux, Montpellier, Limoges, Dijon, Lyon, Nice, Foix, and Tarbes) using a standardized protocol which included a scan with required sequences (3DT1, T2FLAIR, T2TSE, and T2GRE) and optional sequences of resting state f-MRI and DTI. Each center was asked to test the protocols on one volunteer before the MRI assessments on MAPT participants and quality controls on 3DT1 acquisition were performed. The total intracranial volume (TIV) was computed based on the baseline 3DT1-weighted sequence using the SPM5 toolbox (fil.ion.ucl.ac.uk/spm).

In the DTI analysis, MRI images obtained from four centers (Toulouse, Bordeaux, Montpellier, and Nice) were available for analysis. Image processing was performed following the standard ENIGMA DTI protocol (<http://enigma.ini.usc.edu/protocols/dti-protocols>). Diffusion images were first preprocessed using the BrainSuite Diffusion Pipeline (version: 2017a) to correct susceptibility distortions. The FSL eddy tool (FSL version: 5.0.11)²³ was used to correct eddy current-induced distortions and subject movements. FreeSurfer (version: 6.0.0) and FSL bet2 (FSL version: 5.0.11) were used to compute anatomical and diffusion volume brain masks, respectively. Tract-based spatial statistics analysis²⁴ was then performed using the ENIGMA FA and FA skeleton template (downloadable at <http://enigma.ini.usc.edu/wp-content/uploads/2013/02/enigmaDTI.zip>). DTI metrics were projected on the template skeleton and the WMTs were labeled using the JHU ICBM-DTI-81 white-matter atlas provided with FSL (version: 5.0.11).²⁵ DTI parameters of FA, MD, AxD, and RD were analyzed over all the 48 WMTs (21 tracts with bilateral values (right and left sides, separately) and 6 tracts with singular values). All DTI parameters of WMTs, except for FA which is

