Associations Between Blood-Based Biomarkers and Cognitive and Functional Trajectories Among Participants of the MEMENTO Cohort

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Abstract

Background and Objectives
Elevated levels of Alzheimer disease (AD) blood-based biomarkers are associated with accelerated cognitive decline. However, their distinct relationships with specific cognitive and functional domains require further investigation. We aimed at estimating the associations between AD blood-based biomarkers and the trajectories of distinct cognitive and functional domains over a 5-year follow-up period.

Methods
We conducted a clinic-based prospective study using data from the MEMENTO study, a nationwide French cohort. We selected dementia-free individuals at baseline aged 60 years or older. Baseline measurements of β-amyloid (Aβ) 40 and 42, phosphorylated tau (p-tau181), and neurofilament light chain (NfL) concentrations were obtained using the Simoa HD-X analyzer. Mini-Mental State Examination (MMSE), Free and Cued Selective Reminding Test (FCSRT), animal fluency, Trail Making Tests A and B, Short Physical Performance Battery (SPPB), and Instrumental Activities of Daily Living were administered annually for up to 5 years. We used linear mixed models, adjusted for potential confounders, to model AD biomarkers' relation with cognitive and functional decline.

Results
A total of 1,938 participants were included in this study, with a mean (SD) baseline age of 72.8 (6.6) years, and 62% were women. Higher baseline p-tau181 and NfL were associated with significantly faster decline in most cognitive, physical, and functional outcomes (+1 SD p-tau181: $\beta_{MMSE} = -0.055$, 95% CI −0.067 to −0.043, $\beta_{FCSRT} = -0.034$, 95% CI −0.043 to −0.025, $\beta_{fluency} = -0.029$, 95% CI −0.038 to −0.020, $\beta_{SPPB} = -0.040$, 95% CI −0.057 to −0.022, and $\beta_{4IADL} = -0.115$, 95% CI 0.091–0.140. +1 SD NfL: $\beta_{MMSE} = -0.039$, 95% CI −0.053 to −0.025, $\beta_{FCSRT} = -0.022$, 95% CI −0.032 to −0.012, $\beta_{fluency} = -0.014$, 95% CI −0.024 to −0.004, and $\beta_{4IADL} = 0.077$, 95% CI 0.048–0.105). A multiplicative association of p-tau181 and NfL with worsening cognitive and functional trajectories was evidenced. Lower Aβ42/40 ratio was only associated with slightly faster cognitive decline in FCSRT and semantic fluency (+1 SD: $\beta = 0.011$, 95% CI 0.002–0.020, and $\beta = 0.011$, 95% CI 0.003–0.020, respectively). These associations were not modified by *APOE* ε4, sex, nor education level.

Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **CDR** = Clinical Dementia Rating; **FCSRT** = Free and Cued Selective Reminding Test; **IADL** = Instrumental Activities of Daily Living; **IQR** = interquartile range; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **NfL** = neurofilament light chain; **p-tau** = phosphorylated tau; **SCC** = isolated cognitive complaint; **SPPB** = Short Physical Performance Battery; **TMT** = Trail Making Test.

Discussion

In a memory clinic sample, p-tau181 and NfL, both independently and jointly, are linked to more pronounced cognitive, physical and functional declines. Blood-based biomarker measurement in AD research may provide useful insights regarding biological processes underlying cognitive, physical, and functional declines in at-risk individuals.

Introduction

Alzheimer disease (AD), the most prevalent type of dementia, is histologically characterized by the progressive accumulation of β-amyloid (Aβ) plaques and tau neurofibrillary tangles. These pathologic changes ultimately lead to neurodegenerative processes.[1] These brain alterations are known to appear years before clinical symptoms appear.[2] Yet, a better understanding of AD biomarkers and their relation to cognitive decline is necessary to gain insights into the course of AD preceding dementia onset. Currently, biomarkers indicative of AD pathology are primarily assessed using PET imaging and/or CSF measurements.[3] However, their high cost, limited availability, invasiveness (CSF), and interpretation challenges often restrict their implementation, leading to their use in selected research settings and samples.

With the recent availability of highly sensitive immunoassays, blood-based biomarkers such as Aβ42/Aβ40 ratio, phosphorylated-tau (p-tau), and neurofilament light chain (NfL) have thus recently been developed.[4] They have been shown to be associated with amyloid and tau PET results, as well as with CSF biomarkers and neurodegeneration markers.[5-9] Several studies have also evidenced their associations with faster cognitive decline and higher dementia risk in both cognitively unimpaired older adults and symptomatic patients.[8-17] Yet, previous studies investigating the association between blood-based biomarkers and cognitive decline have focused primarily on global cognitive performances,[8,13,14,17-20] leaving specific cognitive domains relatively underexplored. In addition, sex differences, genetic susceptibility, or cognitive reserve may influence these associations, but few studies have looked for the moderating effect of sex, *APOE* ε4 status, or education level.

While cognitive decline is a hallmark of AD, disease progression also gradually affects physical health such as balance, gait speed, and strength, as well as autonomy in daily living. Existing literature has shown that biomarkers of AD pathology, measured by either PET or CSF, were associated with reduced gait speed and decreased autonomy on the Instrumental Activities of Daily Living (IADL).[21-23] Nevertheless, only a limited number of studies have investigated the relationships between blood-based AD biomarkers and indicators of physical health and autonomy.[24-26] For instance, a study including 1,327 cognitively unimpaired participants aged 66 years on average reported higher plasma Nfl levels and lower plasma Aβ40 and Aβ42 levels to be associated with worse functional performances as measured by the Short Physical Performance Battery (SPPB) test.[24] Another study including 452 older adults, 70 years and older with memory complaints or functional limitations, also showed that combined low plasma Aβ42/Aβ40 ratio and high plasma NfL level was associated with greater declines in gait speed.[25] No studies looking at p-tau were identified.

The aim of this study was thus to investigate the relationships between baseline blood-based AD biomarkers and the trajectories of distinct cognitive and functional domains among participants of the MEMENTO cohort. An exploratory aim was to assess whether these associations were modified by sex, *APOE* ε4 status, or education level.

