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# Voxel based assessments of treatment effects on brain evolution in the MAPT cohort

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## 1 Abstract

**Objective** The Multidomain Alzheimer Preventive Trial (MAPT) was designed to assess the effect of omega-3 supplementation and a multidomain intervention (physical activity, cognitive training and nutritional advice) on cognitive decline of people with subjective memory complaint. In term of cognitive testing, no significant effect on cognitive decline was found over the 3-year follow-up. Yet, in the context of dementia-related conditions, brain morphological changes can be used to foretell the cognitive evolution. In this paper, we evaluate the effect of the interventions on the evolution of the brain morphology using the MR images acquired during MAPT.

**Methods** Subjects in the MAPT cohort with two MRI acquisitions, at baseline and at 36 months, were included, resulting in a subset of 376 subjects distributed in the 4 intervention groups: multidomain intervention plus omega-3, multidomain intervention plus placebo, omega-3 alone, and placebo alone. The morphological changes were assessed from volume measurements of regions of interest and a voxel-wise deformation-based approach. The primary outcome is the longitudinal deformation observed between the baseline image and the 3-year follow-up.

**Results** The multi-domain intervention is associated with a significant effect on the 3-year morphological evolution. The effect is similar within the two groups undergoing the intervention regardless of the omega-3 or placebo treatment. The voxel-wise deformation-based approach shows that the differences are mainly located in the left peri-ventricular area next to the temporoparietal junction (TPJ). These morphological changes correspond to a slower morphological evolution and are correlated with a better performance in cognitive assessments. These results could not be observed using the volumetric morphometry approach. No effect of omega-3 was observed.

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**Discussion** In this study, we found that the multidomain intervention has a significant effect on morphological changes that are usually associated with the cognitive decline. This result suggests that effects at the level of cognitive decline may be visible in the long term, and that the cognitive scores may not be powerful enough to detect changes after 3 years. We argue that the use of neuroimaging could help define whether early intervention strategies are effective to delay cognitive decline and dementia.

**Keywords:** multidomain intervention, clinical trial, subjective memory complaint, deformation-based morphometry

## 2 Introduction

### 2.1 The MAPT study

Subjective memory complaint (SMD) in individuals with unimpaired performance on cognitive tests is regarded as a possible risk factor of Alzheimer’s disease (AD) (van Oijen et al., 2007). For this reason, people with SMD represent a promising population to put in place early interventions, and prevention strategies (Andrieu et al., 2008). Current evidence suggests that multi-domain interventions targeting nutrition, physical exercise, cognitive activity and social stimulation may improve cognitive health (Kivipelto et al., 2018) in older adults with SMD (Ngandu et al., 2015). For instance, an increase in omega-3 polyunsaturated fatty acid intake has been proposed as a possible intervention for preventing or delaying age-related cognitive decline (Dacks et al., 2013).

The Multidomain Alzheimer Preventive Trial (MAPT) was a 3-year multi-centric randomized placebo-controlled trial designed to assess the effect of omega-3 supplementation and a multidomain intervention (MDI) on cognitive decline of patients SMD. The multidomain intervention consisted of regular group sessions focusing on physical activity, cognitive training, nutritional advice and social stimulation and an individual preventive consultation to follow each participant. The supplementation in omega 3 polyunsaturated fatty acids was tested in comparison with a placebo. 1680 Subjects were randomized in four parallel groups including three intervention groups (omega-3 alone, MDI plus placebo, MDI plus omega-3) and a placebo control group. All participants in the MAPT study underwent extensive and longitudinal clinical testing, including classical clinical scales and tasks to assess the physical and cognitive functioning, the autonomy in activities of daily living, and the presence cognitive and behavioral disturbances. Furthermore, a sub-sample of participants underwent structural magnetic resonance imaging (sMRI) both at baseline and at the end of the 3-year trial. A complete description of the trial is published in Vellas et al. (2015).

Andrieu et al. (2017) studied the effects of the treatments on the cognitive evolution, as indexed by a combination of classical clinical and cognitive tests, and found no significant differences between any of the three intervention groups and the placebo group. In this paper, we want to investigate the effect of the interventions on the brain morphology.

### 2.2 Measuring the evolution of the brain morphology

Structural magnetic resonance imaging (sMRI) has been proven helpful to characterize neuropsychiatric conditions (Bron et al., 2015; Jack et al., 2016; Lorenzi et al., 2017) or to assess the efficacy of specific treatments (Lieberman, 2005).

In particular, knowledge of the spatial pattern and rate of decline of cerebral brain volume provide valuable information for detecting early neurodegenerative disease such as Alzheimer’s disease at different stages of disease progression (McDonald et al., 2009). For example, atrophy in Alzheimer’s disease is not uniform across brain regions, nor does it follow a linear trajectory. The atrophy rate is greater in early disease stages within the medial temporal cortex, and in later stages within prefrontal, parietal, posterior temporal and cingulate cortex (Risacher et al., 2010). This non linear behavior of the atrophy is also characterized by an acceleration phase during the early stages of the disease, specifically hippocampal and entorhinal atrophy

in mild cognitive impairment (Sabuncu et al., 2011; Devanand et al., 2007; Colliot et al., 2008). However, to our knowledge, there is no strong evidence that measure of regional brain atrophy is relevant to predict symptomatic change in patients with cognitive complaints and normal neuropsychological tests (Saykin et al., 2006; Sluimer et al., 2008).

These usual morphometric features are generally obtained from *a priori* defined regions of interests (ROIs) such as the hippocampi or the ventricles. They offer valuable quantitative assessments but can be limited and many alternatives have been proposed during the last decades to assess the local differences in brain tissues composition and shape (Ashburner and Friston, 2000; Qiu et al., 2007; Hutton et al., 2009).