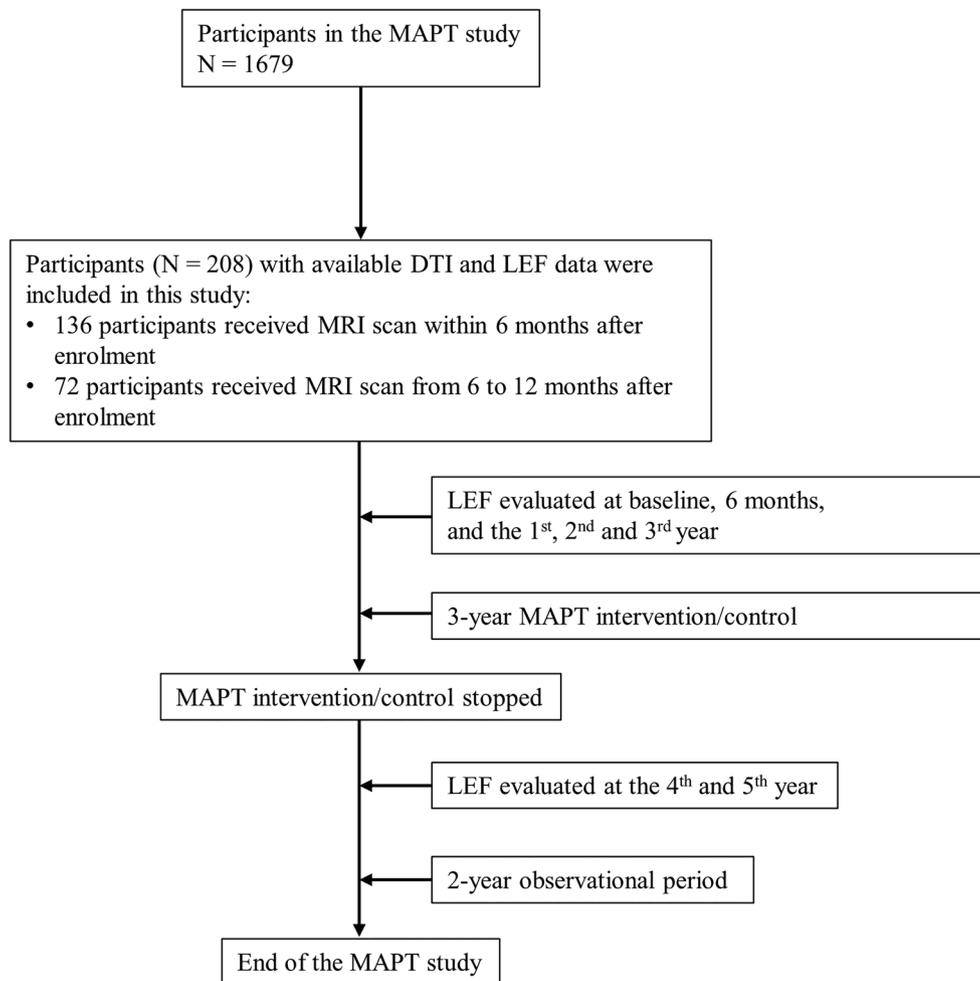


Figure 1. Flowchart of test process.

dimensionless, were continuous variables measured in unit of mm^2/s .

Covariates

Our analyses were controlled for sex, age, body mass index, MAPT group allocation, vascular risk (participants were assumed to have a vascular risk if they had any of the following conditions: diabetes mellitus, hypertension, or hypercholesterolemia; dichotomous variable), TIs between the first MRI scan and SPPB measurements at each time point, and TIV.

Statistics

Descriptive data were presented as mean \pm standard deviation or absolute numbers and percentage, as appropriate. To analyze associations between baseline DTI parameters and each LEF parameter over the 5-year period, mixed-effects models were used. Specifically, the LEF parameters at each time point were used as dependent variables, and the baseline DTI-by-TI interactions were used as independent variables. Models were controlled for the covariates specified above. A random effect of participants and a random slope of TIs were assumed with unstructured covariance structure. To further adjust for the analyses on MRI sites, sensitivity analyses were

also performed using mixed-effects models with random effects in different MRI sites and participants nested within each MRI site. Bonferroni correction was used to correct *P*-values of DTI-by-TI interactions within each of the four DTI parameters (FA, MD, AxD, and RD). A corrected *P*-value of smaller than .05 was regarded as significant.

Since an SPPB change of .5 point was regarded as a small meaningful change (with an effect size of .2),²⁶ a time window was calculated based on the mean value of each significant DTI parameter to estimate the time (in days) it would take for a meaningful decline to take place in our participants. The calculation is presented as:

$$\text{Time} = \frac{.5}{-\text{Coef}_{\text{TI}} - \text{Coef}_{\text{Interact}} \times \text{DTI}_{\text{mean}}},$$

where DTI_{mean} is the mean value of corresponding DTI, Coef_{TI} is the coefficient of TI obtained from the mixed-effects models, and $\text{Coef}_{\text{Interact}}$ is the coefficient of DTI-by-TI interaction.

All analyses were performed using SAS 9.4.

Data Availability

All data will be shared after ethics approval if requested by other researchers for purposes of replicating the results.

Table 1. Characteristics of Participants in the Study

Parameters	Sample Size	Values
Age (year), mean (SD)	208	75 (4)
Female, n (%)	208	124 (60%)
Vascular risk, n (%)	208	148 (72%)
Baseline MRI scan within the first 6 months after then enrolment, n (%)	208	136 (65%)
Baseline BMI (kg/m ²), mean (SD)	206	25.6 (3.8)
Baseline TIV (cm ³), mean (SD)	208	1,411.2 (135.8)
Baseline SPPB score, mean (SD)	203	10.7 (1.7)
Baseline gait speed (m/s), mean (SD)	206	1.0 (0.2)
Baseline chair stands performance (s), mean (SD)	191	11.4 (3.1)
Baseline MMSE, mean (SD)	208	28.2 (1.5)
Education level		
No primary education	204	18 (9%)
Primary school level	204	26 (13%)
Secondary school level	204	66 (32%)
Highschool level	204	33 (16%)
University level	204	61 (30%)
Disease condition		
Asthma or COPD, n (%)	208	11 (5%)
Stroke, n (%)	208	3 (1%)
Ischemic heart disease, n (%)	208	14 (7%)
Diabetes mellitus, n (%)	208	18 (9%)
Hypertension, n (%)	208	100 (48%)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; MMSE, Mini-Mental State Examination, a 30-point questionnaire-based measurement on cognitive impairment; MRI, magnetic resonance imaging; SPPB, short physical performance battery; TIV, total intracranial volume which was computed based on the baseline 3DT1-weighted sequence using the SPM5 toolbox; vascular risk, a dichotomous variable that was recorded as "positive" if participants had any of the following conditions, diabetes mellitus, hypertension, or hypercholesterolemia.

