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Jérémy Raffin, Yves Rolland, Lingxiao He, Lisa Perus, Jean-François Mangin, et al.. Cross-sectional and longitudinal interaction effects of physical activity and APOE- ϵ 4 on white matter integrity in older adults: The MAPT study. *Maturitas*, 2021, 152, pp.10-19. 10.1016/j.maturitas.2021.06.010 . hal-04506396

HAL Id: hal-04506396

<https://ut3-toulouseinp.hal.science/hal-04506396>

Submitted on 22 Jul 2024

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Cross-sectional and longitudinal interaction effects of physical activity and *APOE-ε4* on white matter integrity in older adults: the MAPT study

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ABSTRACT¹

Background: Physical activity (PA) has been shown to modulate the detrimental effect of carrying the apolipoprotein-E epsilon 4 (*APOE-ε4*) allele on brain structure. However, the current literature mainly provides cross-sectional data, and longitudinal studies investigating the interaction between genotype and PA on white matter (WM) integrity are lacking.

Objectives: We investigated both the cross-sectional and the longitudinal interactive effects of *APOE-ε4* and PA on WM integrity in older adults.

Methods: Fractional anisotropy, as well as axial, radial, and mean diffusivity, extracted from brain diffusion tensor imaging (DTI) were used to assess WM integrity in non-demented older adults. They were categorized according to their *APOE-ε4* status (carriers vs. non-carriers), and their level of total (TPA), moderate to vigorous (MVPA) and light (LPA) PA were assessed using a questionnaire. Mixed model regressions were performed to test the interactive effects of *APOE-ε4* status and PA on WM integrity at baseline and over a 3-year follow-up.

Results: 190 subjects with a mean age 74.5 years (SD = 3.9) were examined. Despite a lack of cross-sectional associations, sensitivity analyses revealed that, in the carrier group only, higher levels of LPA, but not MVPA, were mainly associated with higher axial and mean diffusivity values over time.

Conclusions: This study partially confirms the previously reported interactive associations between PA, *APOE-ε4* genotype and WM integrity, supporting the hypothesis that PA may protect against fiber loss in WM tracts containing crossing fibers. Future studies assessing sedentary behaviors in addition to PA could bring relevant contributions to the field.

Clinical trial registration number from ClinicalTrials.gov: NCT00672685

¹ ApoE-ε4: Apolipoprotein-E epsilon 4; ROI: Region of Interest; ApoE-ε4: Apolipoprotein-E epsilon 4; WM: White matter; CG: Cingular gyrus, CH: Cingular hippocampus, SLF: Superior longitudinal fasciculus, Fx: Fornix Stria terminalis, SS: Sagittal stratum; ALIC: Anterior Limb of the Internal Capsule, ACR: Anterior corona radiata; PCR: Posterior Corona radiata; SCR: Superior Corona Radiata; UF: Uncinate Fasciculus; CSp: Corticospinal tract; InfCP: Inferior Cerebellar Peduncle; MidCP: Middle Cerebellar Peduncle; SupCP: Superior Cerebellar Peduncle; PonCro: Pontine crossing tract; BDC: Body of corpus callosum; GCC: Genu of corpus callosum; SCC: Splenium of corpus callosum; CP: Cerebral Peduncle; PLIC: Posterior limb of internal capsule; RIC: Retrolenticular part of internal capsule L: left; R: Right; PA: Physical activity; MET: Metabolic equivalent task.

Keywords: Physical exercise, brain structure, genotype

1. Introduction

Brain white matter (WM) deterioration is a well-known marker of cerebral aging [1] which can be assessed through diffusion tensor imaging (DTI), the most widely used technique for measuring the microstructural integrity of WM fiber tracts [2,3]. DTI metrics include fractional anisotropy (FA), as well as axial (AxD), radial (RD) and mean diffusivity (MD). FA and MD are overall indicators of WM tract integrity, with high FA and low MD values indicating high WM integrity [4]. AxD and RD respectively reflect the diffusivity along and perpendicular to the main axis of the WM tracts [4]. The former typically represents axonal integrity while the latter characterizes myelin damages. DTI-metrics values can also be affected by macrostructural factors such as changes in fiber alignment [5,6] or the presence of crossing fibers [7,8]. Cross-sectional studies reported an overall age-related pattern characterized by a decrease in FA and AxD along with an increase in RD and MD, although both increases and decreases in AxD have been documented [6]. This detrimental effect observed during aging on brain structure may be worsened by genetic susceptibility such as carrying the apolipoprotein-E epsilon 4 (*APOE-ε4*) allele [9–11], although its impact on WM integrity remains discussed [9].

Physical activity (PA) represents a major tool to counteract the deleterious effects of aging on brain, and has been shown to be particularly effective in at-risk populations such as *APOE-ε4* carriers. Cross-sectional studies have demonstrated that older *APOE-ε4* carriers who remain physically active do not have lower scores of cognitive performance [12], higher load of amyloid deposition [13], or worse brain function [14] than non-carriers, whereas sedentary carriers do. Previous researches have also suggested a positive effect of PA on DTI metrics, that is, higher values of FA [15] and lower values of RD and MD [15–17]; however, most of these studies were cross-sectional and did not take *APOE-ε4* genotype into consideration. A cross-sectional study [18] testing the association of the PA-by-*APOE-ε4* interaction with white matter DTI-derived measures found paradoxical results. While *APOE-ε4*

non-carriers with high PA levels had higher FA and lower MD and RD, which are good and expected outcomes, in *APOE-ε4* carriers, high PA was related with lower FA and higher MD and RD, which generally indicates WM microstructure impairment. Examining the relationships between PA-*APOE-ε4* status and the overtime changes of DTI parameters will enrich the understanding of the PA-*APOE-ε4*-related beneficial effects on cognitive decline [12] and dementia [19].