Deformation based approaches describe the voxel-wise shape remodeling (Ashburner et al., 1998). Anatomical differences and morphological evolutions are estimated using registration and modeled by diffeomorphic deformations. These transformations of the space give us direct information on the visible evolution of the brain. These approaches can be really powerful describe the aging brain evolution (Sivera et al., 2019, in press) and to explore the potential morphological changes to suggest morphological correlates (Schmidt-Wilcke et al., 2009).

## 3 Method

### 3.1 Participants

Subjects of the MAPT cohort with two MRI acquisitions at baseline and 36 months are included. The total sample includes 377 subjects, randomized in the MDI plus omega-3 group (N=98), the MDI plus placebo group (N=100), the omega-3 alone group (N=87), or the placebo control group (N=92). The demographic features and the genetic, cognitive and functional profile of subjects at baseline are reported in Table 1. One subject was later excluded during processing due to a failure of execution of the processing pipeline.

In order to verify that the 3-year evolution of the subjects cognitive, behavioral and functional profile in our sub-sample (N=377) is comparable to the original study population (N=1680), we submitted the evolution of the scores (results at M36 minus results at baseline) of each of the available tests to separate ANOVAs with Group (MDI plus omega-3, MDI plus placebo, omega-3 alone, placebo) as between-subject factor.

### 3.2 Regional atrophy and cortical thickness assessments

First, the longitudinal morphological evolution is evaluated using cortical thickness and sub-cortical volumetric measures. The data is processed using the longitudinal stream available in the FreeSurfer software (Reuter et al., 2012). We decided to focus our analysis on the longitudinal evolution of the regions of the brain well known to be atrophying in dementia from early stages (MCI) to severe stages (Whitwell et al., 2007). The evolution is measured between the baseline and the 36-month follow-up.

For the volumetric information 24 regions are selected and total left plus right changes are computed for 9 of these regions. The cortical thickness is evaluated in 34 regions of each hemispheres. Similarly the left/right averages are added to the analysis. We also evaluate the effect on the total white and grey-matter volume and the brain parenchyma fraction (BPF). In total the evolution is characterized by 142 morphological variables (the extensive list is available in supplementary material) in order to get a exploratory overview of the possible morphological changes.

The difference between the treatment groups are tested using an ordinary linear model with no cross effect. A non-parametric re-randomization test is performed to correct for multiple comparisons.

	Multidomain plus polyunsaturated fatty acids (n=98)	Multidomain plus placebo (n=100)	Polyunsaturated fatty acids (n=87)	Placebo (n=92)	Overall (n=377)
<b>Age, years</b>	74,96 [4,22]	74,34 [3,84]	74,67 [3,68]	74,48 [4,03]	74,61 [3,95]
<b>Female sex</b>	59 (60,2)	69 (69,0)	57 (65,5)	57 (62,0)	242 (64,2)
<b>Education</b>					
No diploma or primary school certificate	16 (16,5)	14 (14,0)	14 (16,3)	16 (17,58)	60 (16,0)
Secondary education	38 (39,2)	27 (27,0)	23 (26,7)	26 (28,57)	114 (30,5)
High school diploma	16 (16,5)	13 (13,0)	14 (16,3)	10 (11,0)	53 (14,2)
University level	27 (27,8)	46 (46,0)	35 (40,7)	39 (42,9)	147 (39,3)
<b>APOE ε4 (n=23 missing data)</b>	19 (20,7)	26 (28,3)	16 (19,5)	21 (23,9)	82 (23,2)
<b>Mini Mental State Examination</b>	28,13 [1,53]	28,38 [1,43]	28,39 [1,48]	27,99 [1,56]	28,22 [1,50]
<b>Clinical dementia rating</b>					
0	57 (58,2)	54 (54,0)	49 (56,3)	44 (47,8)	204 (54,1)
0-5	41 (41,8)	46 (46,0)	38 (43,7)	48 (52,2)	173 (45,9)
<b>Free and Cued Selective Reminding Test</b>					
Free recall*	27,70 [5,51]	28,26 [6,88]	29,16 [5,47]	27,36 [6,78]	28,10 [6,22]
Total recall*	45,45 [3,08]	45,73 [3,22]	46,37 [2,40]	45,30 [4,33]	45,70 [3,35]
<b>Trail Making Test</b>					
Part A	44,11 [16,71]	44,27 [16,28]	43,71 [13,58]	43,22 [12,91]	43,84 [14,98]
Part B (n=2 missing data)	107,41 [46,70]	106,91 [42,35]	110,94 [43,39]	110,40 [53,83]	108,82 [46,59]
<b>Verbal fluency</b>					
Category Naming Test	28,17 [6,70]	28,11 [7,98]	28,44 [6,92]	28,58 [7,37]	28,32 [7,24]
Controlled Oral Word Association Test	22,16 [5,78]	22,44 [7,54]	22,05 [5,89]	22,46 [5,81]	22,28 [6,30]
<b>DSST (WAIS—R coding)</b>	40,59 [10,29]	41,10 [10,48]	39,30 [8,91]	39,36 [8,16]	40,13 [9,55]
<b>Memory functioning‡</b>	48,64 [16,17]	48,57 [16,98]	47,39 [15,94]	49,42 [18,85]	48,53 [16,97]
<b>Consequences of everyday life‡</b>	39,77 [24,72]	36,14 [23,57]	37,94 [24,32]	38,37 [21,95]	38,04 [23,61]
<b>Geriatric Depression Scale (n=2 missing data)</b>	2,80 [1,94]	3,28 [2,44]	3,41 [2,46]	3,18 [2,82]	3,16 [2,43]
<b>Short Physical Performance Battery</b>	11,00 [1,44]	11,14 [1,26]	10,76 [1,28]	11,01 [1,39]	10,98 [1,35]

Data are mean (SD), or n (%), unless otherwise specified. Percentages were calculated on the basis of the number of participants for whom data were available for each criterion. DSST=Digit Symbol Substitution Test. WAIS—R=Wechsler Adult Intelligence Scale—Revised. ADCSADLPI=Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument. \*48 is the total possible score. ‡Measured on a visual analogue scale.

