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RESEARCH ARTICLE

Subjective cognitive and non-cognitive complaints and brain MRI biomarkers in the MEMENTO cohort

Virginie Dauphinot[1] | **Vincent Bouteloup**[2,3] | **Jean-François Mangin**[4,5] | **Bruno Vellas**[6,7] | **Florence Pasquier**[8] | **Frédéric Blanc**[9] | **Olivier Hanon**[10] | **Audrey Gabelle**[11] | **Cédric Annweiler**[12,13] | **Renaud David**[14] | **Vincent Planche**[15] | **Olivier Godefroy**[16,17] | **Thérèse Rivasseau-Jonveaux**[18,19] | **Marie Chupin**[4,5] | **Clara Fischer**[4,5] | **Geneviève Chêne**[2,3] | **Carole Dufouil**[2,3] | **Pierre Krolak-Salmon**[1,18,19]

[1] Clinical and Research Memory Centre of Lyon, Lyon Institute for Elderly, Charpennes Hospital, University Hospital of Lyon, Lyon, France

[2] Inserm, Bordeaux Population Health Research Center, UMR 1219, Bordeaux University, ISPED, Bordeaux University, Bordeaux, France

[3] University hospital of Bordeaux, Public Health Center, Bordeaux, France

[4] CATI Multicenter Neuroimaging Platform (http://cati-neuroimaging.com), Gif-sur-Yvette, Paris, France

[5] Neurospin, CEA, Paris-Saclay University, Gif-sur-Yvette, France

[6] Gérontopôle, University hospital of Toulouse (CHU Toulouse), Toulouse, France

[7] Inserm UMR1027, University of Toulouse III Paul Sabatier, Toulouse, France

[8] Univ Lille, Inserm 1171, CHU, Clinical and Research Memory Research Centre (CMRR) of Distalz, Lille, France

[9] Clinical and Memory Research Centre of Strasbourg (CMRR), University hostpital of Strasbourg, Geriatrics unit, Geriatric Day Hospital, Strasbourg, France

[10] Geriatry unit, Paris Descartes UniversityBroca hospital, Paris, France

[11] Clinical and Research Memory center of Montpellier, Department of Neurology, Gui de Chauliac Hospital, University of Montpellier, Montpellier, France

[12] Department of Geriatric Medicine, Angers University Hospital, Angers University Memory Clinic; Research Center on Autonomy and Longevity; UPRES EA 4638, University of Angers, Angers, France

[13] Robarts Research Institute, Department of Medical Biophysics, Schulich School of Medicine and Dentistry, the University of Western Ontario, London, Ontario, Canada

[14] Clinical and Research Memory Centre of Nice, University hospital of Nice, EA COBTeK, Côte d'Azur University, Nice, France

[15] Clinical and Research Memory Centre of Bordeaux, Clinical neurosciences centre, University hospital of Bordeaux, F-33000 Bordeaux, France et 2. Univ. Bordeaux, CNRS, gérontopole Institute of Neurodegenerative Diseases, Bordeaux, France

[16] Departments of Neurology, Amiens University Hospital (CHU Amiens), and Laboratory of Functional Neurosciences (EA 4559), Jules Verne University of Picardie, Amiens, France

[17] Institute of the Brain and Spinal Cord, Inserm, U1127,3 CNRS, UMR 7225, Sorbonne University, Paris, France

[18] Clinical and Research Memory Centre of Lorraine, Hospital of Brabois, Cognitive-behavioral unit, Paul Spillmann Centre, CHRU de Nancy, France

[19] Communications Research Group, Interpsy EA4432 Psychology, University of Lorraine, Nancy, France

Correspondence
Dr. Virginie Dauphinot, Clinical and Research Memory Centre of Lyon, Hôpital des Charpennes, 27 rue Gabriel Péri, 69100 Villeurbanne, France.
Email: virginie.dauphinot@chu-lyon.fr

Abstract

Introduction: Subjective cognitive complaints may be a signature of preclinical stage Alzheimer's disease. However, the link between subjective cognitive and non-cognitive complaints and brain alterations remains unclear.

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Methods: The relationship between cognitive and non-cognitive complaints and brain biomarkers, measured by structural magnetic resonance imaging, was investigated in 2056 participants of the MEMENTO cohort of outpatients, who were dementia-free at baseline. We assessed whether the cognitive status at inclusion or the presence of the apolipoprotein E gene variant (*APOE*) ε4 could modulate the association between the intensity of complaints and brain lesions.

Results: Smaller hippocampal volume was associated with higher memory complaints and discomfort in daily life. In *APOE* ε4 carriers, smaller whole-brain white matter and gray matter volumes and gyrification indices in several regions of interest of the parietal and temporal lobes, in the entorhinal and the para-hippocampal gyrus, were associated with higher memory complaint score.

Conclusions: The intensity of subjective complaints in not only memory but discomfort in daily life was associated with brain degeneration markers. The presence of *APOE* ε4 modulated the relationships between subjective memory complaints and brain alterations.

KEYWORDS
magnetic resonance imaging, multi-center cohort, preclinical AD, subjective health complaints