In this study, we investigated the associations of *APOE-ε4* genotype-by-PA interaction with both cross-sectional and longitudinal WM integrity in community-dwelling older adults free of dementia. We hypothesized that PA would modulate the effect of genotype susceptibility on WM microstructure and that low active people would experience faster WM structural changes than their active peers, regardless of their *APOE-ε4* status. We further expected that the effect of PA would be greater in *APOE-ε4* carriers compared with non-carriers.

2. Methods

This study used DTI data from the large-scale multicenter 3-year randomized placebo controlled Multidomain Alzheimer's Preventive Trial (MAPT) Study (clinicaltrials.gov; NCT00672685). The MAPT Study aimed to assess the efficacy of isolated omega-3 polyunsaturated fatty acid (PUFA) supplementation, isolated multidomain intervention (physical activity and nutritional counseling, and cognitive stimulation), or their combination compared to placebo on cognitive function in older adults. The results demonstrated no significant effects of any of the intervention on cognitive function [20]. In addition, the MAPT intervention demonstrated favorable effects on PA levels during the first 6 months of the follow-up and limited the decline of PA levels over the long term [21]. Furthermore, the relationships between PA level and WM integrity in the MAPT population were previously investigated without, however, taking *APOE-ε4* genotype into consideration. The authors reported faster overtime alterations of WM integrity in the uncinat fasciculus only [16]. Brain imaging data were obtained from the magnetic resonance imaging (MRI) substudy of MAPT which was approved by the ethical committee in Toulouse (CPP SOOM II). All participants provided written informed consent.

2.1. Study population

Subjects of the MAPT study (n=1679) were non-demented community-dwelling people aged 70 years and above, and having at least one of the following criteria: spontaneous memory complaint, slow gait speed (≤ 0.8 m/s), and limitation in one instrumental activity of daily living. Exclusion criteria were: mini mental state examination (MMSE) score lower than 24, diagnosed dementia, difficulties in basic activity of daily living, or taking polyunsaturated fatty acid supplementation. All MAPT participants who underwent a MRI measurement, as well as *APOE* genotyping and PA assessment, were included in the present work.

2.2. MRI acquisition and analyses

In this study, MRI was used for DTI metrics and white matter hyperintensities (WMH) volume measurements. Participants underwent their first MRI assessment within the first year of their enrollment in the MAPT study, and follow-up exams were performed at 3 years. Volunteers underwent a standardized MRI procedure including DTI sequences from 3 centers (Bordeaux, Montpellier, Toulouse). Certificates of quality were provided by the MRI coordinating center (CATI and Cogimage). The standard ENIGMA DTI protocol (available online at <http://enigma.ini.usc.edu/protocols/dti-protocols/>) was used to extract DTI values. Images artifacts were first corrected using Brainsuite software (version 2017a, <http://brainsuite.org/>) for susceptibility correction and FSL 5.0.11 eddy tool [22] for subject's movements and eddy currents. Anatomical and diffusion volume brain masks used during preprocessing were respectively computed using FreeSurfer (version 6.0.0) and FSL bet2 tools, and FA brain images were generated using FSL dtifit tool. Tract based spatial statistics (TBSS) [23] analyses were applied, first to register participants FA brain images to ENIGMA-DTI FA template, and then to project participants FA on ENIGMA-DTI FA skeleton (both templates are available at <http://enigma.ini.usc.edu/wp-content/uploads/2013/02/enigmaDTI.zip>). Individual FA were then intersected with the John Hopkins University (JHU) white matter parcellation atlas [3] and FA values were averaged over each region of interest (ROI) of the atlas. The other diffusivity metrics such as AxD, MD, and RD were also derived

for each ROI, using the protocol specifications for non-FA images. Measurements procedures of WMH have been described elsewhere [24].

2.3. Outcome measure

Baseline and the overtime changes of DTI indices over the three years of the MAPT intervention were the main outcome measures of the present study. Due to the hypothesis-driven nature of this work, a ROI-based analyses approach was preferred over whole brain tract analyses [25] because interactions between PA and genotype were expected only in some specific WM tracts, those containing large amounts of crossing fibers, as reported in previous literature [18]. Therefore, based on previous literature reporting significant PA by *APOE-ε4* genotype interactions [18], we defined FA, AxD, RD and MD from 18 brain regions as the regions of primary interest: bilateral cingulum (cingulate gyrus), bilateral cingulum-hippocampal projection hippocampus, bilateral superior longitudinal fasciculus, bilateral fornix (cres)/stria terminalis, bilateral sagittal stratum, bilateral anterior limb of internal capsule, and bilateral anterior, posterior, and superior corona radiata. Additionally, we performed exploratory analyses on other 19 brain regions: bilateral uncinate fasciculus, middle cerebellar peduncle, bilateral superior and inferior cerebellar peduncles, pontine crossing tract, bilateral corticospinal tract, body, genu and splenium of the corpus callosum, bilateral cerebral peduncle, bilateral posterior limb of the internal capsule and bilateral retrolenticular part of the internal capsule.

2.4. Physical activity assessment

Participants' PA level was assessed at baseline and after the 3-year follow-up using the short form of the Minnesota Leisure Time Activities questionnaire [26,27], which asks about the duration and the frequency of leisure time and household physical activities performed during the past two weeks. The total weekly PA (TPA) volume was calculated and reported in metabolic equivalent task (MET) minutes per week (MET-min/week). This unit was preferred over the activity metabolic index (AMI) provided by the Minnesota questionnaire in order to facilitate the understanding, the generalization, and the comparison of the PA volumes of our subject sample with other studies and to put it in the context of the current recommendations of PA. The computation was performed through the following

steps: First, intensity (MET) of each reported physical activity was estimated on the basis of the Compendium of Physical Activities [28] by two experienced raters, who worked independently. Disagreements between raters were solved by discussion. The intensity, the frequency, and the duration of each activity were multiplied together and divided by 2 to obtain the weekly volume (MET-min/week) of each activity. The total volumes of light PA (LPA; < 3MET) and moderate to vigorous PA (MVPA; ≥ 3 MET) [29] were obtained for each participant by summing the volumes of all light activities together and the volumes of all moderate to vigorous activities together, respectively. The sum of LPA volume and MVPA volume provided the TPA volume. Each participant had hence three continuous measures of PA: one for LPA, one for MVPA, and one for TPA.

