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RESEARCH ARTICLE

Physical activity, biomarkers of brain pathologies and dementia risk: Results from the Memento clinical cohort

Leslie Grasset¹ | Vincent Planche² | Vincent Bouteloup^{1,3} | Chabha Azouani⁴ |
Bruno Dubois⁵ | Frédéric Blanc⁶ | Claire Paquet⁷ | Renaud David⁸ |
Catherine Belin⁹ | Thérèse Jonveau¹⁰ | Adrien Julian^{11,12} | Jérémie Pariente^{13,14} |
Jean-François Mangin^{4,15} | Geneviève Chêne^{1,3} | Carole Dufouil^{1,3} | on behalf of the
Memento Cohort Study Group

¹University of Bordeaux, Inserm, Bordeaux Population Health Research Center, UMR 1219, CIC1401-EC, Bordeaux, France

²University of Bordeaux, CNRS UMR 5293, Institut des Maladies Neurodégénératives, Centre Mémoire de Ressources et de Recherches, Pôle de Neurosciences Cliniques, CHU de Bordeaux, Bordeaux, France

³Pole de sante publique Centre Hospitalier Universitaire (CHU) de Bordeaux, Bordeaux, France

⁴CATI multicentre imaging platform, US52-UAR2031, CEA, ICM, SU, CNRS, INSERM, APHP, Gif-sur-Yvette, France

⁵IM2A AP-HP INSERM UMR-S975 Groupe Hospitalier Pitié-Salpêtrière Institut de la Mémoire et de la Maladie d'Alzheimer Institut du Cerveau et de la Moelle épinière Sorbonne Université Paris, Paris, France

⁶ICube laboratory, Pôle de Gériatrie, Université de Strasbourg, CNRS, UMR 7357, Fédération de Médecine Translationnelle de Strasbourg, Centre Mémoire de Ressources et de Recherches, Strasbourg, France

⁷Université de Paris Cité, Centre de Neurologie Cognitive GHU APHP Nord Hôpital Lariboisière, INSERMU1144, Paris, France

⁸Department of Old Age Psychiatry, Nice University Hospital, Nice, France

⁹Service de Neurologie Hôpital Saint-Louis AP-HP, Paris, France

¹⁰Centre Mémoire de Ressources et de Recherche de Lorraine, Service de Neurologie CHRU Nancy, Laboratoire Lorrain de Psychologie et de Neurosciences de la dynamique des comportements 2LPN EA 7489 Université de Lorraine, Nancy, France

¹¹Service de Neurologie CHU La Milétrie Centre Mémoire de Ressources et de Recherche, Poitiers, France

¹²Centre d'Investigation Clinique CIC1402, Poitiers, France

¹³Department of Neurology, Toulouse University Hospital, Toulouse, France

¹⁴Toulouse Neuroimaging Center, Université de Toulouse, Inserm, UPS, Toulouse, France

¹⁵Université Paris-Saclay, CEA, CNRS, Neurospin, UMR 9027, Gif-sur-Yvette, France

Correspondence

Leslie Grasset, INSERM U1219, University of Bordeaux, 146 rue Léo Saignat, 33077 Bordeaux, France.
E-mail: leslie.grasset@u-bordeaux.fr

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Abstract

INTRODUCTION: This study aims to examine whether physical activity moderates the association between biomarkers of brain pathologies and dementia risk.

METHODS: From the Memento cohort, we analyzed 1044 patients with mild cognitive impairment, aged 60 and older. Self-reported physical activity was assessed using the International Physical Activity Questionnaire. Biomarkers of brain pathologies com-

Geneviève Chêne and Carole Dufouil contributed equally to this study.

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prised medial temporal lobe atrophy (MTA), white matter lesions, and plasma amyloid beta (A β)42/40 and phosphorylated tau181. Association between physical activity and risk of developing dementia over 5 years of follow-up, and interactions with biomarkers of brain pathologies were tested.

RESULTS: Physical activity moderated the association between MTA and plasma A β 42/40 level and increased dementia risk. Compared to participants with low physical activity, associations of both MTA and plasma A β 42/40 on dementia risk were attenuated in participants with high physical activity.

DISCUSSION: Although reverse causality cannot be excluded, this work suggests that physical activity may contribute to cognitive reserve.

KEYWORDS

brain changes, cognitive reserve, dementia, physical activity

Highlights

- Physical activity is an interesting modifiable target for dementia prevention.
- Physical activity may moderate the impact of brain pathology on dementia risk.
- Medial temporal lobe atrophy and plasma amyloid beta 42/40 ratio were associated with increased dementia risk especially in those with low level of physical activity.

1 | BACKGROUND

With the rapid aging of the population, a growing number of individuals will be at risk of developing neurodegenerative diseases.¹ In the absence of effective treatments against dementia, identifying protective factors of cognitive decline that could therefore delay dementia onset is of utmost importance. Physical activity represents an interesting modifiable target for prevention strategies, and intervention could be implemented in the elderly population. Indeed, in addition to its global benefits for health,²⁻⁴ a high level of physical activities may lower dementia risk and attenuate cognitive decline, even at older ages.⁵⁻⁸ Interestingly, it has also been shown that higher levels of physical activity are related to better cognitive performance among individuals at higher risk of dementia such as individuals with mild cognitive impairment (MCI).⁹⁻¹¹ Therefore, physical activity should also be explored as a potential target for delaying conversion to dementia in symptomatic older persons with MCI.

Brain pathologic changes, such as small vessel disease, Alzheimer's disease (AD) neuropathology (amyloid plaques and neurofibrillary tangles), and brain atrophy can develop decades prior to dementia diagnosis, and accelerate its clinical onset. There is growing evidence that older adults being physically more active may preserve longer their brain health assessed with brain volume, cortical thickness, or functional activity.¹²⁻¹⁴ A few studies have also reported reduced AD pathology or lower load of cerebrovascular disease with higher physical activity.¹⁵⁻¹⁸ However, whether physical activity may contribute to cognitive reserve and modify the negative impact of these brain changes on dementia risk remains unclear, especially for indi-

viduals already experiencing some cognitive impairment.¹⁹ Cognitive reserve is a concept referring to the ability to maintain adequate cognitive functions despite development of brain pathologies.²⁰ Individuals with higher cognitive reserve may thus be able to compensate for the negative effects of brain pathologies. A factor contributing to cognitive reserve will moderate the impact of brain pathologies on cognitive decline.²¹ Some studies, mainly among cognitively normal individuals, have reported that physical activity moderates the association between some brain pathologies (AD pathology, cerebrovascular injury, or brain atrophy) and cognitive function or decline, which is consistent with the concept of cognitive reserve.^{20,22-27} However, results from some other studies did not support the contribution of physical activity to cognitive reserve.^{22,25,28,29} Inconsistent findings across studies can be explained by selection biases (various sample sizes, convenience sampling, and different study settings) as well as lack of comparability of selected biomarkers of brain pathologies. Moreover, most previous studies were conducted among cognitively healthy older adults, and whether similar relationships are present in cognitively impaired persons, such as MCI participants, remains uncertain. Evidencing a moderating effect of physical activity on brain pathologies over conversion from MCI to dementia would be of interest to delay symptom worsening for individuals at higher risk of dementia.

For this work, we thus aimed to investigate the contribution of physical activity to cognitive reserve among consecutively enrolled MCI patients followed over up to 5 years from a large clinical cohort. In particular, we assessed the moderating effect of physical activity on the association between selected magnetic resonance imaging (MRI) and plasma biomarkers of brain pathology and conversion to dementia.

2 | METHODS

2.1 | Study population

The Memento cohort is a prospective clinic-based study aiming to better understand the natural history of AD and related disorders. Details of the study have been previously published.³⁰ Briefly, 2323 participants consulting within 26 French memory clinics and presenting with either isolated cognitive complaints or recently diagnosed MCI were recruited from April 2011 to June 2014. Clinical MCI was defined as having a Clinical Dementia Rating (CDR) = 0.5. Participants were examined at baseline and followed every 6 to 12 months up to 5 years. Baseline data collection during face-to-face interview included socio-demographic characteristics, lifestyle factors, neurological and physical examination, and a full neuropsychological battery. Baseline brain MRI was mandatory for Memento participants but only 2183 had an MRI due to either post-consent refusal or contraindication. Of the 2183, 86% of participants included in the Memento cohort had a 3.0 Tesla MRI scan (1.5 Tesla for the others). Plasma samples were also obtained at baseline for all participants.