Table 1: Baseline characteristics of the population

### 3.3 Statistical analysis of the deformations

#### 3.3.1 Modeling the brain evolution

The deformation-based approach used in this work is based on an efficient parametrization of diffeomorphisms using stationary velocity fields (Arsigny et al., 2006). In this setting, smooth and reversible deformation that spatially align the anatomies are estimated through non-linear registration (Lorenzi and Pennec, 2014) between pairs of images. These deformations are fully parametrized by the flow of a stationary velocity field (SVF). From these deformations it is possible to compute the corresponding volume changes locally in the brain (Lorenzi et al., 2013), but it is also to analyze the longitudinal intra-subject evolutions directly in the deformation space using the SVFs transported in a common reference space where they can be compared (Hadj-Hamou et al., 2016).

#### 3.3.2 Assessing the effect of the treatments on the brain evolution

We want to evaluate the effect of both interventions on the morphological evolution. To do so, we test the  $H_0$  hypothesis that the treatments are not correlated with the vector fields parametrizing the deformations. However these fields are high dimensional and repeating the test for every voxel will result in a large number of correlated tests. To address this problem, we use a non-parametric re-randomization test to control for family-wise error rate (FWER). This statistical approach does not require strong assumptions on the data distribution, especially when the patients are in a randomized trial, and is well fitted to the neuroimaging settings (Nichols and Holmes, 2002).

Several statistics can be used at the voxel level; most of them are based on the comparison of the residual variance matrix and the model variance matrix. Here, the voxel statistic is based on the likelihood ratio to compare the goodness of fit between the linear model taking into account the treatments and the constant model. No additional covariate are included in our model. The maximum of this statistic is than used to summarize the result over the whole brain.

For each random permutation of the subjects, the maximum of the likelihood-ratio statistic map is computed on the whole brain area. These values give an empirical distribution of the maximum statistic under  $H_0$ . This empirical distribution allows us to compute, for the real group assignment, the resulting p-value.

In order to get a reliable p-value estimation,  $N = 2000$  permutations are computed. Indeed, the standard deviation of the p-value estimation at a significance level of  $\alpha = 0.05$  is equal to:

$$P = \sqrt{\alpha(1 - \alpha)/N} \approx 0.005$$

Additional likelihood ratio analyses are performed to assess the effect of both the omega-3 and the multidomain intervention variables individually. For these analyses the same permutations of the 376 subjects are used, the only difference is that the linear model tested only takes into account one variable of interest.

Results about the existence of a global difference in morphological evolution are not really informative and we are also interested in the interpretation of the eventual difference and their relation to an evolution toward more advanced diseased stages. To achieve this we first visualize the voxel-wise z-value maps. They give insights on where the difference are correlated with the treatments. Then, the mean evolution is computed for each subgroups and the local differences are highlighted. It allows us to make hypotheses about the properties of these differences.

## 4 Results

### 4.1 Cognitive, behavioral and functional assessment

Results regarding the 3-year evolution of the subjects cognitive, behavioral and functional profile in our sub-sample are reported in Table 2. The evolution of the scores (results at M36 minus results at baseline) of

Difference between (score at 3 years - score at baseline)	Multidomain plus polyunsaturated fatty acids (n=98)	Multidomain plus placebo (n=100)	Polyunsaturated fatty acids (n=87)	Placebo (n=92)	p-value <sup>a</sup>
	Mean [SD]	Mean [SD]	Mean [SD]	Mean [SD]	
<b>Mini Mental State Examination</b>	0,14 [1,69]	-0,14 [1,89]	-0,11 [1,89]	-0,28 [2,40]	0,525
<b>Free and Cued Selective Reminding Test</b>					
Free recall*	1,93 [4,95]	1,32 [5,68]	1,59 [5,48]	1,49 [5,61]	0,886
Total recall*	0,27 [2,75]	-0,40 [4,90]	-0,32 [2,99]	-1,12 [6,44]	0,218
<b>Trail Making Test</b>					
Part A	-3,32 [12,30]	-1,93 [17,77]	-1,62 [15,82]	-1,46 [12,52]	0,818
Part B	-1,56 [34,20]	-2,10 [35,37]	-3,78 [36,03]	-2,32 [58,45]	0,988
<b>Verbal fluency</b>					
Category Naming Test	-1,06 [6,10]	1,05 [6,72]	0,90 [8,55]	-1,38 [6,67]	<b>0,027</b>
Controlled Oral Word Association Test	0,36 [5,37]	1,13 [5,69]	1,65 [6,43]	-0,20 [6,38]	0,167
<b>DSST (WAIS—R coding)</b>	0,26 [5,09]	1,13 [5,44]	1,12 [6,42]	-0,31 [6,21]	0,256
<b>Memory functioning‡</b>	-0,78 [17,62]	-0,27 [17,98]	1,48 [17,25]	1,36 [22,82]	<b>0,800</b>
<b>Consequences of everyday life‡</b>	-5,84 [29,48]	-4,76 [23,98]	-3,27 [23,31]	3,13 [26,48]	0,085
<b>Geriatric Depression Scale</b>	0,01 [2,48]	-0,41 [2,53]	0,13 [2,83]	-0,03 [2,43]	0,494
<b>Short Physical Performance Battery</b>	-0,16 [1,68]	-0,10 [1,37]	-0,12 [1,68]	-0,41 [1,62]	0,534

<sup>a</sup>ANOVA

DSST=Digit Symbol Substitution Test. WAIS—R=Wechsler Adult Intelligence Scale—Revised. ADCSADLPI=Alzheimer’s Disease Cooperative Study Activities of Daily Living Prevention Instrument. \*48 is the total possible score. ‡Measured on a visual analogue scale.