RESULTS

Characteristics of Participants

The 208 participants in this study had an average age of 75 years and 60% of them were female (Table 1). Almost three quarters of these participants presented at least one

vascular risk. 65% of the 208 participants (n = 136) completed the baseline MRI scan within the first 6 months after the enrolment in the study; the remaining participants (35%, n = 72) completed the MRI scan within 12 months. The average TI between a participant's enrolment and the baseline MRI scan was 110 ± 97 days. Descriptive data of physical performance over the 5-year period are presented in Supplementary Table S1.

Longitudinal Associations between LEF Parameters and Baseline DTI Values

Only two DTI parameters were associated with the three LEF parameters, all together, over the 5-year period: the RD of the left uncinate fasciculus (UNC_L_RD) (SPPB score $P = .04$, gait speed $P = .02$, chair stands time $P = .04$) and the MD of the right uncinate fasciculus (UNC_R_MD) (SPPB score $P < .001$, gait speed $P = .002$, chair stands time $P = .01$). The RD of the right uncinate fasciculus (UNC_R_RD) was associated with the SPPB score and the chair stands time (SPPB score $P = .002$, chair stands time $P = .009$). Sensitivity analyses by mixed-effects models with participants nested in different MRI sites showed that UNC was the only WMT that was associated with LEF. The RD and MD of UNC demonstrated negative associations with over time change of SPPB score (RD $P = .017$, MD $P = .007$, Supplementary Table S2).

Eight DTI parameters from four WMTs were negatively associated with the SPPB scores (Supplementary Table S3). Inverse relationships were also found between 33 baseline DTI parameters from 24 WMTs with gait speed (Supplementary Table S4), and 3 baseline DTI parameters from 2 WMTs were positively associated with chair stands times (Supplementary Table S5) over the 5-year period. This indicated that in a fixed time period, participants with higher baseline AxD, MD, or RD values, which were usually associated with damaged white matter structure, would experience more decreases in SPPB score and gait speed, and more increases in chair stands time. Moreover, participants with higher baseline FA values of five WMTs also demonstrated more decreases in gait speed (Supplementary Table S4).

Given the mean values of significant DTIs among the participants and the coefficients in mixed-effects models, it would take 12 ± 0.8 years to identify a meaningful .5-point decline in SPPB (Table 2).

Table 2. Estimated Time for a Meaningful 0.5 Score Decline in SPPB (Based on Mean DTI Values)

DTI Parameters	Mean Value (Baseline DTI)	Coefficient (Time)	Coefficient (Baseline DTI × Time)	Estimated Time (Days)	Estimated Time (Years)
SCC_AxD	0.0016	0.0121	-7.4518	3,518	10
SLF_R_AxD	0.0012	0.0088	-7.5780	4,366	12
SLF_R_MD	0.0008	0.0068	-9.1834	4,475	12
UNC_L_MD	0.0008	0.0030	-4.0646	4,141	11
UNC_L_RD	0.0006	0.0024	-4.5926	4,102	11
UNC_R_AxD	0.0012	0.0047	-3.8935	4,447	12
UNC_R_MD	0.0008	0.0057	-7.5839	4,343	12
UNC_R_RD	0.0005	0.0034	-6.6758	4,249	12

Note: DTI annotations are attached in Supplementary Table S8.

DTI Values of WMTs Reported in Previous Studies

Previous studies have reported the association between LEF performances and multiple DTI parameters. We further complement this research on WMTs that are shared in at least two published studies (Supplementary Table S6). Among those shared WMTs, baseline AxD values in the splenium of corpus callosum (SCC) and the SLF were negatively associated with SPPB evolution. AxD values in the cingulum (cingulate gyrus) (CGC), the genu of corpus callosum (GCC), the SCC, the SLF and the sagittal stratum (SS), and MD values of the CGC and the SS were negatively associated with gait speed changes over time (Supplementary Table S7).