Among the 2323 Memento participants, 1194 participants were ≥ 60 years and had clinical MCI at baseline. We then excluded those without follow-up ($n = 15$), as well as participants with missing physical activity status at baseline ($n = 135$), leaving a final analytical sample of 1044 participants.

2.2 | Physical activity definition

Physical activity data were collected using the short version of the International Physical Activity Questionnaire (IPAQ).³¹ It consists of seven questions self-assessing intensity of physical activity (vigorous, moderate, and walking) that people had been doing as part of their daily lives over the past 7 days. It estimates total physical activity in metabolic equivalent of task (MET)-minutes/week by multiplying the number of minutes dedicated to each activity class over a week by the specific MET score for that activity (walking = 3.3 METs, moderate = 4.0 METs, and vigorous = 8.0 METs). In addition, physical activity was also categorized as low, moderate, and high according to the IPAQ scoring protocol³²: (1) high intensity was defined as engaging in either vigorous intensity activity on at least 3 days achieving a minimum total physical activity of at least 1500 MET minutes a week, or 7 or more days of any combination of walking, moderate intensity, or vigorous intensity activities achieving a minimum total physical activity of at least 3000 MET minutes a week; (2) moderate intensity was defined as engaging in either 3 or more days of vigorous intensity activity and/or walking of at least 30 minutes per day, or 5 or more days of moderate intensity activity and/or walking of at least 30 minutes per day, or 5 or more days of any combination of walking, moderate intensity, or vigorous intensity activities achieving a minimum total physical activity of at least 600 MET minutes a week; (3) participants who did not meet the above criteria were classified as having low level of physical activity.

RESEARCH IN CONTEXT

- 1. Systematic Review:** We searched PubMed for all articles investigating the interactions between physical activity and biomarkers of Alzheimer's disease and related dementias in relation to dementia risk or cognitive function or decline published up to October 1, 2022. Few studies investigated the moderating effect of physical activity on the associations between markers of brain pathology and dementia risk.
- 2. Interpretation:** In this prospective clinic-based cohort of participants with mild cognitive impairment (MCI), physical activity modified the association with dementia risk of both medial temporal lobe atrophy (MTA) and plasma amyloid beta ($A\beta$)42/40 ratio. Indeed, strengths of the associations between MTA and plasma $A\beta$ 42/40 ratio and dementia risk were attenuated for participants with higher levels of physical activity.
- 3. Future Directions:** Physical activity in late life may be an interesting modifiable target to reduce the negative impact of brain pathology on conversion from MCI to dementia.

2.3 | Neuroimaging biomarkers of brain pathology

All neuroimaging acquisitions and analyses were coordinated by the Center for Acquisition and Treatment of Images (CATI; catineuroimaging.com), a platform dedicated to the management of multi-center neuroimaging studies.³³ Scans were harmonized across centers, centralized, quality checked, and postprocessed to obtain standardized acquisitions. Medial temporal lobe atrophy (MTA) was rated visually by two trained physicians from the CATI team, using Scheltens' scale.³⁴ MTA was dichotomized according to validated cut-offs: high MTA was defined as a Scheltens' scale score of 2 in either of the two hemispheres in individuals < 75 years, or a MTA score of 3 in individuals aged ≥ 75 years.³⁵ White matter lesion (WML) severity was also rated by visual assessment of whole brain deep and periventricular lesions done centrally by two trained raters using the Fazekas scale.^{36,37} A score of 0 to 3 was assigned separately to periventricular and subcortical WML (sum 0–6), and severe WML was defined as a Fazekas sum score of 4 to 6.

We investigated baseline measurement of MTA as a marker of hippocampal atrophy, a key structure in AD-related neurodegeneration, and WML as a marker of small vessel disease.

2.4 | Plasma biomarkers of brain pathology

Plasma amyloid beta ($A\beta$)42, $A\beta$ 40, phosphorylated tau 181 (p-tau181) concentrations were measured using Simoa technology with

commercial kits on a Quanterix HD-1 analyzer. Measures were performed in the same laboratory for all participants (Bordeaux University Hospital), blinded of clinical outcomes. Plasma A β 42/40 ratio and p-tau181 were used as markers of amyloid and tau pathology, respectively.

2.5 | Outcome definition

During a 5-year follow-up period, patients underwent a clinical and neurologic evaluation every 6 to 12 months. Incident cases of dementia were then assessed by trained neurologist according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Revision (DSM-IV) criteria. AD dementia was ascertained using criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). In addition, all dementia cases were reviewed and validated by an independent endpoint review committee composed of expert neurologists/geriatricians based on individuals' case files.

2.6 | Additional covariables

Education level was categorized as lower versus higher than high school level. Apolipoprotein E (APOE) ϵ 4 status was defined as at least one ϵ 4 allele carried versus none. Smoking status, as well as diabetes status and cardiovascular disease history, were self-reported at baseline. Hypertension was defined as either arterial pressure \geq 140/90 mmHg or antihypertensive drug use. Body mass index (BMI) was objectively measured at baseline examination.

2.7 | Statistical analysis

Participants' characteristics at baseline were compared across physical activity levels using Kruskal–Wallis and χ^2 tests, as appropriate. Associations between physical activity and each marker of brain pathology were tested using logistic regression for MTA and severe WML, and linear regression for plasma A β 42/40 ratio and p-tau181 level, adjusted for age at baseline, sex, APOE ϵ 4 status, education level, hypertension, and BMI.

To estimate dementia risks associated with physical activity, we performed Cox models with delay between study entry and event or censoring being the time scale. Participants who remained free of dementia were censored at the age of their last known dementia-free visit or at age of death. A β 42/40 ratio was reverse coded so that higher levels represented greater amyloid pathology. A β 42/40 ratio and p-tau181 were log-transformed and standardized. First, we evaluated the association between physical activity intensity (modeled either as log-transformed MET-minutes/week, or as categorical physical activity levels [low, moderate, and vigorous]) and dementia risk, without or with adjustments for the four different markers of brain pathologies.

These models were additionally adjusted for age at baseline, sex, APOE ϵ 4 status, education level, hypertension, and BMI.

Then, we generated dementia incidence rates according to levels of physical activity and of each marker of brain pathology using Poisson models adjusted for age at baseline, sex, APOE ϵ 4 status, education level, hypertension, and BMI. For continuous plasmatic biomarkers, incidence rates are presented for both low and high (\pm 1 standard deviation [SD]) pathology (A β 42/40 or p-tau181).

Moreover, interactions between physical activity levels and biomarkers of brain pathologies on dementia risks were added and tested within the initial Cox models (also adjusted for age at baseline, sex, APOE ϵ 4 status, education level, hypertension, and BMI) to investigate the moderating effect of physical activity. Hazard ratios of the associations between each biomarker and dementia risk were presented for the three levels of physical activity. Similar models were performed with AD dementia as the outcome (non-AD dementia cases were censored at the end of the follow-up). In a post hoc analysis, we also tested whether the moderating effect of physical activity differed by biological sex.

Sensitivity analyses were performed to assess the robustness of our findings. The main results reported were based on a complete case analysis under the assumption that missing data for biomarkers and covariates ($n = 134$) were missing completely at random (MCAR). Multiple imputation by chained equations with a fully conditional specification (20 imputed data sets) was used to impute missing data to assess the plausibility of the MCAR assumption. Then, an alternative categorization for physical activity was used based on guidelines for physical activity, with a cut-off of at least 500 MET-minutes/week considered high physical activity. Finally, as plasma AD biomarker variability depend on kidney disease function,³⁸ all models that included AD blood biomarkers either as exposure of interest or as potential confounder were adjusted for the glomerular filtration rate (using the Chronic Kidney Disease Epidemiology Collaboration definition).

Analyses were conducted using R (version 4.1.3).

3 | RESULTS

Analytical sample characteristics are presented in Table 1. Participants were 72.7 years old on average, and more often women (59%). Half of the participants had a high education level, and 30% were APOE ϵ 4 carriers. Compared to participants with low physical activity, those with moderate and high physical activity were more often APOE ϵ 4 carriers, had higher education level, less often had hypertension, and had a lower BMI on average. Table S1 in supporting information shows associations between physical activity and biomarkers of brain pathologies. Globally, we found no differences according to physical activity, with only a trend toward less severe WML and higher levels of p-tau181 with higher levels of physical activity. Participants with missing biomarkers or covariates had higher levels of plasma amyloid pathology and less often severe WML (Table S2 in supporting information).