2.5. APOE genotyping

PAX gene tubes were utilized for blood collection and the QIAamp 96 DNA QIAcube HT Kit (Qiagen, France) was used for genomic DNA extraction. Pyrosequencing analysis was then performed through the use of a Pyromark PCR kit (Qiagen, France) according the manufacturer's instructions in order to determine the ApoE genotype. In this study, participants with at least one *APOE-ε4* allele were considered as carriers, otherwise they were classified as non-carriers.

2.6. Confounders

The confounders used for the analyses were age (continuous), sex, body mass index (BMI), WMH volume (cm³), MAPT group (omega-3 supplementation; multidomain intervention; omega-3 supplementation and multidomain intervention; and placebo), and cardiovascular morbidities (based on declarative information and subjects' medication), defined as having at least one of the following conditions : diabetes mellitus, hypertension and hypocholesterolemia.

2.7. Statistical analyses

Analysis of variance (continuous variables) and Chi-square (categorical variables) tests were used to compare the characteristics of the *APOE-ε4* groups at baseline and after the 3-year follow-up. Attrition rates from baseline to 3 years were compared between carriers and non-carriers using a Chi-square

test. This test compared whether the number of subjects who dropped out during the follow-up were uneven across *APOE-ε4* groups. Cross-sectional analyses were performed using mixed model linear regressions (with a random effect at the MRI site level) in order to test the interaction effects of TPA (continuous variable) and *APOE*-genotype (categorical variable) on the outcome measures. Multilevel mixed model linear regressions (with a random effect at the levels of MRI site and subjects (subjects nested within MRI site) and a random slope on time) were used to analyze the changes of DTI metrics according to subjects' TPA and *APOE-ε4* status over time (continuous variable) and their interactions (*APOE-ε4*, PA, time, covariates, *APOE-ε4* × time, TPA × time, TPA × *APOE-ε4* × time, covariates × time). In the longitudinal model, TPA was set as a time-varying covariate in order to take into account TPA changes over time. For both cross-sectional and longitudinal analyses, significant interactions were followed by prespecified hypothesis tests in order to obtain the effect of TPA within each *APOE-ε4* group. In addition, each of the cross-sectional and longitudinal analyses was followed by sensitivity analyses using MVPA and LPA instead of TPA in two additional separate models. All cross-sectional and longitudinal analyses were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) procedure [30]. The correction was applied separately for the primary and the secondary white matter tracts and for each DTI metric. Inter-visit reliability of the DTI measurements was assessed via intraclass correlations (ICC). Analyses were performed using IBM SPSS Statistics 23 with a significance level set at 5%.

3. Results

3.1. Characteristics of the participants

A flow-chart displaying the inclusion process from the whole MAPT population to the present study sample is given in Figure 1. Among the 1679 participants of MAPT, 228 and 185 subjects respectively underwent DTI measurements at baseline and at 3 years. All of them had physical activity assessment at both time points, and 213 were genotyped. Because of missing data for confounders, a total 145 *APOE-ε4* non-carriers versus 45 *APOE-ε4* carriers at baseline, and 128 *APOE-ε4* non-carriers versus 32 *APOE-ε4* carriers at 3 years, were kept for analyses. Attrition rates did not differ significantly

between carriers and non-carriers ($X^2 = 3,112$, $p = 0.211$). The characteristics of the participants at baseline and after the 3-year follow-up are provided in table 1.

3.2. Cross-sectional analyses

FDR-corrected mixed model regression analyses revealed no significant interaction effect between *APOE-ε4* status and TPA at baseline in any ROIs.

Sensitivity analyses demonstrated significant FDR-corrected interactions between MVPA and *APOE* status for MD and RD in the right retrolenticular part of the internal capsule. In this tract, higher MVPA values were associated with higher MD ($B = 1.44 \times 10^{-8}$; $SE = 0.43 \times 10^{-8}$; adjusted $p = 0.018$) and RD ($B = 1.56 \times 10^{-8}$; $SE = 0.47 \times 10^{-8}$; adjusted $p = 0.021$) values in the carrier group, while no significant associations were observed in non-carriers. No further cross-sectional associations were found in any of the DTI metrics and ROIs. The results of these cross-sectional analyses are presented in Supplementary Tables 1 to 24.

3.3. Longitudinal analyses

The inter-session reliability of the DTI measurements is provided by the ICC coefficients given in Supplementary Table 25. High ICC coefficients were found in most of the ROIs with global values of 0.98, 0.91, 0.97 and 0.95 for FA, AxD, RD, and MD, respectively. However, the bilateral inferior cerebellar peduncle demonstrated low reliability with ICC coefficients, which ranged from 0.93 to 0.34.

Multilevel mixed model regression analyses demonstrated no significant FDR-corrected TPA \times *APOE-ε4* status \times Time interaction for any of the DTI metrics and ROIs.