1 | BACKGROUND

Early identification of individuals at risk of Alzheimer's disease (AD), which accounts for 50% to 75% of all dementias, is critical, as it could be an important window for interventions to delay onset or progression of disease before the common clinical criteria of AD are met.[1,2] There is a growing body of evidence suggesting that subjective cognitive complaints, also referred as subjective memory complaints/impairment or decline, could occur prior to neurocognitive disorders (NCDs) due to AD. Individuals with subjective cognitive complaints may be at higher risk of developing mild cognitive impairment (MCI) or dementia compared to individuals who do not report complaints.[3-5] Previous neuroimaging studies have shown greater reductions in brain volume in regions commonly affected early in AD, that is, in the medial temporal lobe, including the entorhinal cortex (EC), the hippocampus, and the amygdala, and cortical thinning in the EC in individuals with subjective cognitive decline compared to those without.[6-12] Nevertheless, these findings are not definitive, as some studies have not shown brain structure alterations, whereas others have shown brain alterations in different locations.[13-15] This heterogeneity may be explained by differences in study settings (clinical vs population) and methods (imaging, sampling, and measurement of subjective cognitive complaints).[16,17] Furthermore, there is currently no consensus regarding the evaluation of subjective cognitive complaints. This is reflected in the large variability in the proportion of subjects ages 65 and older who are presenting subjective memory or cognitive complaints across studies, ranging from 22% to 56%.[3] Consequently the subjective memory or cognitive complaints are highly prevalent, and they may not be sufficiently specific to detect individuals at an early stage of AD. Although previous research has focused on subjective memory or cognitive complaints potentially related to AD, studies of subjective complaints other than cognition are lacking. However, extending the definition of subjective complaints to domains other than cognition may allow for better understanding the subjective complaints prior to AD onset. Therefore, the link between subjective complaints and brain alterations remains unclear and it has not been explored in a sample of individuals including at the same time individuals with or without objective cognitive impairment (without dementia), whereas not all of them will progress to dementia due to AD. In a meta-analysis, the annual conversion rates to MCI or dementia were 6.6% and 2.3%, respectively, among individuals with subjective memory complaints, and the risk of conversion to MCI or dementia in individuals with subjective memory complaints was twice in comparison to individuals without any.[4] In the study of Gifford et al., participants with subjective complaints were associated with two-fold increases in odds of conversion of cognitively normal (CN) status to MCI, whereas participants with subjective cognitive complaints in MCI were not associated with risk of conversion to dementia.[18]

Furthermore, although previous research has suggested that the presence of the apolipoprotein E (*APOEE*) ε4 allele is a main genetic risk factor for AD and is associated with greater brain atrophy, few have taken into account *APOE* ε4 in the analysis of subjective complaints and brain alterations.[19-21]

In this study, we aimed to assess the association between the intensity of subjective complaints, beyond cognition, and markers of both whole and regional cerebral alterations in a large French multicenter cohort of outpatients from memory clinics without dementia at inclusion. In addition, we assessed whether the cognitive status at inclusion (cognitively normal with isolated subjective cognitive complaint or MCI) or the presence of the *APOE* ε4 could modulate the association between the intensity of complaints and brain lesions.

2 | METHODS

2.1 | Study design and setting

We conducted this analysis using data from the MEMENTO cohort, described in detail elsewhere.[22] The MEMENTO cohort consecutively recruited 2323 dementia-free outpatients attending one of the 26 participating memory clinics between April 2011 and June 2014. The MEMENTO cohort's primary objective is to study the evolution of cognitive symptoms and subjective complaints over a period of at least 5 years (ClinicalTrials protocol number: NCT01926249, https://clinicaltrials.gov/ct2/show/NCT01926249). Study participants were screened for isolated subjective cognitive complaints (iSCCs) or MCI. MCI was defined as (1) performing worse than 1.5 SD to the mean (compared to age and educational norms) in one or more cognitive domains, this deviation being identified for the first time through cognitive tests performed <6 months preceding the screening phase and (2) having a Clinical Dementia Rating (CDR) scale score ≤0.5 and not having dementia. We used the results of the following neuropsychological tests to assess the cognitive domains (memory, language, praxis, attention, executive functions, speed processing, and visual spatial abilities): Free and Cued Selective Reminding Test, Delayed Matching Sample 48, Trail Making Test parts A and B, the Frontal Assessment Battery, Praxis Battery, and semantic (animal) and letter (letter P) 2 minute fluencies. Because participants were recruited from memory clinics, if they did not have objective cognitive deficit, they were considered to be cognitively normal and have iSCCs. They must also agree to undergo a brain magnetic resonance imaging (MRI) and blood sampling[22] and have health care coverage. The cohort's exclusion criteria are pronounced dependency (defined as wardship or living in a nursing home), having a history of neurological disease (treated Parkinson disease, Huntington disease, AD due to genetic mutations, treated epilepsy, a brain tumor, subdural hematoma, progressive supranuclear palsy), a history of head trauma with neurological deficits, a history of intracranial surgery, a history of stroke diagnosed in the past 3 months prior to inclusion, or schizophrenia. Those who were illiterate were also excluded.

2.2 | Study sample

We restricted this analysis to cohort participants who had answered a self-administered questionnaire on subjective complaints and had undergone a brain MRI, resulting in a sample of 2056 participants.

2.3 | Ethical considerations

All participants provided written informed consent. The study was granted ethical approval by a local institutional review board ("Comité de Protection des Personnes Sud-Ouest et Outre Mer III"). The study was conducted according to the standards of the good clinical and epidemiological practice and in compliance with the Declaration of Helsinki.

RESEARCH IN CONTEXT

1. Systematic review: A literature review was performed using PubMed with the terms "subjective memory OR cognitive complaint OR subjective complaint OR impairment OR decline" AND "brain biomarker OR MRI."
2. Interpretation: Early diagnosis of Alzheimer's disease (AD) may provide a window for intervention before common AD criteria are met. Subjective cognitive complaints could be a signature of preclinical stage AD. Our study shows that the intensity of subjective complaints in memory and discomfort in daily life is associated with brain degeneration markers in subjects without dementia. Apolipoprotein E (*APOE*) ε4 allele modulated the relationship between the intensity of subjective memory complaints and brain alterations.
3. Future directions: Longitudinal analysis will allow study of whether higher initial complaints are predictive of evolution toward advanced stages of AD. Future research investigating the link between subjective complaints and AD risk should expand the field of complaint to non-cognitive domains such as physical condition and discomfort in daily life.

2.4 | Subjective complaints assessment

Subjective complaints covered both cognitive domains (memory, language, attention) and non-cognitive domains (physical condition, mood/morale, potential life stress, and sensory organs). Participants were also questioned about their subjective health status: general state of health, discomfort in daily life (or perceived current difficulties), and perceived health status (fifth item of the EQ-5D questionnaire[23] [www.euroqol.org]). For each domain, participants were assessed with respect to their discomfort level using a Visual Analogue Scale (VAS), ranging from 0 (no discomfort/difficulty/concern) to 10 (maximum intensity of discomfort/difficulty/concern). Perceived health status was assessed on a scale of 0 to 100 and divided by 10 for analysis. The different standardized questions are shown in supplementary file S1.