TABLE 1 Description of population characteristics according to physical activity levels, the Memento cohort.

	Total N = 1044	Low N = 199	Moderate N = 422	High N = 423	P-value
Female	616 (59.0)	131 (65.8)	247 (58.5)	238 (56.3)	0.07
Age at baseline	72.7 (6.9)	73.1 (7.5)	73.0 (6.7)	72.1 (6.6)	0.09
APOE ϵ 4 carriers	317 (30.4)	50 (26.3)	120 (30.0)	147 (36.7)	0.02
High education level	521 (49.9)	84 (42.2)	216 (51.2)	221 (52.2)	0.05
Smoker	74 (7.1)	17 (8.5)	31 (7.4)	26 (6.1)	0.53
Diabetes	129 (12.4)	32 (16.1)	45 (10.7)	52 (12.3)	0.16
Hypertension	657 (62.9)	139 (70.9)	271 (65.5)	247 (59.5)	0.02
CVD history	164 (15.7)	32 (16.1)	77 (18.2)	55 (13.0)	0.11
BMI	25.6 (4.3)	26.8 (4.8)	25.6 (4.5)	25.0 (3.7)	<0.01
MET-minute/week	2373 [1052–4568]	495 [244–884]	1646 [1074–2313]	5040 [3906–7383]	<0.01
A β 42/40 ratio	0.05 [0.05–0.06]	0.06 [0.05–0.06]	0.06 [0.05–0.06]	0.06 [0.05–0.06]	0.60
P-tau181	0.95 [0.60–1.45]	0.91 [0.57–1.38]	0.95 [0.60–1.45]	0.98 [0.64–1.50]	0.31
High MTA	208 (19.9)	35 (18.4)	76 (18.7)	97 (23.9)	0.13
Severe WML	292 (28.0)	58 (29.1)	126 (29.9)	108 (25.5)	0.34

Note: Categorical variable: N (%); Continuous variable: mean (sd) or median [IQR] as appropriate. (Missing data: APOE- ϵ 4 = 53, Smoker = 1, Hypertension = 19, BMI = 13, A β 42/40 ratio = 28, P-tau181 = 17, MTA = 42).

Abbreviations: A β , amyloid beta; APOE, apolipoprotein E; BMI, body mass index; CVD, cardiovascular disease; MCI, mild cognitive impairment; MET, metabolic equivalent of task; MTA, medial temporal lobe atrophy; p-tau181, phosphorylated tau; WML, white matter lesions.

TABLE 2 Associations between baseline physical activity and dementia (all and Alzheimer's disease) risks over 5-year follow-up.

N = 910 ^a	All dementia		Alzheimer's disease dementia	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Model 1				
Physical activity (per 1 log MET increase)	0.90 (0.82–0.98)	0.02	0.92 (0.83–1.02)	0.13
Physical activity				
Moderate versus low	0.72 (0.49–1.06)	0.09	0.75 (0.49–1.16)	0.20
High versus low	0.75 (0.51–1.10)	0.14	0.85 (0.56–1.31)	0.46
Model 2				
Physical activity (per 1 log MET increase)	0.83 (0.76–0.92)	0.0002	0.85 (0.7–0.95)	0.003
Physical activity				
Moderate versus low	0.64 (0.44–0.94)	0.02	0.67 (0.43–1.03)	0.07
High versus low	0.58 (0.39–0.86)	0.007	0.66 (0.42–1.02)	0.06

Note: Model 1: adjusted for age at baseline, sex, education level, APOE ϵ 4 status, hypertension, and BMI. Model 2: Model 1 + additionally adjusted for markers of brain changes (medial temporal lobe atrophy, white matter lesions, and plasma levels of A β 42/40 ratio and p-tau181).

^aA total of 134 had missing data (APOE ϵ 4 = 53, hypertension = 19, BMI = 13, A β 42/40 ratio = 28, p-tau181 = 17, MTA = 42).

Abbreviations: A β , amyloid beta; APOE, apolipoprotein E; BMI, body mass index; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; MTA, medial temporal lobe atrophy; p-tau181, phosphorylated tau.

Over the 5-year follow-up, 202 dementia cases were diagnosed. Increasing physical activity (measured as continuous) was associated with lower risk of dementia, without (hazard ratio [HR] for 1 log MET-minute/week = 0.90 [95% confidence interval (CI): 0.82–0.98]) and with (HR = 0.83 [95% CI: 0.76–0.92]) adjustment for markers of brain pathologies (Table 2). Similarly, when studying physical activity as categorical exposure, compared to low physical activity, moder-

ate and high physical activity tended to be associated with decreased dementia risk, although the association did not reach statistical significance (HR = 0.72 [95% CI: 0.49–1.06] and HR = 0.75 [95% CI: 0.51–1.10], respectively). After further adjustment for markers of brain pathologies, compared to low physical activity, the HRs for dementia declined and became statistically significant toward protective association (HR = 0.64 [95% CI: 0.44–0.94] for moderate physical activity

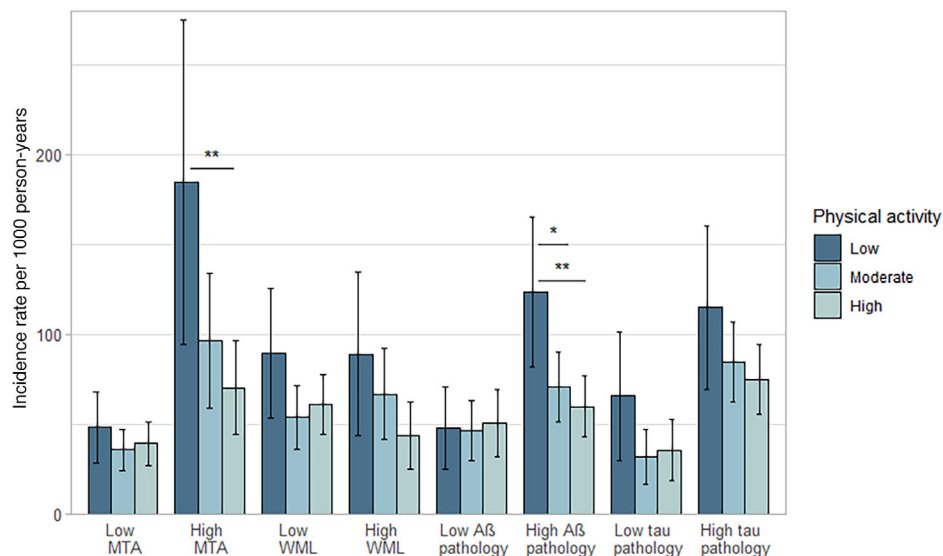


FIGURE 1 Incidence rates of dementia per 1000 person-years according to physical activity and markers of cerebral lesion status. A β , amyloid beta; MTA, medial temporal lobe atrophy; WML, white matter lesions.

and HR = 0.58 [95% CI: 0.39–0.86] for high physical activity). Strengths of the associations between moderate physical activity and risk of AD dementia were similar to the ones of dementia risk, while associations between high physical activity and AD dementia risk were weaker (Table 2).

Incidence rates of dementia per 1000 person-years according to physical activity level and to biomarkers of brain pathologies are displayed in Figure 1. We observe a trend for decreased incidence rates of dementia with increasing levels of physical activity, more marked in participants with higher levels of brain pathology. For high MTA and A β pathology, incidence rates of dementia were statistically significantly lower in people with high physical activity compared to those with low physical activity.

The study of the interactions between physical activity levels and biomarkers of brain pathologies on dementia risk are displayed in Table 3. In the group of participants with high level of physical activity, dementia risks associated with MTA and plasma A β 42/40 ratio were statistically significantly weaker compared to the corresponding risks in the group of participants with low physical activity. As physical activity level increases, associations between MTA or amyloid pathology and dementia risk decreased. For instance, for an increase of 1 SD of A β 42/40 ratio level (reverse coded; i.e., higher pathology levels), HRs for dementia were 1.64 (95% CI: 1.33–2.03) in persons with low physical activity compared to 1.23 (95% CI: 1.03–1.46) in persons with moderate physical activity and 1.09 (95% CI: 0.88–1.33) in persons with high physical activity. There were no statistically significant interactions between severe WML or plasma p-tau181 and physical activity on dementia risk. Regarding AD dementia, physical activity moderated the association between dementia risk and plasma A β 42/40 (but not MTA). In addition, biological sex interacted with physical activity to moderate the associations between MTA or A β 42/40 ratio and dementia risk, but not severe WML or p-tau181 level. MTA and A β 42/40 ratio were more strongly associated with dementia risk in men compared

to women. The moderating effect of physical activity on the association between MTA or A β 42/40 ratio and dementia risk appeared to be stronger among men than women (Table S3 in supporting information).