Sensitivity analyses demonstrated significant FDR-corrected LPA \times *APOE-ε4* status \times Time interactions for AxD in the bilateral superior longitudinal fasciculus, the bilateral anterior limb of internal capsule, and the right posterior corona radiata. Post-hoc analyses revealed significant associations in the carrier group only, in which higher levels of LPA were associated with higher longitudinal levels of AxD in the right ($B = 2.13 \times 10^{-8}$; $SE = 0.64 \times 10^{-8}$; adjusted $p = 0.009$) and left

($B = 1.79 \times 10^{-8}$; $SE = 0.70 \times 10^{-8}$; adjusted $p = 0.049$) superior longitudinal fasciculus and the right posterior corona radiata ($B = 3.48 \times 10^{-8}$; $SE = 1.04 \times 10^{-8}$; adjusted $p = 0.009$). LPA was negatively associated with longitudinal AxD in the right anterior limb of internal capsule of carriers ($B = -2.78 \times 10^{-8}$; $SE = 1.02 \times 10^{-8}$; adjusted $p = 0.040$). Significant interactions were also observed for MD in the bilateral superior longitudinal fasciculus, the right posterior corona radiata, and the right sagittal stratum. Post-hoc analyses demonstrated significant associations in the carrier group only, in which higher levels of LPA were associated with higher longitudinal levels of MD in the right ($B = 1.78 \times 10^{-8}$; $SE = 0.56 \times 10^{-8}$; adjusted $p = 0.011$) and left ($B = 1.83 \times 10^{-8}$; $SE = 0.58 \times 10^{-8}$; adjusted $p = 0.011$) superior longitudinal fasciculus, and in the right posterior corona radiata ($B = 2.85 \times 10^{-8}$; $SE = 0.85 \times 10^{-8}$; adjusted $p = 0.011$). Regression estimates for the longitudinal associations between LPA and AxD, MD, and RD are provided in Tables 2, 3 and 4, respectively. The other longitudinal analyses are provided in Supplementary Tables 26 to 46.

4. Discussion

To the best of our knowledge, this study is the first that examined both the cross-sectional and longitudinal interactive associations of PA and *APOE-ε4* genotype with WM integrity in older adults. Despite that no interaction effect between TPA and *APOE-ε4* genotype was found in both the cross-sectional and longitudinal approach, sensitivity analyses demonstrated significant cross-sectional interaction effects between MVPA, and *APOE-ε4* status in the retrolenticular part of internal capsule. Longitudinally, significant interaction effects were observed between LPA, but not MVPA, and *APOE-ε4* status in the superior longitudinal fasciculus, the anterior limb of internal capsule, the sagittal stratum, and the posterior corona radiata. For both the cross-sectional and longitudinal associations, post-hoc analyses revealed that WM integrity was associated with PA in *APOE-ε4* carriers but not in non-carriers. In the former group, higher levels of PA were mostly associated with higher MD, RD, and AxD values at baseline and over time.

Our results partially confirm previous observations of significant interaction effects between PA and *APOE-ε4* status on brain DTI-derived metrics [18]. Indeed, consistent with Smith et al., we found paradoxical associative patterns between PA and WM microstructure in the carrier group that is, higher PA levels associated with higher MD and RD values [18], which typically reflect reduced white matter integrity and axonal demyelination. It has been hypothesized that PA might specifically benefit *APOE-ε4* carriers by decreasing the rate of fiber loss in WM tracts containing crossing fibers [18], which were shown to decrease FA and increase RD [7]. Given that no significant change was found for AxD, higher MD values may be explained by higher RD values [31]. This is also consistent with the trend (MVPA x *APOE-ε4* Genotype, adj. p = 0.068) observed for FA in the right retrolenticular part of the internal capsule, suggesting lower FA with increasing levels of MVPA in carriers compared with non-carriers (Supplementary Table 18). However, contrary to Smith et al. who reported associations in numerous WM tracts, we only observed a few of cross-sectional associations. Further, in our study, we did not find any significant association in the non-carriers group while Smith et al. did. Such differences might be due in part to the health status differences in the studied samples. Smith et al. included only healthy participants while our sample included people with memory complaints, slow gait speed, and limitations in instrumental activity of daily living. It is possible that greater interaction effects could have been found in healthier individuals. This hypothesis is supported by a systematic review reporting that, in contrast to studies on healthy individuals, studies involving clinical populations, such as frail subjects or patients with mild cognitive impairment or Alzheimer's disease, demonstrated no clear effect of *APOE-ε4* status on the association between PA level and brain structure parameters such as grey and white matter volumes or amyloid- β deposition [32]. In that sense, the moderating effect of *APOE-ε4* status on the association between PA and WM integrity may be reduced by the clinical status of the populations, such that the benefits of PA in *APOE-ε4* carriers become smaller beyond a certain level of brain structure deterioration, making the interaction between PA and *APOE-ε4* genotype more difficult to detect. Another aspect that could explain the discrepancies with Smith et al.'s study is the tool used for PA assessment. The questionnaire we used assessed PA level over a 2-week period while the Stanford Brief Activity Survey used by Smith et al. provides an estimation of PA level over 1 year. Given that an individual's PA level may easily change

over time, and that WM integrity measured at a single time-point is the results of a life-long evolution, estimations of PA performed over long periods of time may better correlate with cross-sectional WM integrity than short period estimations. Consequently, the longitudinal approach using PA as a time-varying covariate may be more robust than the cross-sectional design for detecting associations as it takes into account PA changes over time. This could thus explain why the majority of our findings were longitudinal rather than cross-sectional. Another argument for the lack of associations is our use of PA as a continuous measure, contrary to Smith et al. who defined 2 PA categories. Indeed, it can be hypothesized that the effect of PA is not linear and could reach a cut-off value above which no association remains observable. However, given the small size of our subject sample, we deemed more appropriate to define PA as continuous variable, as dividing our sample in categories would have decreased the statistical power.