2.5 | Brain MRI acquisition and measurements

Brain MRI acquisitions were standardized and centralized according to a systematic qualification procedure, ensuring parameter uniformity and image quality, by the Centre pour l'Acquisition et le Traitement des Images (CATI), a national platform dedicated to neuroimaging (http://cati-neuroimaging.com), described previously.[22,24] Brain MRI images were obtained with 3.0 or 1.5 Tesla scanners. MRI parameters are described in details in supplementary file S2.

Several imaging biomarkers were used for this analysis. The whole-brain and gray/white matter volumes were calculated using three-dimensional (3D) T1-based segmentation method with 1 mm isotropic resolution provided in the Statistical Parametric Mapping version 8 (SPM8) software. The hippocampal volume was calculated using the SACHA software.[25] We used the Brain Parenchymal Fraction (BPF) calculated as the ratio between the volume of tissue (gray/white matter) and the sum of the volumes of gray matter, white matter, and cerebrospinal fluid (CSF) (each class segmented by SPM8 software) to assess changes in brain volume.

The cortical thickness and the gyrification index (GI), defined as the local ratio between the surface areas of the cortex and its convex hull, were measured in the 34 regions of interest (ROIs) using the Desikan-Killiany atlas and the FreeSurfer 5.3 software.[26] The sulcal span was computed with the method Morphologist of BrainVISA package for each sulcus of the Brainvisa Sulci atlas.[27] The means of the left and right hemispheres for each ROI, as well as both left and right hemispheres were considered for the cortical thickness, GI, and when both sides were measured for sulcal span. These four classes of regional biomarkers were used because each of them has specificity for our exploratory approach: Regional gray matter volume allows us to detect any difference leading to high sensitivity; cortical thickness provides specificity to changes of the cortical column content (amount of neurons, neuropil, and glial cells) versus change of the cortical area of the ROI; local gyrification index targets changes of the cortical surface 3D embedding triggered by neurodegeneration. It is probably correlated with changes of surface areas, but has the potential to aggregate several other structural changes occurring for instance in white matter; sulcal span, namely the amount of CSF in a sulcus, is a proxy for regional atrophy occurring on both sides of the sulcus, in the cortical mantle but also in the underlying white matter. It is supposed to be sensitive to the earliest neurodegenerative effects thanks to the strong contrast between CSF and tissue, leading also to robustness to the multicenter design of the MEMENTO cohort.

2.6 | Other covariates

The CDR scale was administered and all participants were categorized for cognitive status according to Petersen criteria as pure amnestic MCI, multi-domain amnestic MCI, pure non-amnestic MCI, and multi-domain non-amnestic MCI.[28,29] Depression symptoms were assessed using the Neuropsychiatric Inventory (NPI).[30] *APOE* genotype was detected using KBiosciences (Hoddesdon, UK; www.kbioscience.co.uk).

2.7 | Statistical analyses

We calculated a standardized domain-specific complaint score for each participant for each of the 10 subjective complaints using the following formula: standardized domain specific complaint score = (raw score at a given domain − mean of all domain raw scores of the individual)/SD of all domains raw scores of the individual). This transformation allows us to identify domains where the participant is complaining more (ie, standardized score >0) or less (ie, standardized score <0) compared to the other domains. It also allows us to control for the mean level of complaints (subjects frequently or never complaining). To allow for comparisons across analyses, brain MRI biomarkers were also standardized.

The relationship between each standardized complaint scores (defined as the dependent variables) and each whole-brain MRI biomarker (ie, whole-brain gray/white matter volumes, hippocampal volume, and BPF defined as the independent variables), as well as ROI brain MRI biomarkers (ie, gray matter volumes, cortical thickness, gyrification indexes, and sulcal spans) was investigated using multiple linear regressions. All models were adjusted for the following potential confounders: sex, age, education level (primary school, secondary school, high school or beyond), depression score (NPI-C clinician score), total intracranial volume (except for BPF),[31] and type of MRI scanner (manufacturer and magnet field).[32] For "Physical condition," "General Health Status," and "Perceived Health" (EQ-5D), we added as cofounders the physical performance measured by the Short Physical Performance Battery (SPPB), the physical activity during the 7 past days measured by the International Physical Activity Questionnaire (IPAQ), and the comorbidities burden estimated by the presence of medical history of cardiovascular diseases, diabetes, cancer, or respiratory diseases. We assessed whether the cognitive status at inclusion (iSCC vs MCI) or the presence of *APOE* ε4 allele modified the association between MRI biomarkers and complaint scores by testing interaction terms. Results for the brain MRI markers of gray matter volume, cortical thickness, and gyrification indexes are summarized with the beta coefficients, representing the measure of association of 1 SD increase of each brain MRI biomarker on each standardized complaint score, their 95% confidence interval (CI), and their *P*-values before and after adjustment for multiple testing. We used the false discovery rate (FDR) method of conceptualizing the rate of type I error when conducting multiple hypothesis tests. Results were stratified according to the cognitive status at inclusion (iSCC vs MCI) or on the presence of *APOE* ε4 allele when the interaction was significant. Furthermore, the potential differential associations between right or left hemispheres were assessed by ROIs using multiple linear regressions; results are summarized in Manhattan plots. A *P* value <.05 was considered statistically significant and all statistical tests were two-sided. Statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC).