Results from sensitivity analyses showed that our results were consistent both after imputing missing data under missing at random scenario and after adjusting for renal function (Table S4 in supporting information). When using a binary categorization of IPAQ (at least 500 MET-minutes/week: yes vs. no) based on physical activity recommendations, the moderating impact of higher physical activity on the association between MTA and dementia risk was attenuated whereas the moderating effect on other brain biomarkers was fairly consistent (Table S5 in supporting information).

4 | DISCUSSION

In this prospective study of MCI patients, higher physical activity levels were associated with reduced risks of developing dementia when controlling for biomarkers of brain pathologies. In addition, physical activity moderated the relationship between biomarkers of both neurodegeneration and amyloid pathology and risk of dementia, leading to attenuated associations of both MTA and plasma A β 42/40 ratio level with dementia risk for participants with the highest level of physical activity. We did not show evidence of a moderating effect of physical activity on the association between biomarkers of WML or tau pathologies on dementia risk. These results suggest that greater engagement in physical activity may contribute to cognitive reserve in specific ways and delay dementia onset in symptomatic older adults.

With the increasing prevalence of dementia, research focusing on modifiable factors promoting resilience, even for individuals at higher risk, is necessary to attempt to reduce the global burden related to dementia. Our findings are somewhat consistent with the rich literature suggesting a protective effect of physical activity on dementia

TABLE 3 Associations between biomarkers of brain pathologies and risk of dementia stratified by levels of physical activity.

	Low PA N = 178 HR (95% CI)	Moderate PA N = 365 HR (95% CI)	High PA N = 367 HR (95% CI)	Moderate versus low P-value*	High versus low P-value*
All dementia					
Medial temporal lobe atrophy	4.48 (2.40–8.33)	2.90 (1.79–4.67)	1.85 (1.18–2.90)	0.28	0.02
Severe white matter lesions	1.01 (0.53–1.90)	1.26 (0.65–2.47)	0.71 (0.44–1.16)	0.56	0.39
A β 42/40 ratio	1.64 (1.33–2.03)	1.23 (1.03–1.46)	1.09 (0.88–1.33)	0.04	0.007
P-tau181	1.33 (0.95–1.85)	1.64 (1.29–2.10)	1.46 (1.14–1.88)	0.31	0.64
Alzheimer's disease dementia					
Medial temporal lobe atrophy	3.21 (1.54–6.71)	3.87 (2.29–6.54)	1.87 (1.15–3.04)	0.69	0.23
Severe white matter lesions	0.84 (0.40–1.76)	1.36 (0.80–2.30)	0.68 (0.40–1.15)	0.29	0.63
A β 42/40 ratio	1.71 (1.35–2.17)	1.19 (0.97–1.46)	1.11 (0.89–1.46)	0.02	0.008
P-tau181	1.82 (1.23–2.69)	1.71 (1.30–2.26)	1.42 (1.08–1.86)	0.81	0.31

Note: Models adjusted for age at baseline, sex, education level, APOE ϵ 4 status, hypertension, BMI, and the three other markers of brain changes. MTA and WML are visually rated from MRI (Scheltens and Fazekas scales respectively), while A β 42/40 ratio and p-tau181 levels are plasma measures. Plasma A β 42/40 ratio was reverse coded so that higher levels represented greater amyloid pathology. Plasma A β 42/40 ratio and p-tau181 were standardized and units correspond to 1 SD increase. HR for MTA and severe WML are presented for presence versus absence, while HR for plasma A β 42/40 ratio and p-tau181 are presented for 1 SD increase.

*P-values of the interactions between physical activity and each biomarker.

Abbreviations: A β , amyloid beta; APOE, apolipoprotein E; BMI, body mass index; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; MRI, magnetic resonance imaging; PA, physical activity; MTA, medial temporal lobe atrophy; p-tau181, phosphorylated tau; SD, standard deviation; WML, white matter lesions.

risk.^{5,39} These results also add knowledge on the impact of physical activity on the conversion from MCI to dementia.^{9,40,41} They also complement evidence showing better cognitive and functional outcomes following exercise interventions among dementia patients.^{42,43} Yet, we did not evidence relationships between physical activity and brain pathologies consistent across the markers investigated. These results do not support the hypothesis that physical activity reduces dementia risk by preventing or delaying brain changes related to dementia development. This hypothesis would still need to be tested further in a setting in which the associations between physical activity and brain pathologies can be studied longitudinally.

Neuropathological and neuroimaging studies have suggested that many people may tolerate considerable cerebral changes without expressing clinical symptoms, consistent with the cognitive reserve concept.²⁰ Our results support this body of literature, as participants with higher physical activity experienced lower dementia risk while presenting with similar levels of brain pathologies. Cognitive reserve can be influenced by the interaction of innate individual differences and lifetime exposures such as lifestyle factors. The biological mechanisms underlying cognitive reserve lie in the adaptability of functional brain processes. Physical activity, by contributing to cognitive reserve, may allow physically active individuals with MCI to compensate, through increased synaptogenesis, for the negative effect of amyloid pathology and atrophy in the brain, thus tolerating more damage before developing cognitive impairment.¹⁹ Late-life physical activity may also enhance efficiency, capacity, or flexibility of brain networks when performing cognitive functions.⁴⁴

To appropriately investigate cognitive reserve mechanisms, a cognitive reserve–related factor, a brain measure, and a cognitive measure

are required.²¹ Up to date, only a few studies have explored the contribution of physical activity to cognitive reserve while accounting for brain pathology.^{22,24–26,28,29,45} They yielded heterogeneous findings. Our work evidenced weaker associations of MTA and plasma A β 42/40 ratio level with dementia risk across increasing levels of physical activity. Two studies from the Chicago Health and Aging Project showed a non-significant trend toward slower cognitive decline with higher physical activity, even for participants with high levels of serum neurofilament light chain and total tau.^{25,26} Another study reported that greater engagement in physical activity was protective against A β -related cognitive decline and neurodegeneration in 182 asymptomatic older adults.²⁴ In addition, from the Rush Memory and Aging Project study that used objectively measured physical activity, it was reported that within-person increase in physical activity attenuated the association between AD pathology and cognition.²⁷ Unlike our results, two other studies reported a moderating effect of physical activity on the associations of white matter hyperintensities with cognition.^{22,46} Memel et al. also reported that baseline physical activity attenuated the association between cerebrovascular pathology and cognition.²⁷ The absence of an interaction between physical activity and severe WML in our work may be due to characteristics of our study sample, as severe WML were not significantly associated with higher dementia risk in our study. However, two studies did not show an association between physical activity and markers of cognitive reserve using a residual approach for cognitive reserve.^{28,29} In addition, although physical activity was associated with better cognition after controlling for different brain pathologies, Buchman et al. did not evidence that a more active lifestyle modified the associations of brain pathologies with cognitive function proximate to death.⁴⁵ Only a few studies

investigated the moderating effect of physical activity on tau pathology with dementia risk or cognition. The absence of interaction we found may be due to the fact that individuals with high tau pathology may be too advanced in the disease process to benefit from physical activity's effects. In addition, only a few studies have looked at tau pathology and cognitive reserve;^{47,48} thus, future studies are needed to validate our results. Taken together, our results and others' support the hypothesis that different lifestyle factors may only moderate specific, but not all, markers of brain pathologies on cognition.

In addition to the type of pathology, both physical activity measurement and population characteristics may contribute to differences in results. Most studies investigating the contribution of physical activity to cognitive reserve used self-reported physical activity measures assessed through standardized questionnaires, which may be unreliable. However, questionnaires allow us to collect information on physical activity intensity and frequency. In our work, moderate physical activity was associated with a lower risk of dementia after adjustment for brain pathologies, but it was not significantly moderating the association between MTA and dementia risk. It seems that only higher levels of physical activity are required to significantly mitigate the negative association between brain atrophy and dementia risk. A few studies also used objective measures through pedometers or accelerometers, yet assessed physical activity over a limited period of time.^{24,27,45} Finally, regarding population characteristics, most studies were realized among population-based clinically normal older adults. This work thus extends previous findings to persons with MCI who are at risk of developing dementia. Moreover, our results suggest that physical activity may contribute to cognitive reserve more strongly in men than in women, potentially due to stronger associations between biomarkers of brain pathologies and dementia risk among men in the Memento cohort. Additional studies are required to confirm these sex differences.