Table 2: Evolution of the cognitive assessments. Differences between (score at 3 years) - (score at baseline)

each of the available tests is evaluated using ANOVAs with Group (MDI plus omega-3, MDI plus placebo, omega-3 alone, placebo) as between-subject factor.

Converging with previous reports (Andrieu et al., 2017), no significant effect of the intervention was found on the evolution of the overall cognitive functioning (Mini-Mental State Examination (Folstein et al., 1975)), depression (Geriatric Depression Scale (Yesavage et al., 1982)), and physical fitness (Short Physical Performance Battery (Guralnik et al., 2000)). Similarly, no consequences were found on everyday life (Alzheimer’s Disease Cooperative Study Activities of Daily Living Prevention Instrument (Galasko et al., 2006)).

Concerning the evolution of the cognitive profile, no effect of group was found on the evolution of memory (as indexed by classical neurophysiological tests – Free and Cued Selective Reminding Test (Grober et al., 1988) – and self-report – Visual-analogue scale EVA (McNair and Kahn, 1983)) attention and executive functions (Digit Symbol Substitution Test (Wechsler, 1981) and TMT-A and TMT-B (Reitan, 1958)) or verbal letter fluency (Controlled Oral Word Association Test (Cardebat et al., 1990)). A significant effect on semantic verbal fluency (Category Naming Test) was found ( $p=.027$ ), but post-hoc comparisons (Bonferroni corrected) revealed no-significant difference between the three intervention groups and the control group. These results argue that our sub-sample ( $N=377$ ) is comparable to the original study population ( $N=1680$ ).

## 4.2 Segmentation-based statistical analysis of the interventions’ effect

These results rely on the longitudinal processing stream of the FreeSurfer software. One subject was excluded from this analysis due to a processing failure that could not be easily manually corrected. All the results for the evolution of every volumes and cortical thickness are reported in supplementary material. Table 3 summarizes the global result. No effect is observable in any regions, including the total white-matter, gray-matter or brain volume to intra cranial volume, for both interventions. This absence of observable effect is not related to the large number variables selected in this exploratory approach. Indeed the strongest difference are measured in the corpus callosum posterior and the left thalamus and their respective p-values without correction (respectively 0.036 and 0.043) are really high. By consequence no meaningful observation or hypothesis can be drawn from this experiment.

maximum Fisher statistic	univariate P-value (parametric)	corrected P-value (2000 permutations)
3.35	0.036	0.80

Table 3: Statistical analysis of morphological assessments relatively to treatment groups. Differences are evaluated using a simple linear model with no cross-effect. We report the global statistic over all the 142 variables. The maximum is attained on the volume of the posterior corpus callosum but the result is not significant after correction for multiple tests.

### 4.3 Deformation-based statistical analysis of the interventions’ effect

A significant effect of the treatments was found on the morphological evolution over the 3 years of follow-up (p-value = 0.018). This result for the primary efficacy analysis jointly consider both treatments (MDI and omega-3) and is corrected for the whole brain voxel-wise comparisons. The localization of this effect is visible on Figure 1(a). The effect is stronger in the peri-ventricular area in the left hemisphere near the temporoparietal junction (TPJ). Few differences are also visible in the right temporal lobe but are not statistically significant.

Further testing is done to evaluate if the effect is associated with the omega-3 or the MDI. The statistical maps are shown in Figure 1(b-c). The linear model associated with the omega-3 is found to be not significantly better than the constant model (p-value = 0.927) while the one with the MDI shows a significant correlation (p-value = 0.026). Furthermore, the model taking into account both variables do not perform significantly better than the one taking into account the MDI only (p-value=0.933). Moreover the pattern observed for the MDI is really similar to the one found for the joint modeling.

To summarize, the observed changes in the morphological evolution are only associated with the MDI. Consequently, in the following we focus on the description of the MDI effect only.

### 4.4 Description of the MDI effect on the brain morphology

In this section we visualize the effect of the MDI. First, the full 3-dimensional statistical z-map is represented in Figure 2. The positive cluster extent in the left posterior peri-ventricular area seems to indicate a relatively localized effect. However we should keep in mind that the displacements which are visible in this area could be induced by morphological changes in other parts of the brain. Moreover the high z-values in the corresponding area in the right hemisphere and in the right temporal lobe may indicate the existence of changes in regions too.

These results impose that the mean evolutions for the group undergoing MDI and the other one are different. Figure 3 represents the mean velocity fields parametrizing the longitudinal deformation for the subjects with or without the MDI. The omega-3 status is ignored to increase sample sizes as no morphological effect was found.

At first glance, both evolutions are similar and correspond to a normal aging process. The difference in the peri-ventricular area is visible and corresponds to a deformation of smaller amplitude. The main effect is visible in the TPJ with a slight asymmetry and a stronger difference on the left. We can also note a reduction of the deformation in both temporal lobes for subjects undergoing the MDI.