3 | RESULTS

3.1 | Characteristics of the study population

Participants were characterized by a median age of 72; 62.4% were women and 54.8% had at least a high school education (Table 1). The majority (83.9%) of participants had MCI and 29.5% were *APOE* ε4 carriers. On average, subjective memory (median: 5, interquartile range [IQR]: 3 to 6) and attention (median: 4, IQR: 3 to 6)

TABLE 1 Baseline characteristics of the analytical sample from the MEMENTO cohort

	Analytic sample (n = 2056)
Female sex, n (%)	1283 (62.4)
Age, median (Q1;Q3)	71.7 (65.6; 77.1)
Educational level ≥ high school diploma, n (%)	1124 (54.8)
APOE ε4 carriers, n (%)	578 (29.5)
CDR at 0.5, n (%)	1221 (59.4)
MMSE, median (Q1;Q3)	28 (27.0; 29.0)
Cognitive status, n(%)	
iSCC	330 (16.1)
Pure amnestic MCI	177 (8.6)
Multi-domain amnestic MCI	872 (42.4)
Pure non-amnestic MCI	359 (17.5)
Multi-domain non-amnestic MCI	318 (15.5)
NPI depression clinician score, median (Q1;Q3)	0 (0.0; 2.0)
Subjective complaint scores, median (Q1;Q3)	
Physical condition	2 (0;5)
Attention	4 (3;6)
Memory	5 (3;6)
Language	3 (1;5)
Mood/morale	2 (1;5)
General health status	3 (1;5)
Life stress	3 (1;6)
Sensory organs	3 (1;5)
Health status (100-EQ-5D)/10)	2 (2;4)
Discomfort in daily life	3(1;5)

Abbreviations: CDR, Clinical Dementia Rating; iSCC, isolated subjective cognitive complaint; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; Q1;Q3, first and third interquartiles.

complaints were numerically higher than in other domains. Among the 2056 individuals, 1783 (86.7%) had a 3T MRI; MRI was 1.5T otherwise.

3.2 | Relationships between subjective complaints and whole-brain MRI biomarkers

Reduced hippocampal volume was associated with higher memory complaints ($P = .0007$) and discomfort in daily life ($P = .023$) scores as well as lower life stress ($P = .011$) complaint score (Table 2). Reduced white matter volume was associated with lower general health complaint ($P = .023$). A significant interaction was observed between white matter volume and presence of *APOE* ε4 allele in the relationship with memory complaints (P for interaction = .0099): smaller white matter volume being associated with a higher memory complaint score among *APOE* ε4 carriers only ($P = .0067$). The analysis of the interaction between cognitive status and MRI biomarkers showed that smaller hippocampal volume was associated with lower language complaint score, and lower BPF was associated with lower general heath complaint score in participants with MCI ($P = .011$ and $P = .010$, respectively) (Table 3).

3.3 | Relationship between subjective complaints by domain and each brain MRI biomarker (volume, thickness, and GI of ROIs of the cortical mantle and width of sulci)

Lower cortical thickness in the posterior cingulate gyrus ($P = .033$), in the lateral occipital gyrus ($P = .03$), in the inferior parietal gyrus ($P = .005$), in the supramarginal gyrus ($P = .012$), and in the majority of the ROIs of the temporal lobe (8/10), that is, superior temporal sulcus ($P = .009$), entorhinal ($P = .027$), fusiform ($P = .005$), inferior temporal ($P = .027$), middle ($P = .012$), superior ($P = .027$) and transverse temporal ($P = .012$), and parahippocampal gyrus ($P = .027$), was associated with a lower life stress complaint score (Figure 1 and supplementary file S3). Wider anterior lateral fissure ($P = .029$) and wider inferior frontal sulcus ($P = .029$) were associated with a lower language complaint score (Figure 2 and supplementary file S3).

APOE ε4 modified several associations between complaints and MRI biomarkers. We observed the following associations in *APOE* ε4 carriers. Regarding memory complaints, local reduced gray matter volumes in the isthmus of the cingulate gyrus ($P = .003$), in the pars triangularis gyrus of the inferior frontal gyrus ($P = .042$), in the supramarginal gyrus of the parietal lobe ($P = .014$), and in the entorhinal ($P = .015$), parahippocampal ($P = .015$), middle ($P = .047$), and superior temporal gyrus of the temporal lobe ($P = .016$) were associated with a higher memory complaint score (supplementary file S3). Smaller GI in the rostral anterior cingulate gyrus ($P = .045$) was associated with a higher memory complaint score, whereas smaller GI in the pars triangularis gyrus ($P = .025$) was associated with a lower memory complaint score. The calcarine sulcus was wider when the memory complaint score was higher ($P = .003$). Regarding complaints in physical domain, a smaller GI in the transverse temporal gyrus and a smaller cortical thickness in the pericalcarine were associated with a higher physical condition complaint score ($P = .016$, and $P = .025$, respectively). With regard to discomfort in daily life (or perceived current difficulties), a smaller GI of the lateral ($P = .017$) and medial orbitofrontal cortex ($P = .007$) was associated with a lower discomfort in daily life score, whereas a smaller cortical thickness in the insula was associated with higher discomfort in daily life score ($P = .005$). With regard to mood, a gray matter volume in the transverse temporal gyrus was smaller when the complaint score was lower ($P = .024$). Regarding complaints in language domain, a wider internal parietal sulcus was associated with a lower language complaint score ($P = .016$). Regarding complaints in attention domain, a smaller GI in the posterior cingulate ($P = .044$) and in the superior temporal sulcus ($P = .049$) was associated with a lower attention complaint score, whereas a smaller GI in the lateral orbitofrontal cortex was associated with a higher score ($P = .009$). The posterior inferior temporal

TABLE 2 Adjusted associations between subjective complaints scores and brain MRI biomarkers (N = 2056), with interaction between MRI biomarkers and presence of *APOE ε4* allele