This study has some limitations. First, physical activity exposure was self-reported at baseline, thus misclassification may have occurred and could have conferred to biased results. Moreover, low engagement in physical activity may be due to reverse causation, that is, people may become less physically active during the years preceding dementia onset, and biomarkers of brain pathologies were only measured once at baseline, thus causal interpretations must be drawn with caution. In addition, our physical activity questionnaire allowed us to assess physical activity within the past 7 days. Although this issue is common in studies assessing physical activity, it may not be representative of long-term physical activity habits. Participants excluded due to missingness had higher plasma amyloid levels and less severe WML; thus, our results may be specific to our study population. The sensitivity analysis using multiple imputation to account for selection yielded similar results, suggesting that the characteristics of the excluded participants in this study did not influence the moderation results. Finally, we used plasmatic markers of AD-related cerebral lesions, which may be less reliable than positron emission tomography or cerebrospinal fluid amyloid/tau markers. Still, plasmatic markers have been shown to associate with AD-related pathology and dementia risk⁴⁹ and our sensitivity analysis accounting for renal function yielded consistent results. In

addition, the Simoa platform was used for plasma AD biomarker quantification. It would be interesting to further assess the robustness of our results using alternative quantification of plasma AD biomarkers such as mass spectrometry-based methods that have been suggested to be stronger predictors of amyloid positivity.⁵⁰ It should also be noted that plasma biomarkers were not measured in duplicate. Nevertheless, several controls of reproducibility were realized on subsets throughout the study, leading to very satisfactory results.

This study also has important strengths and contributes to our understanding of the influence of physical activity with dementia risk. The Memento study provides an adequate setting to investigate, within a large sample size, the contribution of physical activity to cognitive reserve, due to the large availability of various neuroimaging and plasmatic AD-related markers. Additionally, this work relies on well-defined dementia cases, as each case was reviewed by a validation committee. Although self-reported, physical activity was assessed by a standardized and validated questionnaire, allowing us to investigate different levels of activity.

In conclusion, this work suggests that, in persons with MCI, higher levels of physical activity may attenuate the impact of cerebral atrophy and amyloid pathology on the risk of developing dementia. These results suggest potential pathways for modifying the effect of amyloid pathology and cerebral atrophy on cognition and dementia. They also suggest that promoting engagement in physical activity in persons at risk of developing dementia could delay dementia onset. Future studies adding longitudinal measures of markers of brain pathologies are needed to confirm the mechanisms involved in the association between physical activity and dementia.

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CONFLICT OF INTEREST STATEMENT

The authors have nothing to report. Author disclosures are available in the [supporting information](#).

CONSENT STATEMENT

All participants provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX

MEMENTO COHORT STUDY GROUP COLLABORATORS

Name	Degree	Location	Role
Michèle Allard	MD, PhD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Xavier Arnoz, F-33000, Bordeaux, France	Co-investigator
Sandrine Andrieu	MD, PhD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital La Grave-Casselardit, F-31000, Toulouse, France	Co-investigator
Pierre Anthony	MD, PhD	Memory Resource and Research Centre of Colmar, Hôpitaux Civils de Colmar, F-68000, Colmar, France	Co-investigator
Christine Astier	MD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Alexandre Augier	MD, PhD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator
Nicolas Auguste	MD	Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Hôpital de la Charité, F-42000, Saint-Etienne, France	Co-investigator
Sophie Auriacombe	MD, PhD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Pellegrin, F-33000, Bordeaux, France	Co-investigator
John Avet	MD, PhD	Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Hôpital Nord, F-42000, Saint-Etienne, France	Co-investigator
Olivier Bailon	MD, PhD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator
Fabrice-Guy Barral	MD	Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Hôpital Nord, F-42000, Saint-Etienne, France	Co-investigator
Jean Barré	MD	Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Annick Barthelaix	MD, PhD	Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Catherine Bayle	MD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Olivier Beauchet		Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Catherine Belin	MD, PhD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator

(Continues)

Name	Degree	Location	Role
Samia Belkacem	MD	Institute of Memory and Alzheimer's Disease (IM2A), Centre for NeuroImaging Research (CENIR), Brain and Spine Institute (ICM), UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France	Co-investigator
Douraid Ben Salem	MD, PhD	Memory Resource and Research Centre of Brest, CHRU de Brest, F-29000, Brest, France	Co-investigator
Karim Bennys	MD	Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Hôpital Gui de Chauliac, F-34000, Montpellier, France	Co-investigator
Géraldine Bera	MD	Laboratoire d'Imagerie Biomédicale, Sorbonne Universités, UPMC Univ Paris 06, Inserm U1146, CNRS UMR 7371, France NeuroSpin, I2BM, Commissariat à l'Energie Atomique, Paris, France	Co-investigator
Eric Berger	MD	Memory Resource and Research Centre of Besançon, CHU de Besançon, Hôpital Jean Minjoz, Hôpital Saint-Jacques, F-25000, Besançon, France	Co-investigator
Marc G. Berger	MD, PhD	Memory Resource and Research Centre of Clermont-Ferrand, CHU de Clermont-Ferrand, F-63000, Clermont-Ferrand, France	Co-investigator
Emilie Bergouin	MD	Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Hôpital du Bocage, Hôpital de Champmaillot, F-21000, Dijon, France	Co-investigator
François Bertin-Hugault	MD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Guillaume Bertrand	MD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator
François-Xavier Bertrand	MD, PhD	Memory Resource and Research Centre of Nantes, CHU de Nantes, F-44000, Nantes, France	Co-investigator
Catherine Beze	MD	Memory Resource and Research Centre of Center Region, CHRU de Tours, Hôpital Bretonneau, F-37000, Tours, France	Co-investigator
Valérie Boilet		Coordinating Centre, Inserm CIC-1401 Clinical Epidemiology, CHU de Bordeaux, F-33000, Bordeaux, France	Co-investigator
Stéphanie Bombois	MD, PhD	Memory Resource and Research Centre of Lille, CHRU de Lille, Hôpital Roger Salengro, F-59000, Lille, France	Co-investigator
Alain Bonafé	MD, PhD	Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France	Co-investigator
Yasmina Boudali	MD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Hatem Bouhladour	MD, PhD	Memory Resource and Research Centre of Besançon, CHU de Besançon, Hôpital Jean Minjoz, Hôpital Saint-Jacques, F-25000, Besançon, France	Co-investigator
Clémence Bouilly	MD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Isabelle Bourdel-Marchasson	MD, PhD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Xavier Arnoz, F-33000, Bordeaux, France	Co-investigator
Vincent Bouteloup	PharmD	Coordinating Centre, Inserm CIC-1401 Clinical Epidemiology, CHU de Bordeaux, F-33000, Bordeaux, France	Co-investigator
Claire Boutet	MD	Institute of Memory and Alzheimer's Disease (IM2A), Centre for NeuroImaging Research (CENIR), Brain and Spine Institute (ICM), UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France	Co-investigator
Serge Bracard	MD, PhD	Memory Resource and Research Centre of Nancy, CHU de Nancy, F-54000, Nancy, France	Co-investigator
Antoine Brangier	MD	Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Pierre-Yves Brillet	MD, PhD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator
Laure Caillard	MD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Fabienne Calvas	MD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital Purpan, F-31000, Toulouse, France	Co-investigator
Agnès Camus	MD	Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Hôpital du Bocage, Hôpital de Champmaillot, F-21000, Dijon, France	Co-investigator

(Continues)