Methods

Study Population

The MEMENTO cohort is a prospective study conducted across 26 French memory clinics that recruited 2,323 participants seeking consultation between April 2011 and June 2014. The participants were screened for mild cognitive impairment (MCI) or isolated cognitive complaints (SCCs), and they were recruited consecutively. MCI was defined as (1) performing 1 SD worse than the subject's own age, sex, and education-level group mean in 1 or more cognitive domains, this deviation being identified for the first time through cognitive tests performed recently (less than 6 months preceding screening phase), and (2) having a Clinical Dementia Rating (CDR) (10) ≤0.5 and not being demented. A participant was eligible for inclusion in the isolated SCC stratum if he or she had SCCs (assessed through visual analog scales) without any of objective cognitive deficit as defined above and was 60 years or older. The primary aim of the MEMENTO

study was to enhance our understanding of the natural progression of AD and related disorders. Comprehensive details about the study have been previously provided.[27] Participants underwent baseline assessments and subsequent follow-ups at intervals of 6–12 months over a span of 5 years. Baseline data collection involved face-to-face interviews, encompassing sociodemographic characteristics, lifestyle factors, neurologic and physical examinations, and a comprehensive neuropsychological battery. In addition, plasma and serum samples were collected from all participants at baseline. Our study sample design included MEMENTO participants aged 60 years or older and dementia-free at baseline. We further excluded participants with missing measurement of all blood-based biomarkers (n = 38), as well as missing information on education or *APOE* ε4 status (n = 113).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. The MEMENTO cohort protocol has been approved by the local ethics committee ("Comité de Protection des Personnes Sud-Ouest et Outre Mer III"; approval number 2010-A01394-35) and was registered in ClinicalTrials.gov (identifier: NCT01926249).

Blood-Based Biomarker Measurement

Study-specific blood samples were collected at baseline. Gel-separator tubes were used for serum samples while EDTA tubes were used for plasma samples. The collected tubes were left at room temperature for 30 minutes to coagulate, before being centrifuged at 1,500g for 15 minutes at 4°C. After separation, small volumes of serum and plasma were aliquoted to avoid thawing cycles (250 μL in 2 mL Sarstedt cryotubes) and stored in a centralized biobank at −80°C to maintain sample integrity (Bordeaux Biothèques Santé, Biological Resources Center). Consequently, the analyses were performed after only 1 freeze/thaw cycle. AD biomarker concentrations were measured using Simoa technology on a Quanterix HD-1 analyzer with the following commercial kits: Neurology 3-Plex A Advantage Kit (item no. 101995) for Aβ42 and Aβ40, p-tau181 Advantage V2 Kit (item no. 103714) for p-tau181, and NF-light Advantage Kit (item no. 103186) for NfL. The selection of blood-based Aβ42/40 concentration ratio, p-tau181, and NfL as markers of AD pathology was based on the ATN framework.[28] All measurements were conducted in the same laboratory for all participants (Bordeaux University Hospital, Health Research Analytical Platform [PARS-Immunology]), blinded of clinical outcomes.

Assessment of Cognitive and Physical Functioning and Autonomy

At baseline, participants were administered a neuropsychological test battery comprising the following cognitive tests: (1) Mini-Mental State Examination (MMSE), a global cognitive screener[29]; (2) Free and Cued Selective Reminding Test (FCSRT),[30] which measures verbal episodic memory—we used the sum of the 3 free recalls, providing an overall measure of an individual's ability to recall and retrieve information from memory without specific cues or prompts—(3) semantic fluency test (animal),[31] assessing lexical access (i.e., the ability to retrieve words from memory), semantic memory (i.e., the ability to recall and categorize words based on their meaning), and the cognitive processes involved in spontaneously generating words; and (4) Trail Making Tests A and B (TMT-A and TMT-B).[32] Specifically, we used the TMT_{B-A} score, calculated by subtracting the time taken to complete TMT_A from the time taken to complete TMT_B. This score provides a measure of the additional time required to complete the more complex task compared with the simpler one. A higher TMT_{B-A} score indicates greater cognitive flexibility deficits and difficulty with mental shifting and task switching. It is often used as an indicator of executive dysfunction. Inversely, higher scores on the MMSE, FCSRT, and semantic fluency tests indicate better performances.

In addition, we assessed physical performance using the Short Physical Performance Battery (SPPB) test scores,[33] which assess balance, gait speed, strength, and the ability to rise from a seated position. Scores range from 0 to 12, with higher values indicating better performances. For autonomy assessment, we included the 4 Instrumental Activities of Daily Living (4IADL), which assess 4 critical activities for independent living: telephone use, transportation, responsibility for medications, and financial management. Scores range from 4 to 16, with higher scores indicating lower autonomy.[34]

Statistical Analysis

Participants' characteristics were described for the entire analytical sample, and comparisons of baseline characteristics were made between participants included in the analytical sample and those excluded.

We used separate linear mixed models, known for their robustness in handling missing-at-random data for the dependent variables, to investigate the associations between each baseline blood-based biomarker (Aβ42/40 ratio, p-tau181, and NfL) and cognitive and functional trajectories over a 5-year follow-up period. The 3 biomarkers were log-transformed and standardized for comparison purposes. Outcome measures were transformed to account for ceiling and floor effects and curvilinearity. Specifically, MMSE scores were normalized using the NormPsy R package, resulting in a normalized scale ranging from 0 to 100 (equivalent to 30 in the original scale). The TMT_{B-A} score was log-transformed, and cognitive scores were standardized to enable cross-domain comparisons. In addition, longitudinal SPPB and 4IADL scores were optimally transformed using a spline transformation from the lcmm function of the lcmm R package.[35]

To best fit the data, we applied a quadratic trajectory of time, with correlated individual random intercept and slope. Time

Table 1 Participants' Baseline Characteristics, MEMENTO Cohort, 2011–2020

	N = 1,938 n (%)	
Age	72.8 (6.6)	
Female	1,190 (61.4)	
APOE ε4 carriers	577 (29.8)	
High education level	1,064 (54.9)	
CDR = 0.5	1,114 (57.5)	
	Mean (SD)	**Median (IQR)**
Blood-based biomarkers		
Aβ42/40 ratio	0.06 (0.02)	0.06 (0.05–0.06)
p-tau181, pg/mL	1.07 (0.80)	0.88 (0.56–1.35)
NfL, pg/mL	21.7 (13.1)	19.0 (14.5–25.6)
Neuropsychological tests		
MMSE	27.9 (1.9)	28 (27–29)
FCSRT free recall	25.9 (8.2)	27 (21–32)
Semantic fluency	28.2 (8.7)	28 (22–34)
TMT$_{B-A}$	68.1 (56.1)	52.0 (32.0–85.0)
Functional measures		
SPPB	10.5 (1.9)	11 (10–12)
4 IADL	4.2 (0.7)	4 (4–4)