DISCUSSION

To the best of our knowledge, this is the first study that examined associations between DTI parameters and the progression of LEF, which was assessed by three complementary and validated parameters (the SPPB score, the gait speed and the chair stands time) over a 5-year period among older adults. We found that all the three parameters that characterized the LEF were associated with only two DTI parameters on the UNC: the RD of the left UNC and the MD of the right UNC, implying that the UNC tract might be closely associated with the LEF. Additionally, specific DTI parameters were negatively associated with SPPB score and gait speed, and positively associated with chair stands time, indicating that worse initial WMT structure may predict decline in physical performance over time. We further estimated a delay of 12 years to observe a reduction of .5 points of the SPPB total score. Although the SPPB is scored by one point, a decline of .5 point is considered as clinically relevant.²⁶ These changes in the DTI parameters appeared to be very early in the time course of motor dysfunctions.

Previous studies about WMTs DTI parameters and LEF performances were mainly cross-sectional analyses on gait patterns and only focused on the FA parameter, which is an indicator of the WMT microstructure change.⁸ Bruijn et al.¹² compared the gait data between young and older adults and found that lower FA value in the left SLF was associated with smaller step widths and weaker stability. Tian et al.¹⁴ analyzed the walking variability in older adults and reported that FA values of the SLF and the UNC were reversely associated with mean lap time in fast walking. Recent studies on other DTI parameters (MD, AxD, and RD) have identified more WMTs, such as cingulum (cingulate gyrus),¹⁰ cerebral peduncle,¹⁰ posterior corona radiata,¹¹ posterior limb of internal capsule,¹⁰ and splenium of corpus callosum,¹¹ to be closely associated with gait performance. In consistence with previous findings, all these WMTs demonstrated close associations the evolution of gait speed in our results. Although other tracts such as corticospinal tract (CST),¹² anterior thalamic radiation^{12,15} and anterior corona radiata^{14,27} were also identified in previous studies, none of those tracts were found with significance in our results.

In respect of chair stands performance, Demnitz et al.¹⁶ studied 387 adults (mean age 69 years) and reported that decreased RD and AxD values in bilateral anterior corona radiata and the genu of corpus callosum were associated

with better performance (shorter time) in the chair stands test. None of these tracts were connected with chair stands time in our population. Instead, the RD and MD values of bilateral UNC were identified. The UNC is a long-range association fiber connecting the frontal and temporal lobes, and it has been linked with episodic memory functions. Dysfunctions of the tract may cause cognitive problems and disrupt the acquisition of certain types of learning and memory such as reversal learning, semantic memory and social-emotional processing.²⁸ Therefore, the identification of UNC might be related to the fact that our participants were older adults with clinical frailty criteria defined as at-risk to develop cognitive decline due to the presence of a slowing of the gait speed or a memory cognitive complaint without dementia. Since the MD is sensitive to cellularity, edema, and necrosis, and the RD is associated with demyelination and diameter or density changes in axonal,⁸ our results indicated a possible relationship between decreased chair stands performance and declined learning and memory abilities reflected by alterations in corresponding WMTs.

Besides analysis on gait speed and chair stands time, our study also examined DTI parameters with the SPPB score, which has never been reported before. Negative associations between SPPB score and AxD, MD, and RD values of the SCC, the SLF and the UNC have been identified in our results. After adjusting for the analyses on different MRI sites, the UNC was still significantly associated with over time changes of SPPB score. The SCC is the posterior part of the corpus callosum and consists of forceps major, which connects the occipital lobes. Clinical studies have found that patients with SCC lesions demonstrate multiple memory and motor control impairments such as confusion, ataxia, seizure and increased muscle tones.^{29,30} The SLF consists of four components, among which the dorsal component (SLF I) connects the supplementary motor cortex and the ventral component (SLF III) terminates in the ventral premotor and prefrontal regions. Therefore, the SLF is believed to be associated with working memory and motor regulation.³¹ Since the DTI parameter AxD is indicative of a broad range of white matter changes and axonal injuries,³²⁻³⁵ the negative associations between the AxD values of the SCC and the SLF with the evolution of physical function in a later time not only indicates continuous neural degeneration during aging but also implies that older adults with more SCC or SLF damage (higher AxD values) will experience a greater loss in LEF with the time.