Name	Degree	Location	Role
Vincent Camus	MD, PhD	Memory Resource and Research Centre of Center Region, CHRU de Tours, Hôpital Bretonneau, F-37000, Tours, France	Co-investigator
Sandrine Canaple	MD	Memory Resource and Research of Amiens, CHU Amiens Picardie, F-80000, Amiens, France	Co-investigator
Antoine Carpentier	MD, PhD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator
Pascaline Cassagnaud	MD	Memory Resource and Research Centre of Lille, CHRU de Lille, Hôpital Roger Salengro, F-59000, Lille, France	Co-investigator
Françoise Cattin	MD	Memory Resource and Research Centre of Besançon, CHU de Besançon, Hôpital Jean Minjoz, Hôpital Saint-Jacques, F-25000, Besançon, France	Co-investigator
Ludivine Chamard	MD	Memory Resource and Research Centre of Besançon, CHU de Besançon, Hôpital Jean Minjoz, Hôpital Saint-Jacques, F-25000, Besançon, France	Co-investigator
Stéphane Chanalet	MD	Memory Resource and Research Centre of Nice, CHU de Nice, Hôpital Pasteur, F-06100, Nice, France	Co-investigator
Mathieu Chastan	MD	Memory Resource and Research Centre of Rouen, CLCC Henri Becquerel, Rouen, France	Co-investigator
Sophie Chauvelier	MD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Valérie Chauvire	MD	Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Samia Cheriet	MD, PhD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital Purpan, F-31000, Toulouse, France	Co-investigator
Anthony Clotagatide	MD	Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Hôpital Nord, F-42000, Saint-Etienne, France	Co-investigator
Emmanuel Cognat	MD, PhD	Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France	Co-investigator
Lora Cohen	PhD	Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France	Co-investigator
Jean-Marc Constans	MD, PhD	Memory Resource and Research of Amiens, CHU Amiens Picardie, F-80000, Amiens, France	Co-investigator
Marie-Hélène Coste	MD, PhD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Jean-Philippe Cottier	MD, PhD	Memory Resource and Research Centre of Center Region, CHRU de Tours, Hôpital Bretonneau, F-37000, Tours, France	Co-investigator
François Cotton	MD, PhD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Isabelle Couret	MD	Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Hôpital Gui de Chauliac, F-34000, Montpellier, France	Co-investigator
Olivier-François Couturier	MD, PhD	Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Pascale Cowpli-Bony	MD, PhD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Pellegrin, F-33000, Bordeaux, France	Co-investigator
Véronique Cressot	MD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Xavier Arnoz, F-33000, Bordeaux, France	Co-investigator
Benjamin Crétin	MD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Keren Danaila	MD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Jacques Darcourt	MD, PhD	Memory Resource and Research Centre of Nice, CLCC Antoine Lacassagne, Nice, France	Co-investigator
Jean-François Dartigues	MD, PhD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Pellegrin, F-33000, Bordeaux, France	Co-investigator
Ana-Maria Dascalita	MD, PhD	Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Hôpital de la Charité, F-42000, Saint-Etienne, France	Co-investigator

(Continues)

Name	Degree	Location	Role
Renaud David	MD, PhD	Memory Resource and Research Centre of Nice, CHU de Nice, Institut Claude Pompidou, F-06100, Nice, France	Co-investigator
Xavier De Petigny	MD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Delphine De Verbizier-Lonjon	MD	Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Hôpital Gui de Chauliac, F-34000, Montpellier, France	Co-investigator
Marielle Decousus	MD, PhD	Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Hôpital Nord, F-42000, Saint-Etienne, France	Co-investigator
Isabelle Defouilloy	MD, PhD	Memory Resource and Research of Amiens, CHU Amiens Picardie, F-80000, Amiens, France	Co-investigator
Christine Delmaire	MD, PhD	Memory Resource and Research Centre of Lille, CHRU de Lille, Hôpital Roger Salengro, F-59000, Lille, France	Co-investigator
Julien Delrieu	MD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital La Grave-Casselardit, F-31000, Toulouse, France	Co-investigator
Catherine Demuyinck	MD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Vincent Deramecourt	MD, PhD	Memory Resource and Research Centre of Lille, CHRU de Lille, Hôpital Roger Salengro, F-59000, Lille, France	Co-investigator
Hervé Deramond	MD, PhD	Memory Resource and Research of Amiens, CHU Amiens Picardie, F-80000, Amiens, France	Co-investigator
Thomas Desmidt	MD, PhD	Memory Resource and Research Centre of Center Region, CHRU de Tours, Hôpital Bretonneau, F-37000, Tours, France	Co-investigator
Marie-Dominique Desruet	PharmD, PhD	Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France	Co-investigator
Julien Detour		Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Agnès Devendeville	MD	Memory Resource and Research of Amiens, CHU Amiens Picardie, F-80000, Amiens, France	Co-investigator
Mira Didic	MD, PhD	Memory Resource and Research Centre of Marseille, CHU de Marseille, Hôpital La Timone, F-13000, Marseille, France	Co-investigator
Maritchu Doireau	MD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Pellegrin, F-33000, Bordeaux, France	Co-investigator
Antonio Dos Santos	MD	Institute of Memory and Alzheimer's Disease (IM2A), Brain and Spine Institute (ICM), UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France	Co-investigator
Patrice Douillet	MD	Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Hôpital Gui de Chauliac, F-34000, Montpellier, France	Co-investigator
Foucaud Du Boisguezeneuc	MD	Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Hôpital de La Milétrie, F-86000, Poitiers, France	Co-investigator
Delphine Dubail	MD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Laure Ducroq-Ducastaing	MD	Memory Resource and Research Centre of Brest, CHRU de Brest, F-29000, Brest, France	Co-investigator
Julien Dumurgier	MD, PhD	Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France	Co-investigator
Diane Dupuy	MD, PhD	Memory Resource and Research of Amiens, CHU Amiens Picardie, F-80000, Amiens, France	Co-investigator
Emmanuelle Duron	MD, PhD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Inna Dygai-Cochet	MD, PhD	Memory Resource and Research Centre of Dijon, CLCC Georges François Leclerc, Dijon, France	Co-investigator
Véronique Eder	MD, PhD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator

(Continues)

Name	Degree	Location	Role
Stéphane Epelbaum	MD, PhD	Institute of Memory and Alzheimer's Disease (IM2A), Brain and Spine Institute (ICM), UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France	Co-investigator
Frédérique Etcharry-Bouyx	MD, PhD	Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Daniel Fagret	MD, PhD	Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France	Co-investigator
Catherine Faisant	MD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital La Grave-Casselardit, F-31000, Toulouse, France	Co-investigator
Karim Farid	MD, PhD	Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France	Co-investigator
Denis Fédérico	MD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Olivier Felician	MD, PhD	Memory Resource and Research Centre of Marseille, CHU de Marseille, Hôpital La Timone, F-13000, Marseille, France	Co-investigator
Philippe Fernandez	MD, PhD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Pellegrin, F-33000, Bordeaux, France	Co-investigator
Pacôme Fosse	MD	Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Alexandra Foubert-Samier	MD, PhD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Pellegrin, F-33000, Bordeaux, France	Co-investigator
Isabelle Franck	MD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Monique Galitzky	MD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital Purpan, F-31000, Toulouse, France	Co-investigator
Céline Gallazzini-Crepin	MD	Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France	Co-investigator
Radka Gantchev	MD	Memory Resource and Research Centre of Marseille, CHU de Marseille, Hôpital La Timone, F-13000, Marseille, France	Co-investigator
Laurence Garbarg-Chenon	MD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator
Guillaume Gautier	MD, PhD	Memory Resource and Research Centre of Marseille, CHU de Marseille, Hôpital La Timone, F-13000, Marseille, France	Co-investigator
Emmanuel Gerardin	MD, PhD	Memory Resource and Research Centre of Rouen, Neuroradiology Department, Rouen University Hospital, F-76031, Rouen, France	Co-investigator
Claire Gervais	MD	Memory Resource and Research Centre of Nice, CHU de Nice, Institut Claude Poupidou, F-06100, Nice, France	Co-investigator
Jean-Claude Getenet	MD	Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Hôpital Nord, F-42000, Saint-Etienne, France	Co-investigator
Nadine Girard	MD, PhD	Memory Resource and Research Centre of Marseille, CHU de Marseille, Hôpital La Timone, F-13000, Marseille, France	Co-investigator
Fabienne Giraud	MD	Memory Resource and Research Centre of Marseille, CHU de Marseille, Hôpital La Timone, F-13000, Marseille, France	Co-investigator
Chantal Girtanner	MD	Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Hôpital de la Charité, F-42000, Saint-Etienne, France	Co-investigator
Valérie Gissot	MD	Memory Resource and Research Centre of Center Region, CHRU de Tours, Hôpital Bretonneau, F-37000, Tours, France	Co-investigator
Caroline Grangeon	PharmD	Memory Resource and Research Centre of Nice, CHU de Nice, Institut Claude Poupidou, F-06100, Nice, France	Co-investigator
Daniel Grucker	MD, PhD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Eric Guedj	MD, PhD	Memory Resource and Research Centre of Marseille, CHU de Marseille, Hôpital La Timone, F-13000, Marseille, France	Co-investigator
Claude Gueriot	MD	Memory Resource and Research Centre of Marseille, CHU de Marseille, Hôpital La Timone, F-13000, Marseille, France	Co-investigator