Abbreviations: Aβ = β-amyloid; FCSRT = Free and Cued Selective Reminding Test; IADL = Instrumental Activities of Daily Living; MMSE = Mini-Mental State Examination; NfL = neurofilament light chain; p-tau = phosphorylated tau; SPPB = Short Physical Performance Battery; TMT = Trail Making Test. TMT$_{B-A}$ score is calculated by subtracting the time taken to complete TMTA from the time taken to complete TMTB.

since study entry was defined as the time scale. In a first step, each model was adjusted for age at baseline, sex, *APOE* ε4 genotype (determined by KBiosciences,[27] at least 1 ε4 allele carried vs none), education level (less than high school level vs high school level and higher), and their interactions with time (when significant or when improving model fit based on the Akaike information criterion). For models related to cognitive outcomes, we included an additional adjustment for practice effect as a binary indicator.[36] In the second step, each model was further adjusted for each biomarker of interest and their interaction with linear time. The simple effect of each biomarker (per 1 SD increase) quantified the differences in the level of the transformed scores (in SD) at baseline while interactions with time quantified the impact of biomarkers on the evolution of the transformed scores over time (slope). Mean predicted trajectories over time for ±1 SD of biomarker values were evaluated in both the transformed (for comparison across biomarkers and outcomes) and original (for clinical relevance) scales. In the third step, for each outcome, we run models that included all 3 biomarkers simultaneously to

assess their independent effects. In the fourth step, we explored potential cumulative effects of different biomarkers by including 3-way interactions with each combination of biomarkers and time. Global *p*-values for both linear and quadratic slopes were obtained using multivariate Wald testing.

In addition, we conducted exploratory analyses to investigate the moderating effect of sex, *APOE* ε4 status, and high education level on the associations between each biomarker and cognitive or functional decline. We introduced 3-way interactions (biomarker × moderator × time) into the models generated during the second step of our analysis. To account for multiple testing, we applied a false discovery rate method.

Finally, we performed a different sensitivity analysis based on the models from the second step. First, the initial analysis only considered the interaction between biomarkers and a simple term of time for interpretation purposes. Thus, we also performed similar models while also adjusting for the interaction between each biomarker and the quadratic term of time. Second, because our primary results were derived from a complete cases analysis, assuming missing data occurring completely at random for independent variables (n = 122), we used multiple imputation by chained equations with a fully conditional specification (10 imputed data sets) to impute missing data. Third, we analyzed the associations between biomarkers and the evolution of gait speed over time, which is a component of the Short Physical Performance Battery. Fourth, considering that blood-based biomarker levels may be influenced by renal function,[37] we made additional adjustment for glomerular filtration rate, as defined by CKD-EPI.[38] Finally, we reran our primary analysis stratified according to MCI status at baseline: MCI (CDR = 0.5) vs non-MCI (CDR = 0).

All analyses were performed using R (version 4.1.3).

Data Availability
Anonymized data will be shared by request from any qualified investigator for the sole purpose of replicating procedures and results presented in the article and as long as data transfer is in agreement with EU legislation on the general data protection regulation.

Results

Among the 2,323 participants from the MEMENTO cohort, 2,060 were 60 years or older and dementia-free. Furthermore, a total of 1,938 participants had at least 1 measure of blood-based biomarker available along with complete information on covariates (*APOE* ε4 status and education level) and were included in this work. Compared with participants within the analytic sample, those excluded exhibited CDR scores of 0.5 more frequently, more elevated baseline NfL concentrations, and lower initial FCSRT scores (eTable 1). Baseline characteristics of the analytical sample are presented in Table 1 while

Table 2 Associations Between Individual Blood-Based AD Biomarkers and Cognitive Trajectories, MEMENTO Cohort, 2011–2020

	MMSE		FCSRT		Fluency (animal)		TMT B-A	
	β (SD)	*p* Value	β (SD)	*p* Value	β (SD)	*p* Value	β (SD)	*p* Value
Aβ42/40 (per +1 SD)	0.016 (0.02)	0.41	0.054 (0.02)	0.010	0.054 (0.02)	0.007	−0.011 (0.02)	0.56
Time	0.029 (0.02)	0.17***	0.081 (0.02)	<0.001***	0.001 (0.02)	0.95***	−0.002 (0.07)	0.93*
Time^2	−0.013 (0.004)	0.0003	−0.014 (0.003)	<0.001	−0.004 (0.003)	0.16	0.004 (0.004)	0.40
Aβ42/40 × time	0.009 (0.02)	0.13	0.011 (0.01)	0.01	0.011 (0.01)	0.01	−0.007 (0.005)	0.14
p-tau181 (per +1 SD)	−0.105 (0.02)	<0.001	−0.176 (0.02)	<0.001	−0.075 (0.02)	<0.001	0.134 (0.02)	<0.001
Time	0.016 (0.02)	0.45***	0.079 (0.02)	<0.001***	−0.0008 (0.02)	0.94***	−0.005 (0.03)	0.86**
Time^2	−0.012 (0.004)	<0.001	−0.015 (0.003)	<0.001	−0.005 (0.002)	0.02	0.004 (0.005)	0.34
p-tau181 × time	−0.055 (0.006)	<0.001	−0.034 (0.005)	<0.001	−0.029 (0.004)	<0.001	0.010 (0.005)	0.04
NfL (per +1 SD)	−0.079 (0.02)	<0.001	−0.082 (0.02)	<0.001	−0.074 (0.02)	0.001	0.050 (0.02)	0.03
Time	0.017 (0.02)	0.44**	0.077 (0.02)	<0.001***	0.0009 (0.02)	0.93***	−0.003 (0.02)	0.92**
Time^2	−0.012 (0.004)	<0.001	−0.015 (0.003)	<0.001	−0.005 (0.002)	0.01	0.004 (0.004)	0.37
NfL × time	−0.039 (0.007)	<0.001	−0.022 (0.01)	<0.001	−0.014 (0.005)	0.006	0.010 (0.005)	0.06