Although higher FA values were associated with better white matter integrity,^{8,9} our results showed that higher FA values in five tracts (right cingulum (hippocampus), bilateral inferior, and superior cerebellar peduncle) were connected with a greater loss in gait speed. Notably, four of the identified tracts are from the cerebellum, a key player of the motor system, indicating that cerebellum might be a very special brain region where FA has to be interpreted differently. Yet, further studies are still needed to explore the relationship between cerebellum tracts and physical performance.

CST contains projection fibers originated from multiple motor-related cerebral areas such as the primary and secondary motor cortices. Yet, our results did not show any

association between the integrity of baseline CST and over time changes of physical performance. Such findings were consistent with previous DTI studies on gait speed and chair stands in older adults.¹⁰⁻¹⁶ A possible explanation might be that the CST integrity is quite stable across age span in non-dementia adults.^{36,37}

Our DTI results suggest that the microstructure characteristics of some brain regions that are often involved in memory function²⁸ can also be associated with alterations in physical performance. These results support the findings of Verwer et al.,³⁸ who reported that poorer physical performance was associated with abnormality of white matter network regardless of the presence of vascular brain injury. Our work adds insight into the mechanism of mobility decline in older adults from the WMT aspect. Although the clinical implications of these findings are still needed to be determined, it is possible to think that WMT integrity (evaluated by DTI parameters) might be used to explore potential causes of impaired mobility in older adults when no clear explanations can be found.

Despite the associations between baseline DTI parameters and over time changes of physical performance demonstrated in our results, it is important to note that this is a secondary analysis from a randomized controlled trial, which means the MAPT study was not designed to test the associations between WMT in the brain and physical performance deterioration. A well-powered study specifically designed to investigate the associations between WMTs and physical performance would help to confirm our findings. Moreover, the DTI assessments were performed at different time points over the first year of the study. The lack of longitudinal data of the DTI parameters also impeded us from exploring the association between changes in DTI and changes in physical performance. Even though we can expect similar findings on older adult populations similar to the MAPT study sample (in particular, community-dwelling older adults with spontaneous memory complaint), caution must be taken when generalizing our findings to other populations.

To conclude, the current study analyzed associations between DTI parameters in 48 WMTs and a 5-year evolution of LEF in older adults. Thirty-five DTI parameters from 24 WMTs were closely connected to changes of SPPB scores, gait speed or chair stands time over the five-year period, and the MD and RD values in the UNC tract were significantly associated with all functional parameters. Our findings suggested that white matter lesions might partially explain mobility disorders in older adults and DTI parameters of WMTs related to learning, memory, or motor control might be able to predict physical performance declines in a later period. Further longitudinal studies on paired DTIs and physical performance data at each time point are still needed to elucidate the relationship between DTI changes and physical performance evolution in older adults.

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Conflict of Interest: The authors declare no conflicts of interest.

Author Contributions: Dr. Lingxiao He analyzed the data and drafted the manuscript. Dr. Philippe de Souto Barreto, Dr. Kelly Virecoulon Giudici, Dr. Audrey Gabelle, Dr. Jean-Fran ois Mangin and Ms. Lisa Perus interpreted the data and revised the manuscript for intellectual content. Dr. Yves Rolland designed the physical and nutritional intervention in the MAPT study and revised the manuscript for intellectual content. Dr. Bruno Vellas was the principal investigator and revised the manuscript for intellectual content.

Sponsor's Role: Sponsors had no role in the design, methods, subject recruitment, data collection, analysis and preparation of the paper.

APPENDIX A.

MAPT STUDY GROUP/DSA GROUP

The members of the MAPT/DSA study group are:

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1: Descriptive data of physical performance over the 5-year period.

Supplementary Table S2: DTI parameters of WMTs that showed significant DTI-by-time interaction with SPPB (Mixed-effects models adjusted for MRI sites).

Supplementary Table S3: DTI parameters of WMTs that showed significant DTI-by-time interaction with SPPB.

Supplementary Table S4: DTI parameters of WMTs that showed significant DTI-by-time interaction with gait speed.

Supplementary Table S5: DTI parameters of WMTs that showed significant DTI-by-time interaction with chair stands time.

Supplementary Table S6: Summary of previous studies on DTI parameters and lower extremity function (LEF).

Supplementary Table S7: Significant DTI parameters of WMTs shared in previous studies.

Supplementary Table S8: Abbreviations and annotations.