Regarding the longitudinal approach, the sensitivity analyses interestingly revealed that higher levels of LPA, but not TPA or MVPA, were mainly associated with higher values of MD and AxD over time. Furthermore, trends for higher RD values with increasing levels of LPA were also found in the same regions (Table 4). In accordance with the cross-sectional findings, the longitudinal associations were significant in *APOE-ε4* carriers only. In agreement with our interpretation of our cross-sectional findings, we hypothesize that in WM tracts containing crossing-fibers, the preservation of the fibers running along the main axis keeps AxD high, while the preservation of the fibers crossing the main axis keeps RD high. These changes would explain why MD remains high also, given its mathematical relationship with RD and AxD (Acosta Cabronero 2010). Moreover, the fact that LPA but not MVPA was associated with WM integrity is in line with Burzynska et al. who demonstrated that light PA and MVPA were differently associated with DTI values in a region-specific manner [33]. Moreover, the same authors reported a detrimental association between WM integrity and sedentary time [33], and other investigators have also demonstrated that PA duration, but not intensity, was associated with FA [34]. Taken together, these data suggest that even small doses of PA may counteract the negative effect of genetic susceptibility on WM microstructure and that higher PA intensity may not lead to any additional effects. Moreover, it is known that LPA time, rather than MVPA time, is strongly inversely

related with sedentary time [35,36]. Thus, from this point of view, sedentary behavior (defined as any waking behavior with an intensity of 1.5 MET or less [37]), rather than PA level, may be a key factor for WM microstructure changes in *APOE-ε4* carriers. Of note, a genome wide association study reported that people carrying the *APOE-ε4* allele have higher levels of PA compared to the other genotypes [38], which is consistent with the fact that this allele is the ancestral form of the *APOE* gene and originally evolved from non-sedentary hunter gather ancestors [39]. Although other authors reported no differences in PA based on *APOE-ε4* status [40], it can be hypothesized that a typical contemporary inactive lifestyle may be more deleterious among *APOE-ε4* carriers than in $\epsilon3$ and $\epsilon2$ populations who appeared later during the course of evolution [39,41]. Consequently, spending less time in sedentary behavior by engaging in LPA may particularly benefits older *APOE-ε4* carriers. Future studies measuring sedentary times in addition to PA behavior are required to test this hypothesis. Also, it is important to mention that despite that the directions of the associations we found were rather similar to those reported by Smith et al., an opposite pattern was observed in the anterior limb of internal capsule. In this region, higher PA levels were associated with lower AxD values over time, in the carrier group. Further investigations are thus required to clarify these discrepancies on the relationship between PA, *APOE-ε4* status and WM integrity. Overall, the literature on the interactive associations of PA and *APOE-ε4* with brain health remains mixed, as indicated by a recent systematic review reporting inconclusive results [32].

Beside the clinical status of the studied sample, the use of PA as a continuous variable, the tools used for PA assessment, and the role of physical inactivity discussed above, the lack of significant associations in this study may also lies in several additional reasons. First, it is possible that greater interaction effects could have been found in younger individuals since it has been suggested that age may modulate the interaction between PA and *APOE-ε4* [42]. Another possibility is that PA is indirectly linked to WM integrity through the mediation of aerobic fitness, which is both inherited and influenced by lifestyle habits. This hypothesis is corroborated by Voss et al.'s study that showed that, compared with controls, one year of exercise intervention did not impact WM microstructure but exercise-induced increases in aerobic power were associated with increases in WM integrity [43].

Such results suggest that cardiorespiratory fitness improvements may be able to enhance WM integrity. This hypothesis is also consistent with other DTI studies reporting greater WM integrity in older athletes compared to sedentary age-matched peers [15]; as well as with studies demonstrating that physical exercise, but not daily life PA [17] or leisure-time PA other than exercise [44], is associated with better DTI indices. Thus, while a lack of PA may be deleterious for WM integrity, especially in *APOE-ε4* carriers, it is possible, on the other hand, that exercise training may induce true WM integrity improvements through the mediation of cardiorespiratory fitness. Future investigations exploring the distinct effects of sedentary lifestyles, PA, and exercise training according to *APOE-ε4* status would bring important contribution to the field. Another explanation could be that the modulatory effect of PA on the relationship between *APOE* genotype and WM integrity may take longer durations to become significant. Although observational longitudinal DTI studies taking into account both *APOE* genotype and PA level are lacking, a recent investigation involving the MAPT participants demonstrated that PA was prospectively associated with changes in WM integrity in only one WM tract, namely, the uncinate fasciculus [16]. Furthermore, exercise training protocols reported no effect of 6 months aerobic and dance exercise interventions on WM integrity in old individuals [45–47]. On the other hand, master athletes who have exercised for more than 15 years expressed better DTI values than sedentary people [48], suggesting a long-term effect of physical activity on WM structures. Consequently, longer follow-up might be needed to reveal significant longitudinal PA by *APOE-ε4* interaction effects on WM.

The key strength of our study lies in the fact that we investigated both cross-sectional and longitudinal associations between PA and WM integrity while considering *APOE-ε4* status. To date, the $PA \times APOE-ε4$ interaction on DTI parameters has been examined in only one cross-sectional study [18]. A further strength relies to the concomitant assessment of WM integrity and PA level over time, which allowed us to explore the aging-related trajectory of WM microstructure and its association with PA. A first limitation is the use of self-reported PA rather than an objective measurement of PA. However, the use of questionnaires allows us to assess large sample sizes and was thus more appropriate for the design of the MAPT Study which gathered 1679 participants. Another weakness is

the relatively small number of *APOE-ε4* carriers compared to non-carriers along with the attrition effect over time which may have limited the power to detect an association. A third limitation relates to the fact that the PA level of our subject sample was rather high, and a lack of low active individuals could have made the associations harder to detect. This could be due to a selection bias in the MAPT study toward highly active older adults. Volunteers interested in participating in randomized controlled trials involving PA intervention like MAPT may be more active than their age –matched peers who do not want to participate in research investigations. Another reason is that people may have overestimated their true PA levels, a phenomenon that is known when using subjective assessment of PA [49]. A last limitation is the use of data from a randomized control trial that could have had an effect on the investigated outcomes.

In conclusion, this study partially replicates the results of previous investigations demonstrating *APOE-ε4* genotype-by-PA interactive effects on WM microstructure [18]. Despite that the number of significant associations was small, the present study adds to the current literature by its longitudinal approach demonstrating that LPA, but not TPA and MVPA was associated with WM integrity in *APOE-ε4* carriers. In this group, higher levels of LPA were mainly associated with higher diffusivity values over time, supporting the hypothesis that PA may protect against fiber loss in WM tracts containing crossing fibers. Further longitudinal studies measuring both sedentary and PA times are thus required to fulfill the remaining gaps of the current literature. Exercise training interventions stratified by *APOE-ε4* status would also provide insightful information given the known association between exercise and cardiorespiratory fitness, and this latter with WM microstructure in the overall elderly population [17].