Abbreviations: Aβ = β-amyloid; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; NfL = neurofilament light chain; p-tau = phosphorylated tau; SPPB = Short Physical Performance Battery; TMT = Trail Making Test.
All models were adjusted for age at baseline, sex, *APOE* ε4 status, education level, and practice effect. Each biomarker was log-transformed and standardized. Owing to score transformations, parameter units correspond to SD and parameters can be compared across biomarkers and cognitive tests. Yet, parameters cannot be interpreted according to the scores' natural scales. Biomarker × time interaction represents score change (in SD) per year per SD log biomarker level.
Multivariate Wald testing *p* value for overall time effect: **p* < 0.05, ***p* < 0.01, ****p* < 0.001.

eFigure 1 illustrates the distribution of the biomarkers. The mean age of participants at baseline was 72.8 years, and 61.4% were women. Nearly 30% of participants were *APOE* ε4 carriers, and over half held a high school degree. At baseline, 54.9% had a CDR score of 0.5, other participants having a CDR score of 0. The median (interquartile range [IQR]) duration of follow-up was 5.0 years (3.6–5.1), with 65% of participants reaching the 5-year follow-up visit. Moreover, the median (IQR) number of visits was 9 (6–10), with 42% of participants having completed the maximum of 10 visits after inclusion. Over the 5-year follow-up period, 273 participants developed dementia (201 being AD or mixed dementia) and 68 participants died.

The mean predicted cognitive and functional trajectories (eFigure 2) revealed a small yet statistically significant decline over the 5-year follow-up period for the MMSE, with mean predicted scores in the original scale decreasing from Pred$_{baseline}$ = 28.6 (95% CI 28.1–28.8) to Pred$_{5-year}$ = 27.7 (95% CI 27.1–27.9) and the semantic fluency test, from mean Pred$_{baseline}$ = 31.6 (95% CI 31.0–32.2) to mean Pred$_{5-year}$ = 30.8 (95% CI 30.1–31.5). An increase in TMT$_{B-A}$ completion times was observed from mean Pred$_{baseline}$ = 47.4 seconds (95% CI 44.1–50.8) to mean Pred$_{5-year}$ = 52.9 seconds (95% CI 49.7–56.4). There was no significant overall decline in FCSRT scores over time. Instead, an initial increase was noted during the first 3 years of follow-up, followed by a subsequent decrease. The mean predicted scores were Pred$_{baseline}$ = 30.0 (95% CI 29.3–30.7) at baseline and Pred$_{5-year}$ = 30.4 (95% CI 29.7–31.1) at 5 years. Furthermore, there was a small yet statistically significant decline in SPPB scores, with mean predicted scores decreasing from Pred$_{baseline}$ = 10.8 (95% CI 10.7–10.9) to Pred$_{5-year}$ = 10.4 (95% CI 10.2–10.5). Finally, there was a slight increase in 4IADL scores over the 5-year follow-up, with mean predicted scores going from Pred$_{baseline}$ = 4.1 (95% CI 4.1–4.2) at baseline to Pred$_{5-year}$ = 4.6 (95% CI 4.5–4.6) at 5 years.

The associations between blood-based biomarkers, presented in their transformed scales, and cognitive and functional trajectories are presented in Tables 2 and 3, respectively. Mean predicted cognitive trajectories based on biomarker levels are displayed in the transformed scales in Figure 1 and in eFigure 3, displaying the original test scales. Meanwhile, mean predicted functional trajectories according to biomarker levels are shown in their original scales in Figure 2. A higher Aβ42/40 ratio was associated with a modest deceleration in the decline of both FCSRT and semantic fluency scores over the follow-up period (+1 SD: β = 0.011, 95% CI 0.002–0.020, and +1 SD: β = 0.011, 95% CI 0.003–0.020, respectively). When expressed in the original test scales, +1 SD decrease in the log-transformed Aβ42/40 ratio at baseline led to a 0.9-point lower FCSRT score and a 1.0-point lower semantic fluency test score at 5-year follow-up (eFigure 4). Furthermore, a higher

Table 3 Association Between Individual AD Plasma Biomarkers and Functional Decline, MEMENTO Cohort, 2011–2020

	SPPB		Continuous 4IADL	
	β (SD)	*p* Value	β (SD)	*p* Value
Aβ42/40	−0.029 (0.03)	0.37	−0.045 (0.03)	0.14
Time	0.038 (0.04)	0.37*	0.098 (0.04)	0.01***
Time²	−0.015 (0.008)	0.06	−0.0005 (0.007)	0.94
Aβ42/40 × time	0.017 (0.009)	0.05	−0.045 (0.01)	<0.001
p-tau181	−0.133 (0.03)	<0.001	0.045 (0.03)	0.15
Time	0.034 (0.04)	0.42**	0.131 (0.04)	<0.001***
Time²	−0.016 (0.008)	0.04	−0.002 (0.007)	0.75
p-tau181 × time	−0.040 (0.009)	<0.001	0.115 (0.03)	<0.001
NfL	−0.112 (0.04)	0.002	0.070 (0.04)	0.04
Time	0.035 (0.04)	0.40**	0.124 (0.04)	0.002***
Time²	−0.015 (0.008)	0.06	−0.003 (0.007)	0.68
NfL × time	−0.016 (0.03)	0.12	0.077 (0.01)	<0.001

Abbreviations: Aβ = β-amyloid; 4IADL = 4 Instrumental Activities of Daily Living; NfL = neurofilament light chain; p-tau = phosphorylated tau; SPPB = Short Physical Performance Battery.
All models were adjusted for age at baseline, sex, *APOE* ε4 status, and education level. Owing to score transformations, parameters cannot be interpreted according to the scores' natural scales. Each biomarker was log-transformed and standardized. Biomarker × time interaction represents score change (in SD) per year per SD log biomarker level.
Multivariate Wald testing *p* value for overall time effect: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Aβ42/40 ratio was associated with a slower increase in the 4IADL score over 5 years (+1 SD: β = −0.045, 95% CI −0.070 to −0.020). Models accounting for all biomarkers simultaneously yielded similar results, with only slightly attenuated estimates (eTables 2 and 3).