It is also possible to visualize the atrophy associated with these deformations. Indeed any spatial transformation can induce local volume changes. In our model, the relative volume change in each voxel is given by the log-Jacobian map (see Figure 4). Here the difference clearly shows a reduction of the atrophy in the whole brain (less atrophy in the parenchyma and less expansion in the CSF). However the pattern previously observed on the deformation was more localized. It suggests that the difference of evolution is associated with a global difference in volume loss but also a more complex reconfiguration of the morphology.

Integrating the log-Jacobian using a predefined segmentation can be used to assess the volume change of specific brain areas. Here, using a segmentation of 44 regions provided the FreeSurfer software, the main regions affected by the MDI are the left lateral ventricle, the left inferior ventricle and the right hippocampus. No region shows a significant effect when correcting for multiple comparisons for this volumetric approach.

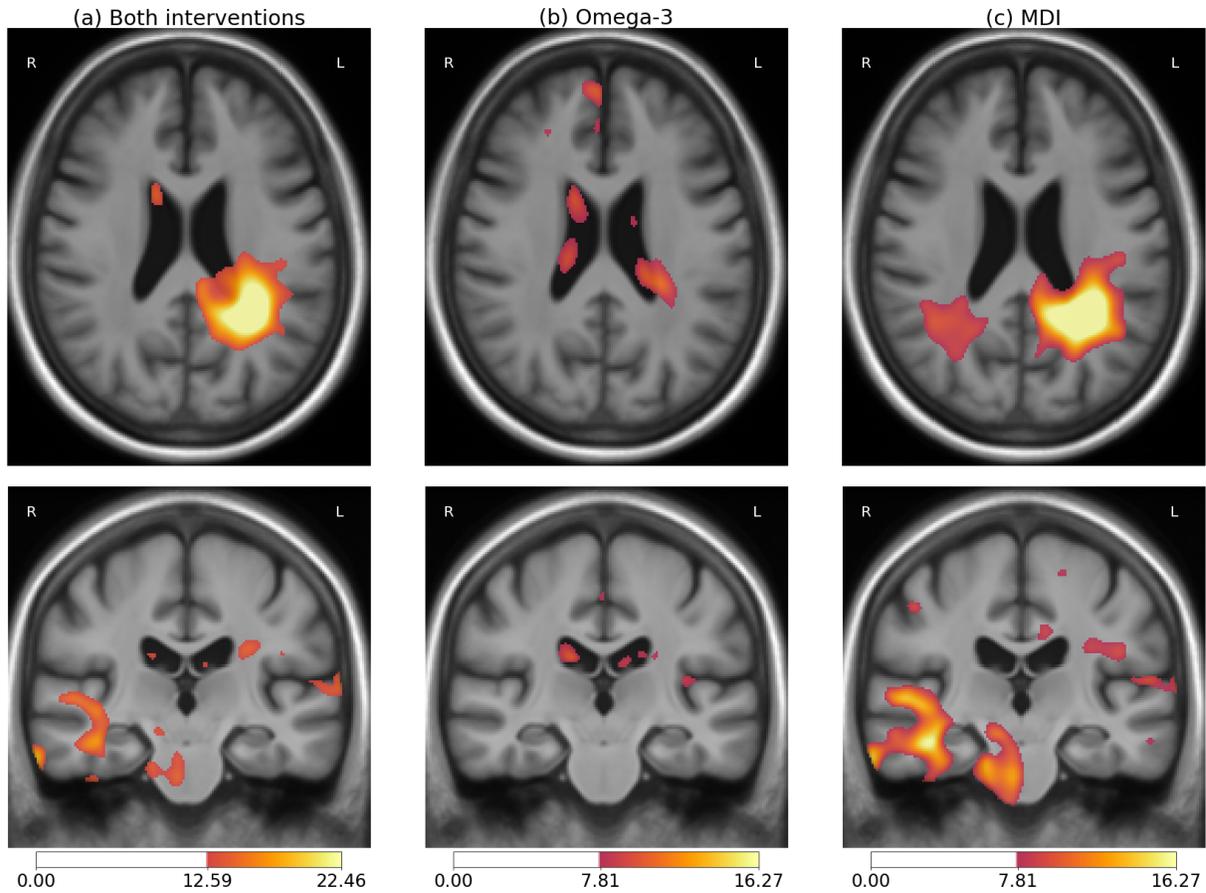


Figure 1: Voxel-wise z-values of the likelihood ratio test for the linear model taking into account: (a) both categorical variables associated with the omega-3 supplementation and the multidomain intervention, (b) omega-3 only, (c) multidomain intervention only. High values indicate a good fit of the model relatively to the constant model. Intensity thresholds correspond to the independent parametric testing at level 0.05 (lower threshold) and 0.001 (higher threshold).