		Change in complaint for +1 SD of brain MRI biomarker[a]				Interaction between MRI biomarkers and presence of *APOE ε4* allele		*APOE ε4* allele non-carrier			*APOE ε4* allele carrier		
		Beta	[95% IC]	*P*[b]	*P* (FDR)[b]	P[b]	*P* (FDR)[b]	Beta	[95% IC]	*P*	Beta	[95% IC]	*P*
Physical condition	BPF	−0.032	[−.085;0.021]	0.24	0.48	0.93	0.93						
	White matter	−0.045	[−.183;0.092]	0.52	0.64	0.76	0.93						
	Gray matter	−0.054	[−.280;0.173]	0.64	0.64	0.43	0.93						
	Hippocampal volume	0.036	[−.016;0.088]	0.17	0.48	0.76	0.93						
Attention	BPF	−0.005	[−.052;0.041]	0.82	0.82	0.65	0.94						
	White matter	−0.061	[−.181;0.059]	0.32	0.42	0.94	0.94						
	Gray matter	0.114	[−.080;0.307]	0.25	0.42	0.83	0.94						
	Hippocampal volume	−0.031	[−.076;0.014]	0.18	0.42	0.33	0.94						
Memory	BPF	−0.029	[−.077;0.018]	0.23	0.30	0.36	0.36						
	White matter				0.21	0.0099	0.029	−0.081	[−.210;0.047]	0.22	−0.194	[−.335;-.054]	0.0067
	Gray matter				0.34	0.014	0.029	0.146	[−.060;0.351]	0.17	0.039	[−.175;0.252]	0.72
	Hippocampal volume	−0.088	[−.134;-.042]	0.0002	0.0007	0.107	0.142						
Language	BPF	0.025	[−.027;0.077]	0.34	0.59	0.92	0.92						
	White matter	0.036	[−.098;0.171]	0.59	0.59	0.42	0.84						
	Gray matter	0.059	[−.158;0.277]	0.59	0.59	0.73	0.92						
	Hippocampal volume	0.050	[−.000;0.101]	0.052	0.21	0.26	0.84						
Mood	BPF	−0.016	[−.066;0.034]	0.53	0.71	0.38	0.50						
	White matter	0.011	[−.118;0.141]	0.86	0.86	0.089	0.25						
	Gray matter	−0.085	[−.293;0.124]	0.43	0.71	0.123	0.25						
	Hippocampal volume	-0.029	[−.078;0.020]	0.24	0.71	0.66	0.66						
General Health Status	BPF	0.042	[−.006;0.090]	0.087	0.116	0.55	0.71						
	White matter	0.174	[0.051;0.297]	0.0057	0.023	0.71	0.71						
	Gray matter	−0.160	[−.364;0.043]	0.122	0.122	0.64	0.71						
	Hippocampal volume	0.051	[0.004;0.098]	0.032	0.064	0.57	0.71						
Life stress	BPF	0.024	[−.031;0.079]	0.38	0.73	0.18	0.71						
	White matter	0.025	[−.117;0.168]	0.73	0.73	1.00	1.00						
	Gray matter	0.066	[−.164;0.297]	0.57	0.73	0.46	0.91						
	Hippocampal volume	0.082	[0.028;0.135]	0.0028	0.011	0.68	0.91						

(Continues)

TABLE 2 (Continued)

		Change in complaint for +1 SD of brain MRI biomarker[a]				Interaction between MRI biomarkers and presence of *APOE ε*4 allele		*APOE ε*4 allele non-carrier			*APOE ε*4 allele carrier		
		Beta	[95% IC]	*P*[b]	*P* (FDR)[b]	P[b]	*P* (FDR)[b]	Beta	[95% IC]	*P*	Beta	[95% IC]	*P*
Sensory organs	BPF	0.030	[−.025;0.085]	0.29	0.68	0.18	0.36						
	White matter	0.043	[−.099;0.185]	0.55	0.74	0.82	0.96						
	Gray matter	0.024	[−.206;0.255]	0.84	0.84	0.96	0.96						
	Hippocampal volume	0.026	[−.027;0.080]	0.34	0.68	0.136	0.36						
Perceived health (EQ-5D/10)	BPF	0.013	[−.034;0.061]	0.58	0.77	0.56	0.75						
	White matter	−0.006	[−.129;0.117]	0.92	0.92	0.138	0.55						
	Gray matter	0.088	[−.115;0.290]	0.39	0.77	0.30	0.59						
	Hippocampal volume	0.014	[−.033;0.061]	0.56	0.77	0.75	0.75						
Discomfort in daily life	BPF	−0.003	[−.058;0.051]	0.90	0.90	0.60	0.84						
	White matter	−0.020	[−.160;0.120]	0.78	0.90	0.45	0.84						
	Gray matter	−0.017	[−.244;0.209]	0.88	0.90	0.84	0.84						
	Hippocampal volume	−0.074	[−.126;-.021]	0.0059	0.023	0.82	0.84						

Note: MEMENTO cohort.

Abbreviations: BPF, Brain Parenchymal Fraction, FDR, false discovery rate; MRI, magnetic resonance imaging.

[a]Adjusted for sex, age, education level, depression score, total intracranial volume (except for BPF), and type of MRI scanners.

[b]*P* value before and after adjustment for multiple testing using the FDR method.

TABLE 3 Adjusted associations between subjective complaint scores and brain MRI biomarkers (N = 2056), with interaction between MRI biomarkers and cognitive status (iSCC or MCI)