Contributors

Jérémy Raffin conceptualized and designed the paper, analyzed the data, performed statistical analyses, and wrote the manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

Funding

The present work was performed in the context of the Inspire Program, a research platform supported by grants from the Region Occitanie/Pyrénées-Méditerranée (Reference number: 1901175) and the European Regional Development Fund (ERDF) (Project number: MP0022856). This study received funds from Alzheimer Prevention in Occitania and Catalonia (APOC Chair of Excellence - Inspire Program).

The MAPT study was supported by grants from the Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009), Pierre Fabre Research Institute (manufacturer of the omega-3 supplement), ExonHit Therapeutics SA, and Avid Radiopharmaceuticals Inc. The promotion of this study was supported by the University Hospital Center of Toulouse. The data sharing activity was supported by the Association Monegasque pour la Recherche sur la maladie d'Alzheimer (AMPA) and the INSERM-University of Toulouse III UMR 1027 Research Unit.

Ethical approval

The MAPT and the MRI substudy were conducted in accordance with the Declaration of Helsinki and were approved by the ethical committee in Toulouse (CPP SOOM II). All participants provided written informed consent.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The data and the statistical codes used in this study are available upon reasonable request to the corresponding author.

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Figure legends

Figure 1. Flow-chart displaying the inclusion process from the whole MAPT population to the present study sample.

Legend. MAPT: Multidomain Alzheimer Prevention Trial; DTI: Diffusion Tensor Imaging

Table 1: Baseline characteristics of participants.

	Baseline				3 years			
	Total (n=190)	Non Carriers (n = 145)	Carriers (n = 45)	p	Total (n =160)	Non Carriers (n = 128)	Carriers (n = 32)	p
Age, y, mean (SD)	74.5 (3.93)	74.3 (3.86)	74.9 (4.18)	0.43	77.3 (3.76)	77.1 (3.61)	78.2 (4.26)	0.13
Female sex, n (%)	119 (62.6)	89 (61.4)	30 (66.7)	0.60	101 (63.1)	82 (64.1)	19 (59.4)	0.68
Education								
Unknown, n (%)	1 (0.53)	1 (0.69)	0 (0)		1 (0.63)	1 (0.78)	0 (0)	
No diploma, n (%)	2 (1.1)	0 (0)	2 (4.4)		1 (0.6)	0 (0)	1 (3.1)	
Primary school certificate, n (%)	21 (11.1)	18 (12.4)	3 (6.7)		20 (12.5)	17 (13.3)	3 (9.4)	
Secondary education, n (%)	60 (31.6)	44 (30.3)	16 (35.6)	0.12	47 (29.4)	37 (28.9)	10 (31.3)	0.36
High school diploma, n (%)	29 (15.3)	24 (16.6)	5 (11.1)		23 (14.4)	20 (15.6)	3 (9.4)	
University level, n (%)	77 (40.5)	58 (40)	19 (42.2)		68 (42.5)	53 (41.4)	15 (46.9)	
BMI, Kg/m ² , men (SD)	25.31 (3.81)	25.17 (3.69)	25.78 (4.19)	0.35	25.5 (3.99)	25.39 (3.86)	25.95 (4.51)	0.48
TPA, MET-min/week, mean (SD)	1758.5 (2807.7)	1849.4 (3117.6)	1465.7 (1392.1)	0.42	1661.8 (1615.6)	1776.3 (1704.4)	1203.7 (1102.3)	0.07
LPA, MET-min/week, mean (SD)	332.1 (1309.3)	382.8 (1462.1)	168.6 (575.5)	0.34	229.1 (602.1)	244.1 (649)	168.9 (359.3)	0.53
MVPA, MET-min/week, mean (SD)	1426.5 (1695.9)	1466.6 (1845.4)	1297.2 (1089.3)	0.56	1432.7 (1370.1)	1532.2 (1438.9)	1034.9 (970.5)	0.07
Cardiovascular risk factors								
Diabètes, n (%)	14 (7.4)	11 (7.6)	3 (6.7)	1.00	14 (8.8)	10 (7.8)	4 (12.5)	0.48
Hypertension, n (%)	89 (46.8)	68 (46.9)	21 (46.7)	1.00	80 (50)	62 (48.4)	18 (56.3)	0.55
Hypercholesterolemia, n (%)	81 (42.6)	60 (41.4)	21 (46.7)	0.61	67 (41.9)	52 (40.6)	15 (46.9)	0.55
Medication								
Antihypertensive drugs, n (%)	88 (46.3)	69 (47.6)	19 (42.2)	0.61	76 (47.5)	60 (46.9)	16 (50)	0.84
Statins, n (%)	58 (30.5)	43 (29.7)	15 (33.3)	0.71	46 (28.8)	35 (27.3)	11 (34.4)	0.51
Oral antihyperglycemic agents, n (%)	9 (4.7)	7 (4.8)	2 (4.4)	1.00	10 (6.3)	7 (5.5)	3 (9.4)	0.42
Insulin, n (%)	2 (1.1)	1 (0.7)	1 (2.2)	0.42	2 (1.3)	1 (0.8)	1 (3.1)	0.36
Antiplatelet drugs, n (%)	45 (23.7)	37 (25.5)	8 (17.8)	0.32	39 (24.4)	30 (23.4)	9 (28.1)	0.65
Anticoagulants, n (%)	11 (5.8)	7 (4.8)	4 (8.9)	0.29	8 (5)	5 (3.9)	3 (9.4)	0.20
MMSE score, mean (SD)	28.21 (1.51)	28.21 (1.55)	28.18 (1.4)	0.89	(n = 159) 28.35 (1.53)	(n=127) 28.32 (1.53)	28.47 (1.59)	0.63
CDR score = 0,5, n (%)	90 (47.6)	67 (46.2)	23 (52.3)	0.50	74 (46.3)	57 (44.5)	17 (53.1)	0.43
WMH, cm ³ , mean (SD)	12.1 (12)	11.8 (11.1)	13.1 (14.9)	0.53	16.4 (15.7)	16.2 (15.3)	17.1 (17.4)	0.77
FA (Whole Skeleton)	0.43 (0.02)	0.43 (0.02)	0.43 (0.03)	0.80	0.42 (0.02)	0.42 (0.02)	0.42 (0.03)	0.40
MRI site								
Bordeaux, n (%)	29 (15.3)	20 (13.8)	9 (20)		28 (17.5)	23 (18)	5 (15.6)	0.88
Montpellier, n (%)	134 (70.5)	104 (71.7)	30 (66.7)	0.60	109 (68.1)	86 (67.2)	23 (71.9)	0.88
Toulouse, n (%)	27 (14.2)	21 (14.5)	6 (13.3)		23 (14.4)	19 (14.8)	4 (12.5)	0.88
MAPT group								
Multidomain + Omega 3, n (%)	47 (24.7)	35 (24.1)	12 (26.7)		38 (23.8)	31 (24.2)	7 (21.9)	
Omega 3, n (%)	46 (24.2)	37 (25.5)	9 (20)		34 (21.3)	30 (23.4)	4 (12.5)	
Multidomain + Placebo, n (%)	45 (23.7)	32 (22.1)	13 (28.9)	0.71	40 (25)	29 (22.7)	11 (34.4)	0.40
Placebo, n (%)	52 (27.4)	41 (28.3)	11 (24.4)		48 (30)	38 (29.7)	10 (31.3)	