Higher levels of p-tau181 were associated with a steeper decline in MMSE (+1 SD: β = −0.055, 95% CI −0.067 to −0.043), FCSRT (+1 SD: β = −0.034, 95% CI −0.043 to −0.025), and semantic fluency (+1 SD: β = −0.029, 95% CI −0.038 to −0.020) scores over 5 years, as well as worsening in TMT$_{B-A}$ times (+1 SD: β = 0.010, 95% CI 0.000–0.20), SPPB (+1 SD: β = −0.040, 95% CI −0.057 to −0.022), and 4IADL (+1 SD: β = −0.115, 95% CI 0.091–0.140) scores. A +1 SD increase in log-transformed p-tau181 level at baseline corresponded to a 0.8-point lower MMSE score at the 5-year follow-up, a 2.9-point lower FCSRT score, and a 1.9-point lower semantic fluency score at 5 years on the original scale of the cognitive tests (eFigure 4). To provide context, +10 years of age at inclusion leads to differences in scores at 5 years of −1.0 points for MMSE, −5.8 points for FCSRT, and −4.3 points for semantic fluency (data not shown). When considering models that accounted for all biomarkers simultaneously, the results were similar, with slightly attenuated

estimates. However, the association with TMT$_{B-A}$ score evolution was no longer significant (eTables 2 and 3).

Regarding NfL, higher concentration was associated with a steeper decline in MMSE (+1 SD: β = −0.039, 95% CI −0.053 to −0.025) and FCSRT (+1 SD: β = −0.022, 95% CI −0.032 to −0.012) scores, and to a lesser extent, in semantic fluency scores (+1 SD: β = −0.014, 95% CI −0.024 to −0.004). A +1 SD increase in log-transformed NfL level at baseline led to a 0.5-point lower MMSE score at the 5-year follow-up, a 1.6-point lower FCSRT score, and a 1.2-point lower semantic fluency score on the original test scales (eFigure 4). In addition, higher NfL levels were associated with worsening of 4IADL scores (+1 SD: β = 0.077, 95% CI 0.048–0.105). When considering all biomarkers simultaneously, the associations became attenuated and the association with fluency score evolution was no longer significant (eTables 2 and 3). Moreover, the associations between NfL and FCSRT, TMT, and 4IADL scores at baseline were no longer significant.
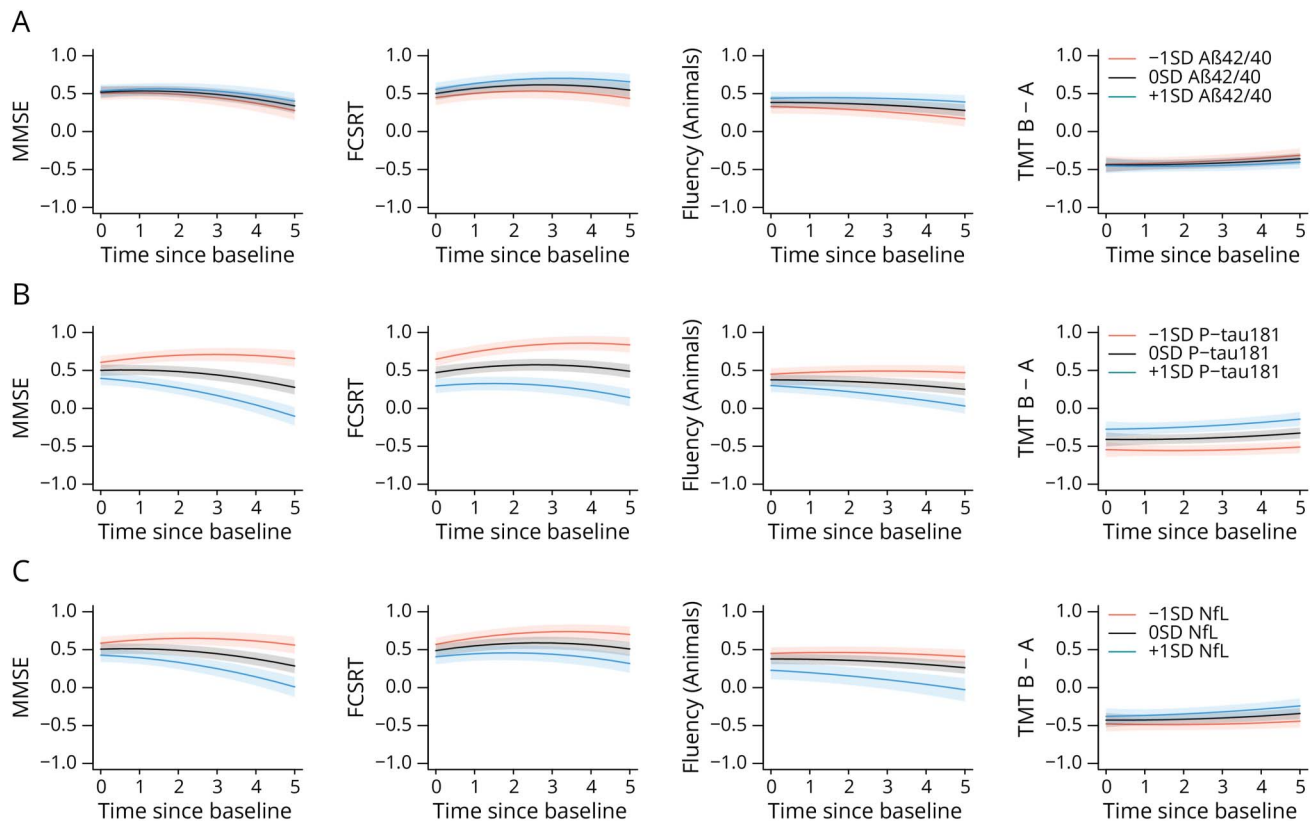
In the analysis investigating the cumulative effect of the different biomarkers (Figure 3, eTables 4 and 5), we observed a significant interaction between p-tau181, NfL, and slope with all outcomes, showing a steeper decline in cognitive and functional scores with higher levels of both p-tau181 and NfL, except for the TMT$_{B-A}$ score. A significant interaction between Aβ42/40 ratio, p-tau181, and the slope was also evidenced for MMSE and FCSRT scores, showing a steeper decline with higher levels of p-tau181 and lower Aβ42/40 ratio.