3D z-value map of the MDI effect

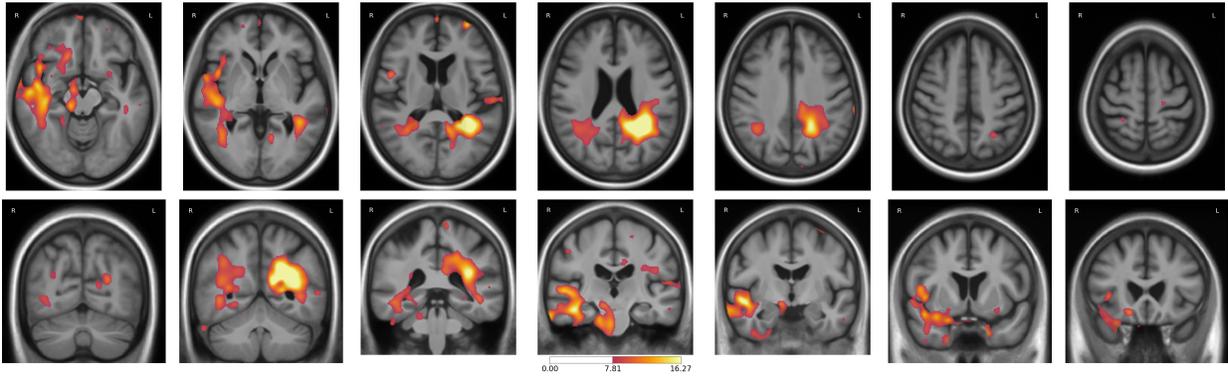


Figure 2: Voxel-wise z-values of the likelihood ratio test for the multidomain intervention effect. Intensity thresholds correspond to the independent parametric testing at level 0.05 (lower threshold) and 0.001 (higher threshold). Slice are sampled regularly every 12 mm in the longitudinal axis and every 15 mm along the axial axis. The central column corresponds to the results shown in Figure 1(c).

This confirms that the difference is only partially due to volume changes and is associated to a more complex morphological reconfiguration.

#### 4.5 Relation to cognitive and behavioral scores

No direct cognitive effects of the treatment was observed. However it is possible to relate the observed morphological differences to clinical assessments in order to better interpret the results. In this section we measure the correlation between the MDI specific morphological effect and the cognitive evolution measured by the clinical scores.

In the previous section, a regression model is used to evaluate the effect of the MDI. The SVFs that parametrize this model can be used to linearly decomposed the individual morphological evolutions. The explanatory variable resulting from this decomposition is then analyzed in relation with the evolution of four cognitive and behavioral scores. The four selected variables, introduced previously, are the Mini Mental State Examination (MMSE), the Geriatric Depression Scale (GDS), the free recall test and the category naming verbal fluency test. The evolution is measured by the difference in score between the 3-year followup and the baseline. The analysis is done using the whole population (i.e. the 376 subjects).

The correlation between the coefficients of the morphological decomposition and each clinical variable is assessed using a Fisher test. The results are presented in Table 4. The intercept measures the average evolution in cognitive score in the whole population while the coefficient corresponds to the average change for a difference in morphological evolution equal to the difference between the control and the MDI group.

The MDI specific brain evolution is statistically associated with positive cognitive and behavioral effects: decrease in the GDS total score and increase of the memory recall test. For comparison, no significant longitudinal evolution in GDS is observed for the control group while a general improvement in recall performance is observed for the overall population (the morphological changes of interest being associated a better amelioration). The effect on MMSE and fluency is not significant but, in both cases, it corresponds to a slowing of the cognitive decline.