Note. SD: Standard deviation; BMI: Body mass index; TPA: Total physical activity; LPA, light physical activity; MVPA: Moderate to vigorous physical activity; MET: Metabolic equivalent task; MMSE: Mini-mental state examination; CDR: Clinical dementia rating; FA: Fractional anisotropy; WMH: White matter hyperintensities; MRI: Magnetic resonance imaging; MAPT: Multidomain Alzheimer Preventive Trial

Table 2: Longitudinal interaction effects of *APOE* genotype and light activity level (LPA) on axial diffusivity (AxD)* in the primary ROIs.

	Non Carriers x LPA x Time				Carriers x LPA x Time				Genotype x LPA x Time	
	B	SE	p	adj p	B	SE	p	adj p	p	adj p
CG L	-0.00029	0.00033	0.385	0.834	0.00017	0.00124	0.888	0.983	.719	0.784
CG R	-0.00012	0.00027	0.674	0.834	0.00054	0.00103	0.605	0.726	.543	0.651
CH L	0.00024	0.00044	0.577	0.834	-0.00164	0.00165	0.321	0.482	.270	0.405
CH R	0.00034	0.00036	0.339	0.834	-0.00012	0.00135	0.928	0.983	.740	0.784
SLF L	-0.00005	0.00019	0.782	0.834	0.00179	0.00070	0.011	0.049	.011	0.041
SLF R	-0.00006	0.00017	0.742	0.834	0.00213	0.00064	0.001	0.009	.001	0.010
Fx L	-0.00013	0.00038	0.734	0.834	0.00120	0.00146	0.409	0.567	.376	0.520
Fx R	-0.00001	0.00029	0.978	0.978	0.00139	0.00111	0.210	0.378	.222	0.363
SS L	-0.00017	0.00028	0.558	0.834	0.00129	0.00108	0.234	0.383	.193	0.348
SS R	-0.00014	0.00027	0.614	0.834	0.00217	0.00102	0.036	0.090	.031	0.079
ALIC L	0.00043	0.00032	0.185	0.834	-0.00284	0.00119	0.018	0.066	.009	0.039
ALIC R	0.00016	0.00027	0.546	0.834	-0.00278	0.00102	0.007	0.040	.005	0.033
ACR L	-0.00022	0.00027	0.416	0.834	0.00213	0.00100	0.035	0.090	.024	0.073
ACR R	-0.00007	0.00026	0.787	0.834	0.00199	0.00096	0.040	0.090	.040	0.089
PCR L	-0.00037	0.00026	0.150	0.834	0.00150	0.00097	0.121	0.243	.062	0.123
PCR R	-0.00033	0.00028	0.234	0.834	0.00348	0.00104	0.001	0.009	.000	0.008
SCR L	-0.00015	0.00030	0.619	0.834	0.00000	0.00111	0.998	0.998	.895	0.895
SCR R	-0.00011	0.00025	0.647	0.834	0.00055	0.00093	0.553	0.711	.489	0.628

Note. ROI: Region of Interest; SE: Standard error; CG: Cingular gyrus, CH: Cingular hippocampus, SLF: Superior longitudinal fasciculus, Fx: Fornix Stria terminalis, SS: Sagittal stratum; ALIC: Anterior Limb of the Internal Capsule, ACR: Anterior corona radiata; PCR: Posterior Corona radiata; SCR: Superior Corona Radiata; L: left; R; Right; PA: Physical activity; *For better readability, values have been multiplied by 10⁵.

Table 3: Longitudinal interaction effects of *APOE* genotype and light activity level (LPA) on mean diffusivity (MD)* in the primary ROIs.