(Continues)

Name	Degree	Location	Role
Yves Guilhermet	MD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Rémy Guillevin	MD, PhD	Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Hôpital de La Milétrie, F-86000, Poitiers, France	Co-investigator
Sophie Haffen	MD	Memory Resource and Research Centre of Besançon, CHU de Besançon, Hôpital Jean Minjoz, Hôpital Saint-Jacques, F-25000, Besançon, France	Co-investigator
Didier Hannequin	MD, PhD	Memory Resource and Research Centre of Rouen, Neurology Department, Rouen University Hospital, F-76031, Rouen, France	Co-investigator
Sandrine Harston	MD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Xavier Arnoz, F-33000, Bordeaux, France	Co-investigator
Anne Hitzel	MD, PhD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital Purpan, F-31000, Toulouse, France	Co-investigator
Caroline Hommet	MD, PhD	Memory Resource and Research Centre of Center Region, CHRU de Tours, Hôpital Bretonneau, F-37000, Tours, France	Co-investigator
Claude Hossein-Foucher	MD, PhD	Memory Resource and Research Centre of Lille, CHRU de Lille, Hôpital Roger Salengro, F-59000, Lille, France	Co-investigator
Fabrice Hubele	MD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Agnès Jacquin-Piques	MD, PhD	Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Hôpital du Bocage, Hôpital de Champmaillot, F-21000, Dijon, France	Co-investigator
Betty Jean	MD	Memory Resource and Research Centre of Clermont-Ferrand, CHU de Clermont-Ferrand, F-63000, Clermont-Ferrand, France	Co-investigator
Joanne Jenn	MD, PhD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Xavier Arnoz, F-33000, Bordeaux, France	Co-investigator
Laure Joly	MD, PhD	Memory Resource and Research Centre of Nancy, CHU de Nancy, F-54000, Nancy, France	Co-investigator
Thérèse Jonveaux	MD	Memory Resource and Research Centre of Nancy, CHU de Nancy, F-54000, Nancy, France	Co-investigator
Adrien Julian	MD, PhD	Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Hôpital de La Milétrie, F-86000, Poitiers, France	Co-investigator
Aurélié Kas	MD, PhD	Laboratoire d'Imagerie Biomédicale, Sorbonne Universités, UPMC Univ Paris 06, Inserm U1146, CNRS UMR 7371, France NeuroSpin, I2BM, Commissariat à l'Energie Atomique, Paris, France	Co-investigator
Anna Kearney-Schwartz	MD	Memory Resource and Research Centre of Nancy, CHU de Nancy, F-54000, Nancy, France	Co-investigator
Alice Keles	MD	Memory Resource and Research Centre of Nancy, CHU de Nancy, F-54000, Nancy, France	Co-investigator
Antony Kelly	MD	Memory Resource and Research Centre of Clermont-Ferrand, Centre de Lutte contre le Cancer, F-63000, Clermont-Ferrand, France	Co-investigator
Nathalie Keromnes	MD	Memory Resource and Research Centre of Brest, CHRU de Brest, F-29000, Brest, France	Co-investigator
Lejla Koric	MD	Memory Resource and Research Centre of Marseille, CHU de Marseille, Hôpital La Timone, F-13000, Marseille, France	Co-investigator
Alexandre Krainik	MD, PhD	Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France	Co-investigator
Stéphane Kremer	MD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Florian Labourée	MD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Franck Lacoeyille	MD, PhD	Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Françoise Lala	MD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital La Grave-Casselardit, F-31000, Toulouse, France	Co-investigator
Chantal Lamy	MD	Memory Resource and Research of Amiens, CHU Amiens Picardie, F-80000, Amiens, France	Co-investigator

(Continues)

Name	Degree	Location	Role
Jean-Louis Laplanche	PharmD, PhD	Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France	Co-investigator
Cyrille Launay	MD, PhD	Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Stéphane Lehericy	MD, PhD	Institute of Memory and Alzheimer's Disease (IM2A), Centre for NeuroImaging Research (CENIR), Brain and Spine Institute (ICM), UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France	Co-investigator
Sylvain Lehmann	MD, PhD	Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Hôpital Gui de Chauliac, F-34000, Montpellier, France	Co-investigator
Hermine Lenoir	MD, PhD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Marcel Levy	MD, PhD	Institute of Memory and Alzheimer's Disease (IM2A), Brain and Spine Institute (ICM), UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France	Co-investigator
Stéphanie Libercier	MD, PhD	Memory Resource and Research Centre of Colmar, Hôpitaux Civils de Colmar, F-68000, Colmar, France	Co-investigator
Marie-Anne Mackowiak-Cordoliani	MD	Memory Resource and Research Centre of Lille, CHRU de Lille, Hôpital Roger Salengro, F-59000, Lille, France	Co-investigator
Eloi Magnin	MD	Memory Resource and Research Centre of Besançon, CHU de Besançon, Hôpital Jean Minjoz, Hôpital Saint-Jacques, F-25000, Besançon, France	Co-investigator
Zaza Makaroff	MD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Athina Marantidou	MD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator
Isabelle Marcet	MD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Pellegrin, F-33000, Bordeaux, France	Co-investigator
Cécilia Marelli	MD, PhD	Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Hôpital Gui de Chauliac, F-34000, Montpellier, France	Co-investigator
Sophie Marilier	MD	Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Hôpital du Bocage, Hôpital de Champmaillot, F-21000, Dijon, France	Co-investigator
Idalie Martin	MD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Olivier Martinaud	MD, PhD	Memory Resource and Research Centre of Rouen, Neurology Department, Rouen University Hospital, F-76031, Rouen, France	Co-investigator
Catherine Martin-Hunyadi	MD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Aïcha Medjoul	MD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator
Isabelle Merlet	MD	Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Hôpital de La Milétrie, F-86000, Poitiers, France	Co-investigator
Danielle Mestas	MD	Memory Resource and Research Centre of Clermont-Ferrand, CHU de Clermont-Ferrand, F-63000, Clermont-Ferrand, France	Co-investigator
Marc-Etienne Meyer	MD, PhD	Memory Resource and Research of Amiens, CHU Amiens Picardie, F-80000, Amiens, France	Co-investigator
Jean-Marc Michel	MD	Memory Resource and Research Centre of Colmar, Hôpitaux Civils de Colmar, F-68000, Colmar, France	Co-investigator
Agnès Michon	MD	Institute of Memory and Alzheimer's Disease (IM2A), Brain and Spine Institute (ICM), UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France	Co-investigator
Isabelle Migeon-Duballet	MD	Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Hôpital de La Milétrie, F-86000, Poitiers, France	Co-investigator
Karl Mondon	MD, PhD	Memory Resource and Research Centre of Center Region, CHRU de Tours, Hôpital Bretonneau, F-37000, Tours, France	Co-investigator

(Continues)

Name	Degree	Location	Role
Clément Morgat	PharmD, PhD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Pellegrin, F-33000, Bordeaux, France	Co-investigator
Véronique Moullart	MD	Memory Resource and Research of Amiens, CHU Amiens Picardie, F-80000, Amiens, France	Co-investigator
Christian Moussard	MD	Memory Resource and Research Centre of Besançon, CHU de Besançon, Hôpital Jean Minjoz, Hôpital Saint-Jacques, F-25000, Besançon, France	Co-investigator
Aurélié Mouton	MD, PhD	Memory Resource and Research Centre of Nice, CHU de Nice, Institut Claude Pompidou, F-06100, Nice, France	Co-investigator
Izzie Jacques Namer	MD, PhD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Georges Niewiadomski	MD, PhD	Memory Resource and Research Centre of Nice, CHU de Nice, Institut Claude Pompidou, F-06100, Nice, France	Co-investigator
Guillaume Nivaggioni	MD	Memory Resource and Research Centre of Nice, CHU de Nice, Institut Claude Pompidou, F-06100, Nice, France	Co-investigator
Marie Noblet	MD, PhD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Michel Nonent	MD, PhD	Memory Resource and Research Centre of Brest, CHRU de Brest, F-29000, Brest, France	Co-investigator
Fati Nourhashemi	MD, PhD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital La Grave-Casselardit, F-31000, Toulouse, France	Co-investigator
Hélène Oesterle	MD	Memory Resource and Research Centre of Colmar, Hôpitaux Civils de Colmar, F-68000, Colmar, France	Co-investigator
Galdric Orvoen	MD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Pierre Jean Ousset	MD, PhD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital La Grave-Casselardit, F-31000, Toulouse, France	Co-investigator
Amandine Pallardy	MD	Memory Resource and Research Centre of Nantes, CHU de Nantes, F-44000, Nantes, France	Co-investigator
Claire Paquet	MD, PhD	Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France	Co-investigator
Pierre-Yves Pare	MD, PhD	Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Anne Pasco	MD, PhD	Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Pierre Payoux	MD, PhD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital Purpan, F-31000, Toulouse, France	Co-investigator
Cécile Pays	MD, PhD	Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Hôpital Gui de Chauliac, F-34000, Montpellier, France	Co-investigator
Isabelle Pellegrin	MD, PhD	Biological Research Centre, CHU de Bordeaux, F-33000, Bordeaux, France	Co-investigator
Rémy Perdrisot	MD, PhD	Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Hôpital de La Milétrie, F-86000, Poitiers, France	Co-investigator
Bertille Perin	MD, PhD	Memory Resource and Research of Amiens, CHU Amiens Picardie, F-80000, Amiens, France	Co-investigator
Christine Perret-Guillaume	MD, PhD	Memory Resource and Research Centre of Nancy, CHU de Nancy, F-54000, Nancy, France	Co-investigator
Grégory Petyt	MD	Memory Resource and Research Centre of Lille, CHRU de Lille, Hôpital Roger Salengro, F-59000, Lille, France	Co-investigator
Nathalie Philippi	MD, PhD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Geneviève Pinganaud	MD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Xavier Arnoz, F-33000, Bordeaux, France	Co-investigator
Matthieu Plichart	MD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Gabriel Pop	MD, PhD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator
Michèle Puel	MD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital Purpan, F-31000, Toulouse, France	Co-investigator