In the exploratory analysis examining potential effect modification by sex, *APOE* status, and education on the associations between biomarkers and cognitive or functional trajectories, no significant interactions were observed (data not shown). Furthermore, the main findings remained unchanged after including an interaction term between each biomarker and quadratic slope (eTables 6 and 7) as well as after multiple imputation for missing independent variables and accounting for glomerular filtration rate (results shown for the MMSE only in eTable 8). The analysis using gait speed instead of total SPPB scores yielded similar results, except for NfL, which was no longer associated with gait speed at baseline (eTable 8). Finally, several associations between AD blood-based biomarkers and cognitive and functional outcomes tended to be stronger among participants with CDR = 0.5 compared with participants with CDR = 0 (eTables 9 and 10).

Discussion

In this population with SCC and MCI consulting in memory clinics, higher plasma p-tau181 levels were associated with greater cognitive deterioration in multiple domains, encompassing episodic memory, semantic fluency, and executive functions. Elevated p-tau181 levels were also associated with a

Figure 1 Predicted Mean Trajectories for the Different Cognitive Tests in Their Transformed Scales According to Baseline Aβ42/40 Ratio (A), p-tau181 (B), and NfL (C) Level (Mean Value and ±1 SD), MEMENTO Cohort, 2011–2020

Trajectories with 95% CIs were predicted using a latent process linear mixed model including a quadratic function of time. Trajectories were plotted for the most common profile of covariates in the study sample: women aged 70 years and non-*APOE* ε4 carriers with a high education level. Aβ = β-amyloid; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; NfL = neurofilament light chain; p-tau = phosphorylated tau; TMT = Trail Making Test.
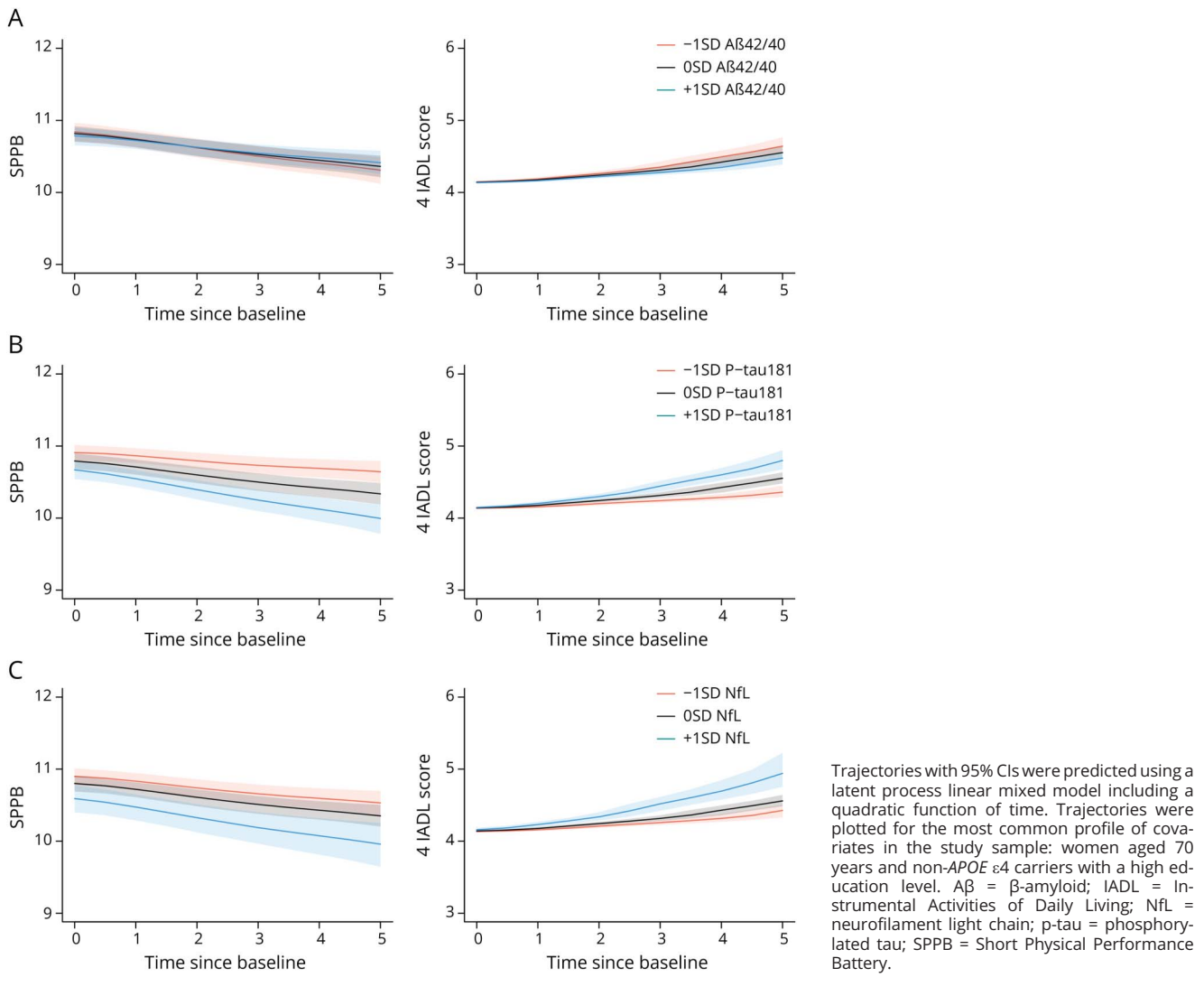
worsening trajectory in functional outcomes. It is of importance that these associations persisted even when other biomarkers were taken into account, confirming the robustness of p-tau181 as a marker of disease progression. Furthermore, elevated levels of blood NfL, a biomarker indicating neuroaxonal damage, were associated with more pronounced deterioration in global cognitive ability, episodic memory, semantic fluency, and autonomy. Although the other biomarkers slightly attenuated these associations, they remained significant for global cognitive ability, episodic memory, and autonomy. A higher Aβ42/40 ratio in blood showed a modest association with deterioration in episodic memory, semantic fluency, and autonomy. Moreover, some associations were mostly driven by participants with CDR = 0.5. Exploring the cumulative effect of these biomarkers on cognitive and functional decline revealed that higher levels of both p-tau181 and NfL were associated with larger deterioration in cognitive and functional outcomes compared with higher levels of each biomarker in isolation.