		Interaction between MRI biomarkers and cognitive status (iSCC or MCI)		iSCC			MCI		
		P[b]	*P* (FDR)[b]	Beta	[95% IC]	*P*	Beta	[95% IC]	P
Physical condition	BPF	0.39	0.39						
	White matter	0.060	0.120						
	Gray matter	0.060	0.120						
	Hippocampal volume	0.33	0.39						
Attention	BPF	0.22	0.58						
	White matter	0.40	0.58						
	Gray matter	0.78	0.78						
	Hippocampal volume	0.44	0.58						
Memory	BPF	0.32	0.86						
	White matter	0.98	0.98						
	Gray matter	0.43	0.86						
	Hippocampal volume	0.65	0.86						
Language	BPF	0.022	0.043	−0.091	[−.202;0.021]	0.111	0.046	[−.009;0.101]	0.101
	White matter	0.70	0.91						
	Gray matter	0.91	0.91						
	Hippocampal volume	0.0083	0.033	−0.111	[−.241;0.019]	0.093	0.068	[0.015;0.121]	0.011
Mood	BPF	0.046	0.18	0.082	[−.026;0.189]	0.135	-0.033	[−.086;0.020]	0.23
	White matter	0.72	0.72						
	Gray matter	0.53	0.70						
	Hippocampal volume	0.21	0.42						
General Health Status	BPF	0.0021	0.0084	−0.102	[−.205;0.001]	0.051	0.066	[0.016;0.117]	0.010
	White matter	0.21	0.29						
	Gray matter	0.17	0.29						
	Hippocampal volume	0.93	0.93						
Life stress	BPF	0.62	0.62						
	White matter	0.0033	0.013	−0.120	[−.291;0.052]	0.17	0.057	[−.086;0.201]	0.43
	Gray matter	0.029	0.057	−0.057	[−.312;0.197]	0.66	0.075	[−.156;0.306]	0.53
	Hippocampal volume	0.40	0.53						
Sensory organs	BPF	0.75	0.86						
	White matter	0.86	0.86						
	Gray matter	0.80	0.86						
	Hippocampal volume	0.127	0.51						
Perceived health (EQ-5D/10)	BPF	0.51	0.73						
	White matter	0.55	0.73						
	Gray matter	0.34	0.73						
	Hippocampal volume	0.92	0.92						

(Continues)

TABLE 3 (Continued)

		Interaction between MRI biomarkers and cognitive status (iSCC or MCI)		iSCC			MCI		
		P[b]	*P* (FDR)[b]	Beta	[95% IC]	*P*	Beta	[95% IC]	P
Discomfort in daily life	BPF	0.85	0.86						
	White matter	0.55	0.86						
	Gray matter	0.86	0.86						
	Hippocampal volume	0.74	0.86						

Note: MEMENTO cohort.
Abbreviations: BPF, Brain Parenchymal Fraction; FDR, false discovery rate; iSCC, isolated subjective cognitive complaint; MCI, mild cognitive impairment; MRI, magnetic resonance imaging.
[a]Adjusted for sex, age, education level, depression score, total intracranial volume (except for BPF), and type of MRI scanners.
[b]*P* value before and after adjustment for multiple testing using the FDR method.

sulcus was also wider when the attention complaint score was higher ($P = .041$).

When the cognitive status was taken into account in the models, the following associations were highlighted in participants with iSCCs (Figures 3 and 4 and supplementary file S4). Local reduced gray-matter volume in the caudal middle frontal gyrus was associated with a higher life stress score ($P = .043$). Reduced gray-matter volume in the lateral occipital gyrus ($P = .0007$) and in the parahippocampal gyrus ($P = .0023$) was associated with a lower perceived health score. Reduced gray-matter volume in the temporal pole was associated with a higher discomfort in daily life score ($P = .023$). Smaller cortical thickness in the medial orbitofrontal cortex was associated with a higher attention complaint score ($P = .012$). Smaller cortical thickness in the temporal pole was associated with a lower memory complaint score ($P = .016$). Smaller cortical thickness in several regions of the brain, that is, central, frontal, occipital, and parietal lobes, and the cingulate, except for those of the temporal lobe, was associated with a lower mood complaint score. Smaller cortical thickness in several regions, that is, the cingulate, in the frontal lobe, as well as in the transverse temporal gyrus in the temporal lobe was associated with a lower life stress score. Smaller cortical thickness in the cuneus and the parahippocampal gyrus was associated with a lower perceived health score ($P = .0036$ and $P = .011$, respectively). Lower cortical thickness in the entorhinal cortex and in the temporal pole was associated with a higher discomfort in daily life score ($P = .0002$ and $P = .004$, respectively). Several associations were also found between the biomarkers of GI and sulcal span and complaint scores in participants with iSCCs. In particular, a smaller GI in the superior frontal gyrus was associated with a higher attention complaint score ($P = .023$). A smaller GI in the middle temporal and superior temporal gyrus was associated with a higher memory complaint score ($P = .019$ and $P = .012$, respectively), and a smaller GI in the caudal anterior cingulate gyrus was associated with a higher discomfort in daily life score ($P = .028$).

In the participants with MCI, the following associations were observed (Figures 3-4 and supplementary file S4). A smaller gray-matter volume in the entorhinal cortex was associated with a lower language complaint score ($P = .012$). A smaller gray-matter volume in several areas—that is, postcentral gyrus ($P = .019$), posterior cingulate ($P = .029$), lateral orbitofrontal ($P = .021$), occipital lingual ($P = .007$), inferior parietal ($P = .014$), three regions of the temporal lobe: middle temporal ($P = .016$), parahippocampal ($P = .0059$), and superior temporal ($P = .018$)—was associated with a lower life stress score. A smaller cortical thickness in the insula was associated with a higher general state of health score ($P = .01$). A smaller cortical thickness in the transverse temporal gyrus was associated with a lower life stress score, and a smaller cortical thickness in the entorhinal cortex was associated with a higher discomfort in daily life score ($P = .05$).

The analyses of differential associations by hemisphere are presented in the supplementary file S5. There was no evidence of major differences.

4 | DISCUSSION

In this study, conducted in a large multicenter cohort of dementia-free outpatients attending a French memory clinic, we assessed the associations between intensity of subjective complaints beyond cognition and brain biomarkers. We observed that reduced hippocampal volume was associated with higher subjective memory and discomfort in daily life complaint scores, after adjusting for potential confounders. Reduced white matter volume was associated with lower general health complaint score. These associations were not modulated by the cognitive status (iSCC or MCI), meaning that the associations were in the same direction in the participants whatever their cognitive status. The presence of *APOE* ε4 allele modulated the association between white matter volume and subjective memory complaint, and smaller white matter volume was associated with higher subjective memory complaint score in *APOE* ε4 carriers only. The analysis of brain biomarkers by ROIs showed that reduced whole-brain white matter volume, reduced gray matter volumes, and smaller GIs in several ROIs of the parietal and temporal lobes as well as in the entorhinal and parahippocampal gyrus were associated with higher subjective memory complaint score