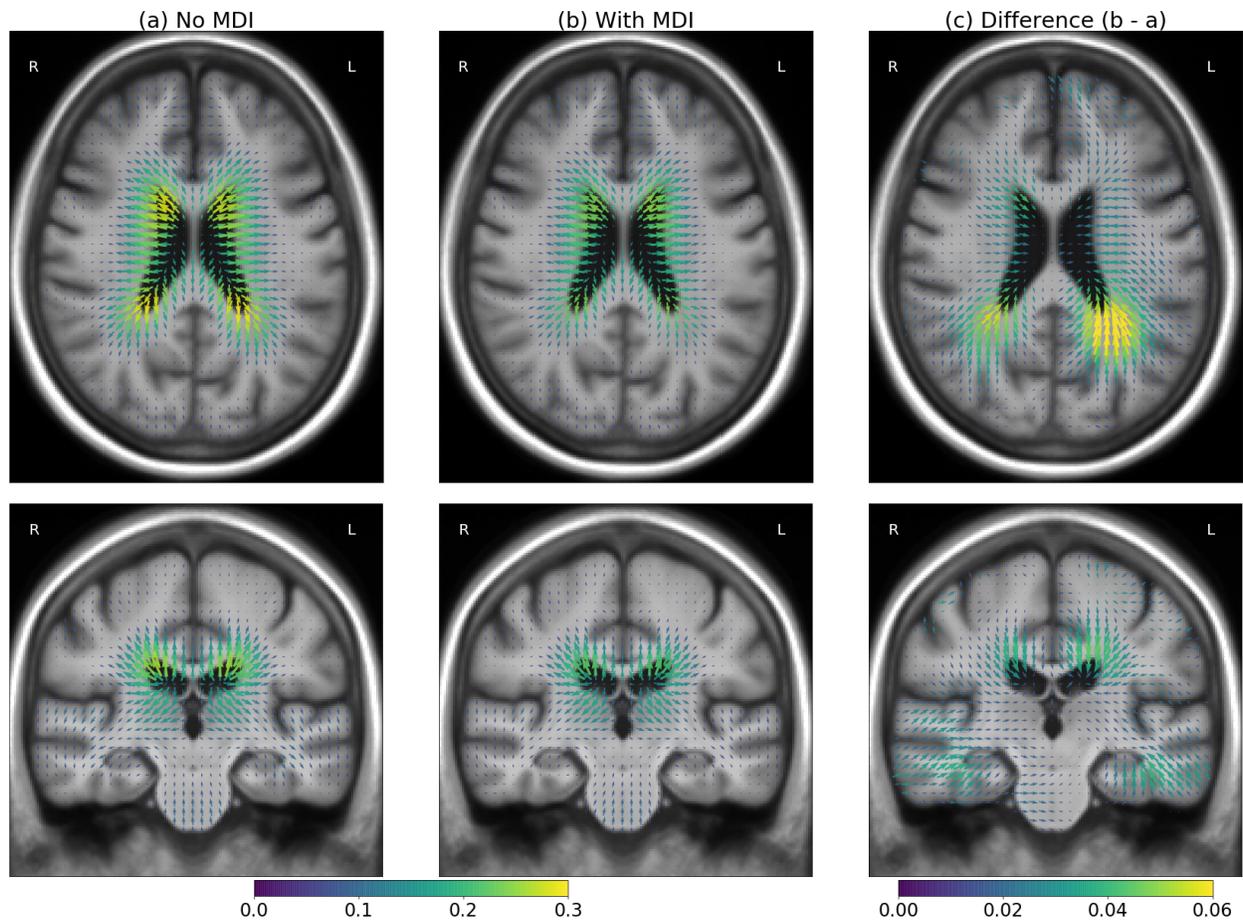


Figure 3: Mean velocity fields parametrizing the deformation for the subjects without MDI (left) and with MDI (center). The difference (right, scaled  $\times 5$ ) highlights the changes associated with the intervention. The two means are really similar, the main difference is a smaller amplitude of deformation in the peri-ventricular area.

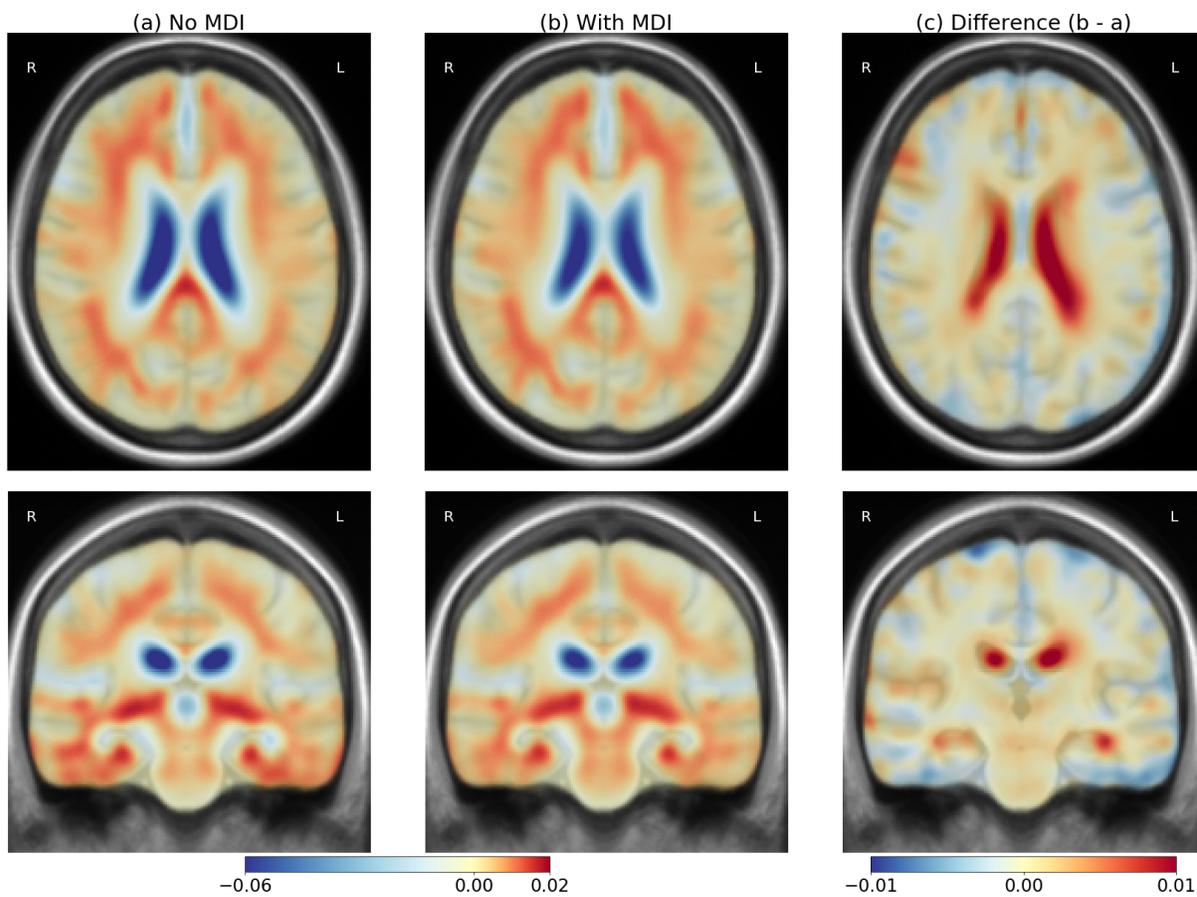


Figure 4: Mean atrophy for the subjects without MDI (left) and with MDI (center) and the difference (right) to highlights the changes associated with the intervention. The two means are really similar, the difference correspond to a global slower atrophy pattern.

	F-test p-value	intercept [CI]	coefficient [CI]
MMSE	0.078	-0.14 [-0.35, +0.066]	0.097 [-0.011, +0.2]
GDS	<b>0.011</b>	0.013 [-0.25, +0.28]	<b>-0.18</b> [-0.32, -0.042]
Recall	<b>&lt;0.001</b>	<b>1.3</b> [+0.71, +1.8]	<b>0.55</b> [+0.26, +0.84]
Fluency	0.44	-0.2 [-0.94, +0.55]	0.15 [-0.23, +0.54]

Table 4: Test for correlation between the MDI morphological effect and the cognitive or behavioral clinical assessments. The intercepts correspond to the average 3-year evolution, the coefficients correspond to the score change for a change in morphological evolution equal to the difference between the control group and the MDI group.