Our study presents compelling evidence of a strong association between serum p-tau181 levels and the progressive deterioration in cognitive and functional abilities across multiple domains. Tau-PET imaging studies have consistently shown a correlation between the accumulation of neurofibrillary tangles and the clinical manifestation and progression of symptoms in AD.[39,40] The regional distribution of neurofibrillary tangles corresponds to deficits observed in specific cognitive domains. Recent studies have shown that, even when measured in blood, p-tau is associated with the cognitive manifestations of AD,[17,18,20,41,42] independent of confounding factors such as renal function. Our findings indicate a significant association between blood p-tau181 levels and global cognition, episodic memory, semantic fluency, and cognitive flexibility. However, when considering the levels of other biomarkers, the association between p-tau181 and executive functions became attenuated, thus no longer significant. These results suggest that alternative pathways influenced by the other biomarkers may mediate the effects on cognitive flexibility and dampen the direct association with p-tau181.

Similar results were observed for NfL levels, albeit to a lesser extent. When considering p-tau181 level alongside NfL, the associations between NfL and cognitive and functional decline were attenuated, suggesting that they primarily reflect the robust associations linked to p-tau181, rather than making

Figure 2 Predicted Mean Trajectories for the Different Functional Tests in Their Original Scales According to Baseline Aβ42/40 Ratio (A), p-tau181 (B), and NfL (C) Level (Mean Value and ±1 SD), MEMENTO Cohort, 2011–2020

Trajectories with 95% CIs were predicted using a latent process linear mixed model including a quadratic function of time. Trajectories were plotted for the most common profile of covariates in the study sample: women aged 70 years and non-*APOE ε4* carriers with a high education level. Aβ = β-amyloid; IADL = Instrumental Activities of Daily Living; NfL = neurofilament light chain; p-tau = phosphorylated tau; SPPB = Short Physical Performance Battery.
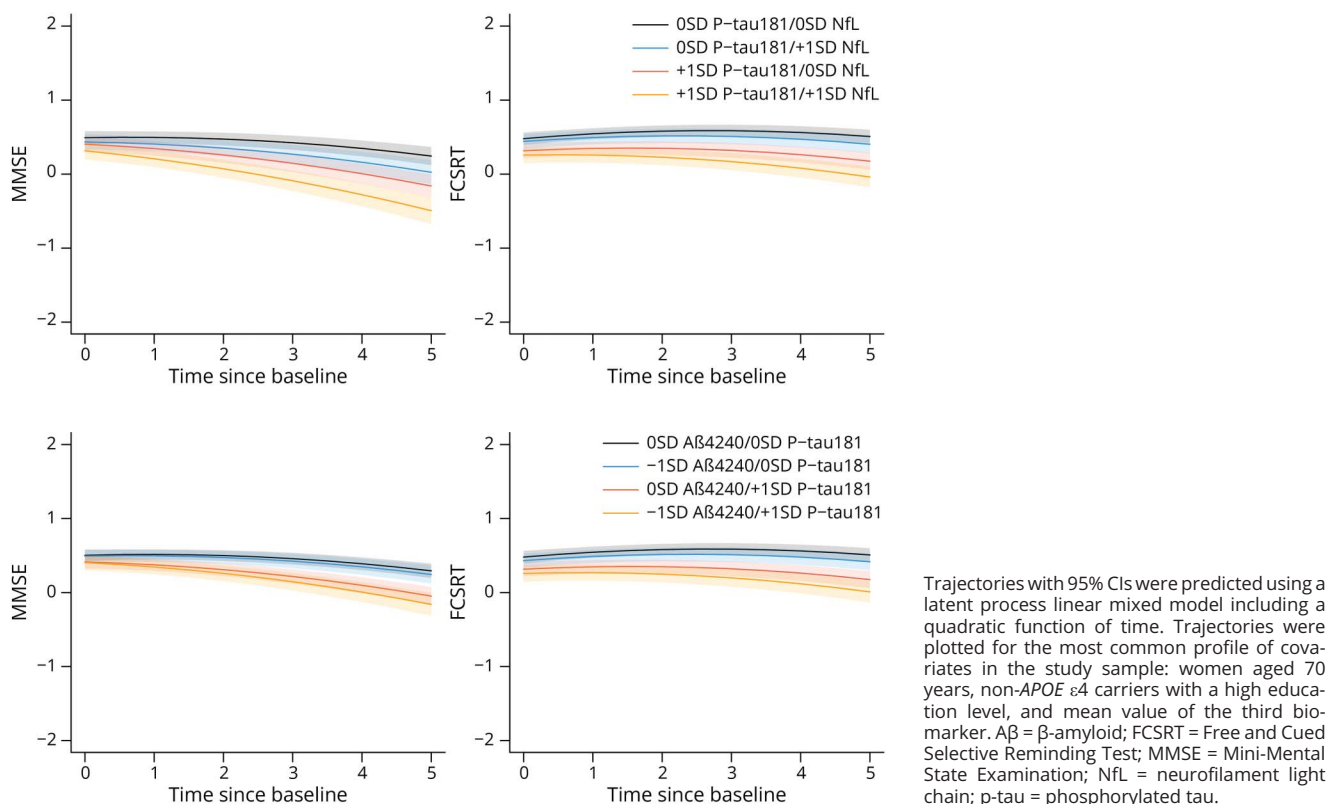
an independent contribution. However, the slight association between NfL and cognition when taking into account the concentration of p-tau181 suggest that NfLs concentrations also reflect neurodegenerative processes of other origins, such as frontotemporal dementias or Lewy body diseases, but we lacked biomarkers of these 2 conditions to investigate these hypotheses further. Previous studies have reported associations between NfL and cognitive function,[15,16,18-20,43] but most of them did not account for p-tau levels. In addition, we found a cumulative effect of p-tau181 and NfL, with the strongest associations observed when p-tau181 and NfL levels were simultaneously elevated. This suggests that beyond the impact of AD pathology measured by p-tau181, the extent of associated neuronal death measured by NfLs affects future decline, possibly reflecting copathologies. The cumulative effect of p-tau181 and NfL may also be explained by shared underlying consequences such as neuroinflammation and synaptic dysfunction. The interplay between these

mechanisms could amplify the detrimental effects on cognitive function when both p-tau181 and NfL levels are elevated.