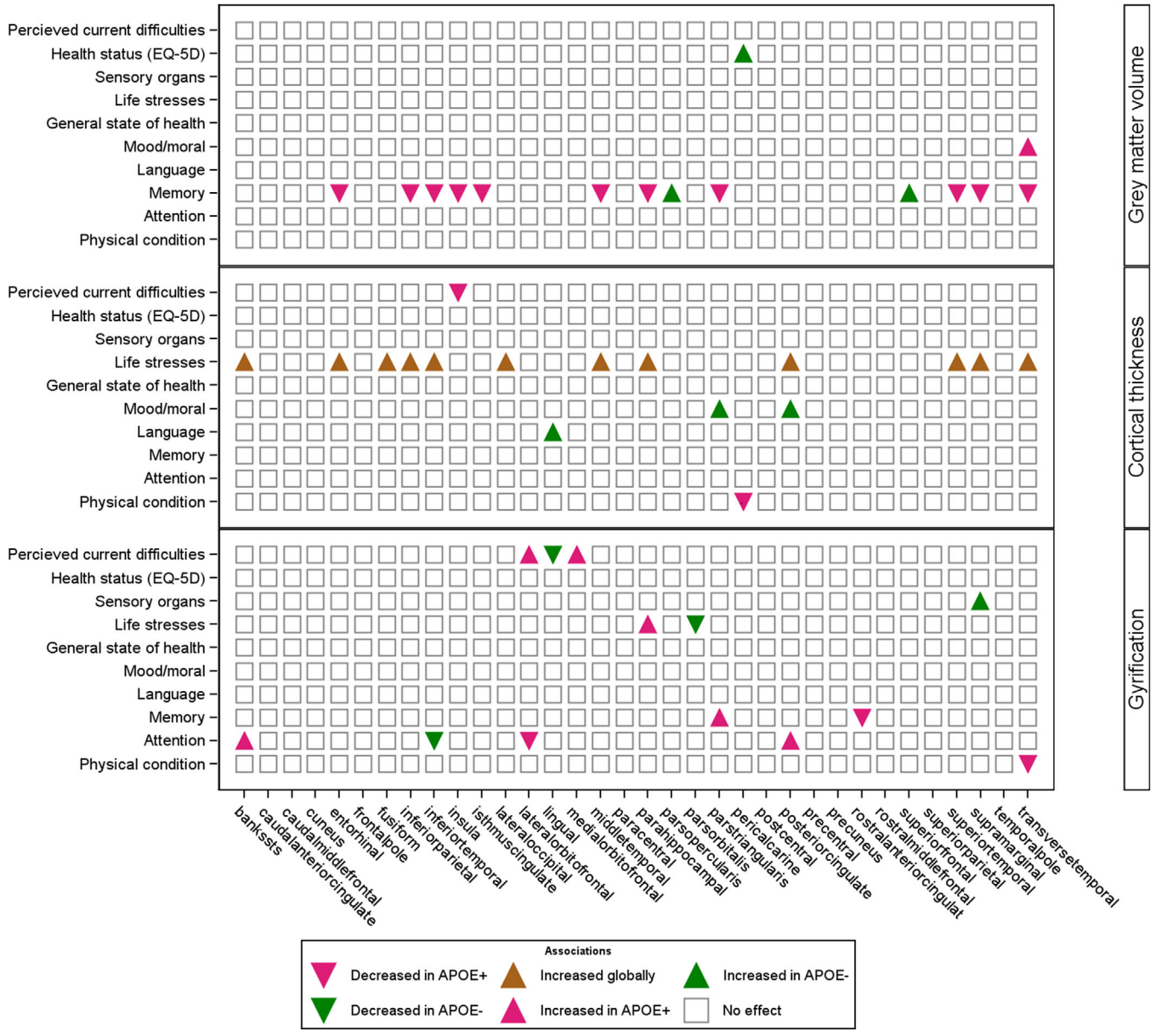


FIGURE 1 Associations between magnetic resonance imaging (MRI) biomarker gray matter volume, cortical thickness, and gyrification index (GI) by regions of interest (ROIs) and the different subjective complaint domains (interaction with *APOE* ε4 status). Figure 1 shows the impact of MRI biomarkers (for +1 SD) on the level of cognitive complaint. A white square indicates no association, whereas an up-triangle indicates an increased and a down-triangle a decreased level of complaint. An interaction with the *APOE* ε4 status was systematically explored, and for a $P < .05$, the figure shows whether the level of complaint was higher/lower in the APOE ε4 carriers (APOE+ in pink) or the non-carriers (APOE− in green). For a non-significant interaction, associations were presented globally (in brown)

in *APOE* ε4 carriers, suggesting a modulating role of *APOE* ε4 allele presence. Our findings regarding regional brain degeneration features associated with higher subjective memory complaint score, specifically hippocampal atrophy, reduced gray matter volume, and reduced cortical thickness in several brain ROIs, confirm and extend the findings of previous studies, which showed brain atrophy in similar regions commonly affected in early AD among individuals with subjective memory complaints.[7,9,10,12,13,33] In addition, these results support and add to the findings of previous studies showing brain alterations in *APOE* ε4 carriers in different contexts and in smaller samples, including the study of Striepens et al., which showed smaller left hippocampal volume in *APOE* ε4 carriers in individuals identified with subjective memory impairment (n = 68), and the study of Lee et al., which showed reduced gray-matter volume in individuals with subjective memory complaints without white matter hyperintensities (n = 26).[19,34-36] The negative effect of the presence of *APOE* ε4 in the brain structure when the level of subjective memory complaint is higher supports that subjective memory complaint may be a feature of preclinical stage of AD.