	Non Carriers x LPA x Time				Carriers x LPA x Time				Genotype x LPA x Time	
	B	SE	p	adj p	B	SE	p	adj p	p	adj p
CG L	-0.00009	0.00015	0.543	0.931	0.00132	0.00059	0.025	0.072	.020	0.056
CG R	-0.00010	0.00016	0.502	0.931	0.00130	0.00059	0.028	0.072	.022	0.056
CH L	0.00004	0.00031	0.897	0.931	-0.00062	0.00115	0.589	0.663	.578	0.651
CH R	0.00012	0.00025	0.637	0.931	0.00010	0.00095	0.916	0.916	.984	0.984
SLF L	0.00006	0.00015	0.703	0.931	0.00183	0.00058	0.002	0.011	.003	0.019
SLF R	-0.00001	0.00015	0.931	0.931	0.00178	0.00056	0.002	0.011	.002	0.019
Fx L	-0.00013	0.00028	0.638	0.931	0.00041	0.00106	0.698	0.739	.620	0.656
Fx R	-0.00006	0.00020	0.764	0.931	0.00058	0.00075	0.439	0.526	.408	0.490
SS L	-0.00002	0.00022	0.915	0.931	0.00145	0.00082	0.077	0.126	.082	0.122
SS R	-0.00015	0.00021	0.478	0.931	0.00193	0.00078	0.014	0.062	.010	0.046
ALIC L	0.00019	0.00029	0.506	0.931	-0.00178	0.00107	0.097	0.145	.075	0.122
ALIC R	0.00003	0.00023	0.896	0.931	-0.00175	0.00087	0.045	0.091	.049	0.088
ACR L	-0.00013	0.00023	0.561	0.931	0.00198	0.00085	0.021	0.072	.017	0.056
ACR R	-0.00006	0.00021	0.760	0.931	0.00172	0.00080	0.032	0.072	.031	0.070
PCR L	-0.00022	0.00021	0.294	0.931	0.00143	0.00078	0.069	0.125	.043	0.085
PCR R	-0.00016	0.00023	0.476	0.931	0.00285	0.00085	0.001	0.011	.001	0.014
SCR L	-0.00003	0.00016	0.858	0.931	0.00055	0.00061	0.370	0.476	.361	0.464
SCR R	0.00003	0.00014	0.855	0.931	0.00072	0.00053	0.174	0.241	.204	0.282

Note. ROI: Region of Interest; SE: Standard error; CG: Cingular gyrus, CH: Cingular hippocampus, SLF: Superior longitudinal fasciculus, Fx: Fornix Stria terminalis, SS: Sagittal stratum; ALIC: Anterior Limb of the Internal Capsule, ACR: Anterior corona radiata; PCR: Posterior Corona radiata; SCR: Superior Corona Radiata; L: left; R: Right; PA: Physical activity; *For better readability, values have been multiplied by 10^5 .

Table 4: Longitudinal interaction effects of *APOE* genotype and light activity level (LPA) on radial diffusivity (RD)* in the primary ROIs.

	Non Carriers x LPA x Time				Carriers x LPA x Time				Genotype x LPA x Time	
	B	SE	p	adj p	B	SE	p	adj p	p	adj p
CG L	-0.00001	0.00019	0.961	0.985	0.00185	0.00072	0.010	0.053	.013	0.052
CG R	-0.00011	0.00018	0.539	0.985	0.00169	0.00070	0.016	0.057	.013	0.052
CH L	-0.00007	0.00029	0.804	0.985	-0.00013	0.00110	0.907	0.961	.961	0.961
CH R	0.00002	0.00028	0.951	0.985	0.00021	0.00105	0.843	0.949	.861	0.933
SLF L	0.00011	0.00017	0.522	0.985	0.00187	0.00063	0.004	0.053	.008	0.052
SLF R	0.00000	0.00017	0.985	0.985	0.00163	0.00064	0.012	0.053	.014	0.052
Fx L	-0.00014	0.00027	0.602	0.985	0.00002	0.00104	0.987	0.987	.882	0.933
Fx R	-0.00008	0.00020	0.692	0.985	0.00018	0.00078	0.812	0.949	.741	0.889
SS L	0.00004	0.00022	0.858	0.985	0.00148	0.00083	0.077	0.155	.096	0.172
SS R	-0.00014	0.00022	0.518	0.985	0.00182	0.00081	0.025	0.076	.020	0.059
ALIC L	0.00009	0.00029	0.763	0.985	-0.00128	0.00109	0.242	0.328	.226	0.339
ALIC R	-0.00003	0.00023	0.901	0.985	-0.00125	0.00088	0.158	0.259	.182	0.298
ACR L	-0.00008	0.00024	0.736	0.985	0.00183	0.00089	0.041	0.106	.039	0.101
ACR R	-0.00007	0.00022	0.763	0.985	0.00163	0.00084	0.052	0.117	.050	0.113
PCR L	-0.00014	0.00023	0.543	0.985	0.00138	0.00087	0.115	0.207	.092	0.172
PCR R	-0.00008	0.00025	0.744	0.985	0.00255	0.00092	0.006	0.053	.006	0.052
SCR L	0.00003	0.00019	0.886	0.985	0.00083	0.00073	0.255	0.328	.287	0.397
SCR R	0.00010	0.00017	0.565	0.985	0.00076	0.00064	0.240	0.328	.322	0.414

Note. ROI: Region of Interest; SE: Standard error; CG: Cingular gyrus, CH: Cingular hippocampus, SLF: Superior longitudinal fasciculus, Fx: Fornix Stria terminalis, SS: Sagittal stratum; ALIC: Anterior Limb of the Internal Capsule, ACR: Anterior corona radiata; PCR: Posterior Corona radiata; SCR: Superior Corona Radiata; L: left; R: Right; PA: Physical activity; *For better readability, values have been multiplied by 10^5 .

Highlights

- *APOE-ε4* status moderated the association between level of physical activity and white matter integrity.
- Physical activity was associated with white matter integrity in *APOE-ε4* carriers but not in non-carriers.
- In *APOE-ε4* carriers, light physical activity but not moderate to vigorous or total physical activity was associated with white matter integrity.
- Higher levels of light physical activity were associated with higher axial and mean diffusivity values over time.
- We hypothesize that light physical activity protects against fiber loss in tracts containing crossing fibers.