## 5 Discussion

The statistical analysis of the brain deformations estimated from structural MRIs shows a possible effect of the MDI on the morphological changes. Differences are observed in peri-ventricular area and in the temporal lobes in an asymmetrical pattern. The effect is stronger in the left hemisphere near the pre-cuneus and using a non-parametric analyses, we show that this effect is statistically significant. No visible effect was found for the omega-3 supplementation relatively to the placebo.

### 5.1 Interpretation of the morphological changes

First we need to note that locally and globally the MDI is also associated with a general pattern of reduction of deformation and atrophy in the whole brain. It would mean that the evolution is similar but slower thanks to the interventions. This evolution is mainly visible through the ventricular expansion and would explain that the effect is visible at the ventricle boundary. However the difference are not uniformly spread in the brain and in particular the left hemisphere is more affected.

The localization of the effect in the deep white matter may also indicate a direct effect on the myelinated axons in this area. Physiological changes in these area could have complex implication on the general cognitive condition. It is particularly interesting as the damage on the white matter tracks is not necessarily correlated with cortical atrophy as shown by Agosta et al. (2011) for amnesic patients with mild cognitive impairment. These observations would give early signs of the decline before the cortical atrophy.

The asymmetry could be related to the selection of exercises proposed in the MDI. A focus on tasks strongly relying on language would be associated with a stronger effect on the left hemisphere. One interpretation is that the intervention would increase or contribute to maintain the cognitive reserve in these areas.

Similarities can be found with early Alzheimer atrophy patterns where cortical atrophy is first observed in the temporal lobes, in the inferior parietal and posterior cingulate (McDonald et al., 2009). The difference of atrophy measured between controls and MDI subjects is smoother and less localized but is not incompatible with this pattern. The atrophy in one region can create a deformation that propagate to neighboring regions where the displacements may be more visible.

Finally, the correlation of the morphological effect with the cognitive and behavioral evolution suggests a possible long-term improvement of the subjects cognitive and behavioural profile. Moreover, the amplitude of the effect could be comparable to the normal speed of the cognitive decline.

### 5.2 Limitations

The selected morphometric approach gives a rough localization of visible structural displacements in the brain. The localization incertitude is reinforced by the fact that registration algorithms are not able to accurately estimate deformations in intensity homogeneous area and by consequence, the method can be more sensitive in high contrast area and miss some information elsewhere. Beside we saw that these deformations may be

not directly related to local volume changes. The use of a full diffeomorphic deformation is powerful to detect subtle changes but the increase in complexity and generality makes the interpretation of the results more difficult.

Moreover, it is difficult to interpret the observed differences because we can only consider the joint effect of the MDI which regroups a large spectrum of activity (social interactions, physical cognitive exercises, nutritional advice, etc.). The interpretation is also made difficult because no direct effect of the treatment on the cognitive evolutions has been shown. And, in this work, the relation between these morphological changes and the cognitive condition studied in section 4.5 is evaluated on the same dataset and could be really sensitive to hidden exogenous variables.

Finally, the implementation of the statistical model has its own limitations. It makes the GLM model applicable to multivariate fields but does not include alternative approaches such as mixed-effect modeling or computational optimisations. It would also be interesting to try to replicate these results with a different morphological modeling and statistical approach as the model choice and the software may influence the findings (Bowring et al., 2018).

### 5.3 Perspectives

Further analyses should be done to better understand the nature of the changes, their localization and the long-term consequence on the cognition.

An analysis of the deformation over a longer time interval could increase the accuracy of the estimation. It would also make it possible to link the local deformations to the cognitive evaluation despite the intrinsic variability of these assessments. Then, in conjunction with structural images, metabolic or functional imaging would give complementary information on the localization and the nature of the changes. Diffusion imaging could help validating the hypothesis concerning the effect of the interventions on the white matter tracks.

In order to design better protocols, it would be interesting to know the relative contribution of each intervention within the MDI. We should however note that the observed joint effect is relatively weak and it would not be an easy task.

Finally, the long-term effect on cognition should be assessed. It could be interesting to focus on cognitive tests evaluating functions which rely on the highlighted areas. The morphological effect of the multi-domain intervention goes against changes that are usually associated with the aging of the brain and the decline of the cognitive functions. However even if these changes are correlated, we have no proof that the MDI has a long-term protective effect that could be used for the prevention of the cognitive decline and of an eventual dementia.

## 6 Conclusion

In the context of the MAPT study, a significant effect of the multidomain intervention on the brain morphology was found. The voxel-wise deformation-based approach highlights differences in the white matter near the left temporoparietal junction. These morphological changes correspond to a slower morphological evolution and are correlated with better performance in cognitive assessments. These results are in agreement with previous studies suggesting a positive effect of a similar intervention on cognitive health in older adults (Kivipelto et al., 2018). To go further, the long-term effects of the intervention on the cognitive and behavioral condition should be evaluated.

From the methodological standpoint, the results of the present study suggest that the statistical analysis of longitudinal deformations may be a really powerful tool to assess the morphological changes and the effect of a treatment even without priors on the affected areas. In this work, we were unable to observe these differences using the volumetric approach, which suggest that the observed effect is associated with a complex morphological reconfiguration that cannot be reduced to simple local volume changes. This work thus suggests that the morphological changes may help to link physiological changes and changes in cognitive functions, even before changes in cognitive functions are clinically relevant.

## 7 Declaration of interests

The authors have no competing interests to declare.

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