Furthermore, while amyloid plaques are a hallmark of AD and play a significant role in the disease process, their direct association with cognitive symptoms is complex. Unlike tau pathology, which is widely acknowledged for its association with clinical manifestation of AD, cortical amyloid accumulation shows a less robust association with cognitive or functional decline.[39,40] In this study, we observed only weak associations between blood-based Aβ42/40 ratio and memory and semantic fluency decline. A recent study similarly failed to evidence an association between plasma Aβ42/40 ratio and global cognitive decline.[20] However, this contrasts with other studies that have reported associations between lower blood-based amyloid beta concentrations and more significant cognitive decline.[13,14,44-46] We cannot exclude that the weak association between blood-based Aβ42/40 ratio and

Figure 3 Predicted Mean Trajectories for the MMSE and FCSRT in Their Transformed Scales According to Different Combinations of Biomarker Values (Top: p-tau181 and NfL, Bottom: p-tau181 and Aβ42/40), MEMENTO Cohort, 2011–2020

Trajectories with 95% CIs were predicted using a latent process linear mixed model including a quadratic function of time. Trajectories were plotted for the most common profile of covariates in the study sample: women aged 70 years, non-*APOE* ε4 carriers with a high education level, and mean value of the third biomarker. Aβ = β-amyloid; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; NfL = neurofilament light chain; p-tau = phosphorylated tau.

cognitive and functional decline found in this work may arise from different factors, including cognitive reserve among highly educated individuals, relatively subtle overall decline in our sample, lower sensitivity in detecting early amyloid pathology in the brain using the Simoa assay compared with other techniques such as immunoprecipitation mass spectrometry[18,47,48] or the potential influence of peripheral amyloid production.[49]

Reports of blood-based biomarkers' relationships with functional and physical outcomes are scarce,[24-26] and none reported the association with p-tau. Our results are consistent with a study from the MAPT trial[26] (n = 507) that reported a cross-sectional association between NfL levels and lower SPPB scores, but no association between Aβ42/40 ratio and SPPB scores. Moreover, another study[24] reported a cross-sectional association between Aβ40, Aβ42, NfL, and SPPB score, although these findings only partially align with our results. Furthermore, unlike the study by He et al.,[25] we did not identify any interactions between Aβ and NfL with regard to functional outcomes. Given the large sample size of participants recruited consecutively from a clinical setting and the availability of major blood-based AD-related biomarkers, our findings significantly contribute to the scarce

literature on the relationships between blood-based biomarkers and functional decline including physical performances or dependency.

While the analyses reported here reveal highly significant associations, it is important to discuss the clinical relevance of the extent of cognitive and functional decline associated with higher levels of biomarkers (e.g., a difference of −0.8 MMSE point after 5 years of follow-up for 1 SD log p-tau181 level increase). This modest clinical impact may stem from the nature of our study sample, wherein approximately half comprise patients with MCI and the remaining half encompass individuals with SCC at baseline. In addition, the relatively mild alterations in cognitive or functional outcomes over the course of the follow-up period may contribute to this result. Finally, associations were not modified by sex, *APOE* ε4 status, and education level, suggesting that findings are consistent across subgroups. Unlike ours, few studies have shown that the association between blood-based biomarkers and cognitive decline or dementia risk was stronger among participants with low education or women.[20,50] However, these studies have methodologic weaknesses, either based on small selected samples, or using less reliable techniques for blood biomarker concentrations. Additional studies

investigating the factors that may influence these associations are thus needed.

This study is a comprehensive examination of the association between blood-based AD biomarkers and various cognitive and functional domains in a large cohort of older adults at risk of AD. The MEMENTO study provides an ideal setting to investigate these relationships, within a large sample size, comprising both cognitively normal individuals and patients with MCI. Our access to detailed cognitive assessments enables the identification of early and potentially subtle differences in cognitive functioning. Nevertheless, there are some limitations to this work. The Simoa assays used in this study are probably not the most accurate to detect disease-specific pathology, especially for amyloid pathology.[48] It would be valuable to further validate our findings regarding Aβ associations using alternative plasma AD biomarker quantification techniques, such as mass spectrometry–based methods. In addition, it is worth noting that plasma biomarkers were not measured in duplicates. Nevertheless, we conducted multiple reproducibility checks on subsets throughout the study, which yielded very satisfactory results.

In conclusion, although most studies have focused on blood-based biomarker relations with cognitive decline, this work highlights that p-tau181 and NfL are more largely related to brain function changes, that is, both cognitive and motor functions, among individuals consulting in a memory clinic with SCC or MCI, while blood-based Aβ42/40 ratio was only weakly associated with changes in some cognitive domains. The measurement of AD blood-based proteins should be more widely used in future observational studies on AD to better understand the multidimensional aspect of AD and its underlying biology.

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Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Appendix 1 Authors

Name	Location	Contribution
Leslie Grasset, PhD	UMR 1219, Bordeaux Population Health Center, University of Bordeaux, Inserm; CIC 1401-EC, Inserm, University of Bordeaux, CHU de Bordeaux, France	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
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Federica Cacciamani, PhD	UMR 1219, Bordeaux Population Health Center, University of Bordeaux, Inserm; CIC 1401-EC, Inserm, University of Bordeaux, CHU de Bordeaux; ARAMISLab, Sorbonne Université, Institut du Cerveau—Paris Brain Institute—ICM, CNRS, Inria, Inserm, AP-HP, Hôpital de la Pitié Salpêtrière; Qairnel SAS, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
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Vincent Planche, MD, PhD	Univ. Bordeaux, CNRS UMR 5293, Institut des Maladies Neurodégénératives, Centre Mémoire de Ressources et de Recherches, Pôle de Neurosciences Cliniques, CHU de Bordeaux, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Geneviève Chêne, MD, PhD	UMR 1219, Bordeaux Population Health Center, University of Bordeaux, Inserm; CIC 1401-EC, Inserm, University of Bordeaux, CHU de Bordeaux; Centre Hospitalier Universitaire (CHU) de Bordeaux, Pole de sante publique, France	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Carole Dufouil, PhD	UMR 1219, Bordeaux Population Health Center, University of Bordeaux, Inserm; CIC 1401-EC, Inserm, University of Bordeaux, CHU de Bordeaux; Centre Hospitalier Universitaire (CHU) de Bordeaux, Pole de sante publique, France	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

Appendix 2 Coinvestigators

Coinvestigators are listed at Neurology.org.

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