(Continues)

Name	Degree	Location	Role
Mathieu Queneau	MD, PhD	Memory Resource and Research Centre of Paris Nord, Centre Cardiologique du Nord, Paris, France	Co-investigator
Solène Querellou	MD	Memory Resource and Research Centre of Brest, CHRU de Brest, F-29000, Brest, France	Co-investigator
Muriel Quillard-Muraine	MD, PhD	Memory Resource and Research Centre of Rouen, Neurology Department, Rouen University Hospital, F-76031, Rouen, France	Co-investigator
Valérie Quipourt	MD, PhD	Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Hôpital du Bocage, Hôpital de Champmaillot, F-21000, Dijon, France	Co-investigator
Chloé Rachez	MD, PhD	Memory Resource and Research Centre of Clermont-Ferrand, CHU de Clermont-Ferrand, F-63000, Clermont-Ferrand, France	Co-investigator
Micheline Razzouk-Cadet	MD	Memory Resource and Research Centre of Nice, CHU de Nice, Institut Claude Pompidou, F-06100, Nice, France	Co-investigator
Anne-Sophie Rigaud	MD, PhD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Hélène Robin-Ismer	MD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Mathieu Rodallec	MD, PhD	Memory Resource and Research Centre of Paris Nord, Centre Cardiologique du Nord, Paris, France	Co-investigator
Yves Rolland	MD, PhD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital La Grave-Casselardit, F-31000, Toulouse, France	Co-investigator
Adeline Rollin-Sillaire	MD, PhD	Memory Resource and Research Centre of Lille, CHRU de Lille, Hôpital Roger Salengro, F-59000, Lille, France	Co-investigator
Olivier Rouaud	MD	Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Hôpital du Bocage, Hôpital de Champmaillot, F-21000, Dijon, France	Co-investigator
Caroline Roubaud	MD, PhD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Isabelle Rouch	MD, PhD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Julie Roux	MD, PhD	Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France	Co-investigator
Guillaume Sacco	MD, PhD	Memory Resource and Research Centre of Nice, CHU de Nice, Institut Claude Pompidou, F-06100, Nice, France	Co-investigator
Pierre-Yves Salaun	MD	Memory Resource and Research Centre of Brest, CHRU de Brest, F-29000, Brest, France	Co-investigator
François Salmon	MD, PhD	Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Hôpital de La Milétrie, F-86000, Poitiers, France	Co-investigator
Alicia Sanchez	MD	Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Hôpital Nord, F-42000, Saint-Etienne, France	Co-investigator
Maria-Joao Santiago-Ribeiro	MD, PhD	Memory Resource and Research Centre of Center Region, CHRU de Tours, Hôpital Bretonneau, F-37000, Tours, France	Co-investigator
Alain Sarciron	MD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Nathalie Sastre-Hengan	MD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital La Grave-Casselardit, F-31000, Toulouse, France	Co-investigator
Mathilde Sauvée	MD, PhD	Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France	Co-investigator
Christian Scheiber	MD, PhD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Anne-Marie Schneider	MD, PhD	Memory Resource and Research Centre of Strasbourg, Hôpitaux Universitaires de Strasbourg, F-67000, Strasbourg, France	Co-investigator
Franck Semah	MD, PhD	Memory Resource and Research Centre of Lille, CHRU de Lille, Hôpital Roger Salengro, F-59000, Lille, France	Co-investigator
Amélie Serra	MD	Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France	Co-investigator

(Continues)

Name	Degree	Location	Role
Marie-Laure Seux	MD	Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France	Co-investigator
Hélène Sordet-Guépet	MD	Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Hôpital du Bocage, Hôpital de Champmaillot, F-21000, Dijon, France	Co-investigator
Maria Eugenia Soto	MD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital La Grave-Casselardit, F-31000, Toulouse, France	Co-investigator
Mathieu Tafani	MD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital Purpan, F-31000, Toulouse, France	Co-investigator
Jean-Yves Tanguy	MD, PhD	Memory Resource and Research Centre of Angers, CHU d'Angers, F-49000, Angers	Co-investigator
Michael Taroux	MD, PhD	Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Hôpital du Bocage, Hôpital de Champmaillot, F-21000, Dijon, France	Co-investigator
Marc Teichmann	MD, PhD	Institute of Memory and Alzheimer's Disease (IM2A), Brain and Spine Institute (ICM), UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France	Co-investigator
Catherine Terrat	MD, PhD	Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Hôpital de la Charité, F-42000, Saint-Etienne, France	Co-investigator
Jamila Thabet	MD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator
Claire Thalamas	MD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital Purpan, F-31000, Toulouse, France	Co-investigator
Catherine Thomas-Anterion	MD, PhD	Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Hôpital Nord, F-42000, Saint-Etienne, France	Co-investigator
Anne-Cécile Troussière	MD	Memory Resource and Research Centre of Lille, CHRU de Lille, Hôpital Roger Salengro, F-59000, Lille, France	Co-investigator
Renata Ursu	MD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator
Pierre Vera	MD, PhD	Memory Resource and Research Centre of Rouen, CLCC Henri Becquerel, Rouen, France	Co-investigator
Martine Vercelletto	MD	Memory Resource and Research Centre of Nantes, CHU de Nantes, F-44000, Nantes, France	Co-investigator
Olivier Vercruyse	MD	Memory Resource and Research Centre of Lille, CHRU de Lille, Hôpital Roger Salengro, F-59000, Lille, France	Co-investigator
Antoine Verger	MD, PhD	Memory Resource and Research Centre of Nancy, CHU de Nancy, F-54000, Nancy, France	Co-investigator
Philippe Viau	MD	Memory Resource and Research Centre of Nice, CHU de Nice, Institut Claude Pompidou, F-06100, Nice, France	Co-investigator
Marie-Neige Videau	MD	Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Hôpital Xavier Arnoz, F-33000, Bordeaux, France	Co-investigator
Thierry Voisin	MD	Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Hôpital La Grave-Casselardit, F-31000, Toulouse, France	Co-investigator
Nathalie Wagemann	MD, PhD	Memory Resource and Research Centre of Nantes, CHU de Nantes, F-44000, Nantes, France	Co-investigator
Aziza Waissi-Sediq	MD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Jing Xie	MD, PhD	Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Hôpital des Charpennes, F-69000, Lyon, France	Co-investigator
Nathanaëlle Yeni	MD	Laboratoire d'Imagerie Biomédicale, Sorbonne Universités, UPMC Univ Paris 06, Inserm U1146, CNRS UMR 7371, France NeuroSpin, I2BM, Commissariat à l'Energie Atomique, Paris, France	Co-investigator
Michel Zanca	MD, PhD	Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Hôpital Gui de Chauliac, F-34000, Montpellier, France	Co-investigator
Jean Zinsner	MD, PhD	Memory Clinic, Hôpital Avicenne, AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, F-93009, Bobigny, France	Co-investigator