We also found that smaller hippocampal volume and brain atrophy in some others ROIs commonly affected at the early stage of AD were

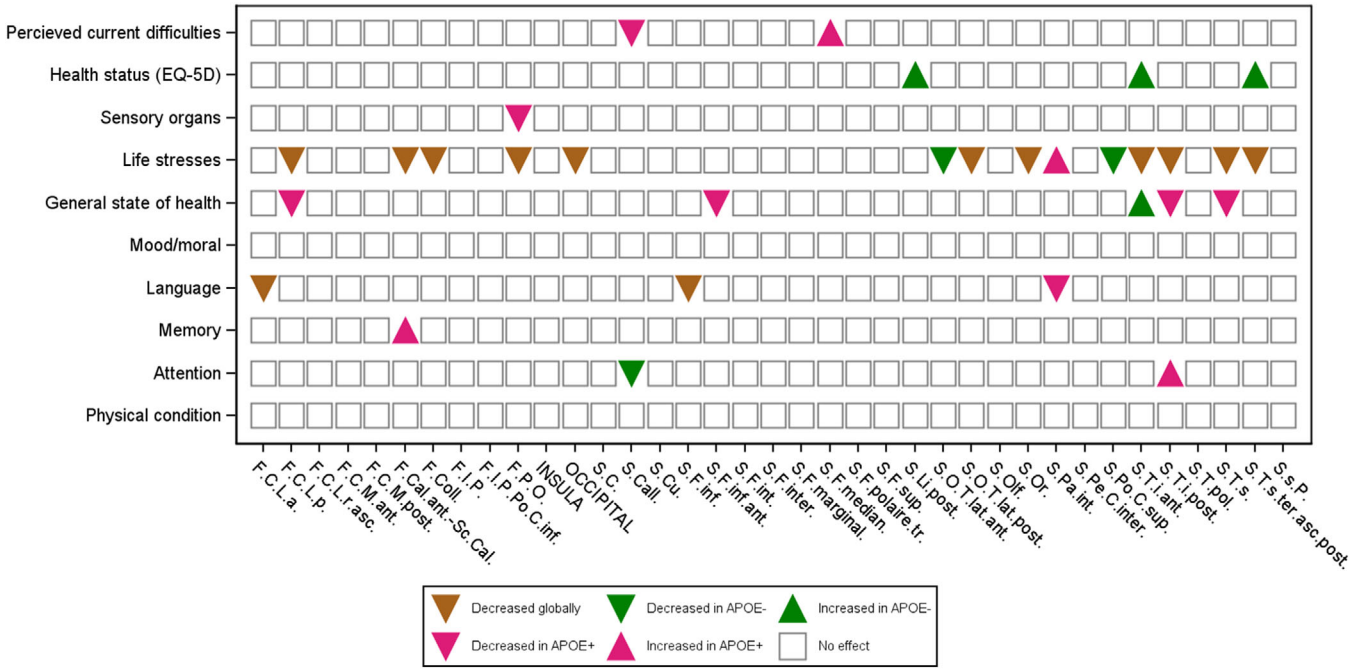


FIGURE 2 Associations between magnetic resonance imaging (MRI) biomarker sulcus spans by regions of interest (ROIs) and different subjective complaint domains (interaction with ApoE-ε4 status). Figure 2 shows the impact of MRI biomarkers sulcus span (for +1 SD) on the level of cognitive complaint. A white square indicates no association, whereas an up-triangle indicates an increased and a down-triangle a decreased level of complaint. An interaction with *APOE* ε4 status was systematically explored, and for a $P < .05$, the figure shows whether the level of complaint was higher/lower in the *APOE* ε4 carriers (APOE+ in pink) or the non-carriers (APOE− in green). For a non-significant interaction, associations were presented globally (in brown)

associated with lower life stress complaint score. This finding may seem counterintuitive because perceived stress has been shown to be associated with smaller hippocampal volume.[37] Nevertheless in the study of Zimmerman et al., the stress was measured differently than in our study (the Perceived Stress Scale including 10 questions to measure the stress during the last month vs VAS with one question to measure the intensity of current life stresses), and the characteristics of the participants were different (community-based sample vs participants attending a memory clinic). A possible explanation of our finding may be that the assessment of the level of life stress complaints may rather reflect a short-term acute situation or stress-including situations such as illness, concern of someone close to the patient, moving, or retirement, in which there is an adaptive or even protective response.[38] Of interest, this finding can be put in parallel with the result showing brain alteration in roughly the same ROIs associated with higher subjective memory complaint score.

Another finding of our study is that the cognitive status does not modulate substantially the associations between whole-brain biomarkers and complaint scores. The only significant associations were found in participants with MCI, for which smaller hippocampal volume was associated with lower language complaint score, and lower BPF was associated with lower general heath complaint score. Although this result does not appear to be in line with expected cognitive alterations in MCI, it is the intensity of the subjective complaint in language and in general health that is assessed in our study, and subjective complaint reported by participants with MCI may have less signification. Indeed, brain alterations can be already present in MCI, and individuals with MCI can have less self-awareness of their troubles, that is, anosognosia.[39] Gifford et al. showed that subjective cognitive complaint reported by individuals with MCI did not predict conversion to dementia.[18]

In the analysis by ROIs, several associations were found different between participants with iSCC or MCI, meaning that the cognitive status may more modulate the associations between brain biomarkers and subjective complaint scores when the brain is studied by ROIs. Among the most notable findings, we found significant associations between lower gray-matter volumes in nine ROIs and lower stress life complaint score in participants with MCI, whereas lower gray-matter volumes in three ROIs were associated with higher stress life complaint score in individuals with iSCC. Smaller gray-matter volume in the entorhinal cortex was associated with lower subjective language complaint score in individuals with MCI. Lower cortical thickness in seven ROIs was associated with higher subjective complaint score in sensory organs in individuals with iSCCs. Taken together, these results add to our findings with the whole-brain biomarkers and suggest that the subjective complaint scores in life stress and sensory organs are more likely to be associated with brain alterations in individuals with iSCCs, whereas the subjective complaint scores in life stress and language collected in individuals with MCI do not allow detection of brain alterations. The meaning of the subjective cognitive complaint in MCI has been questioned previously, as individuals with MCI have been found to underestimate their cognitive difficulties compared to their informant, and they may

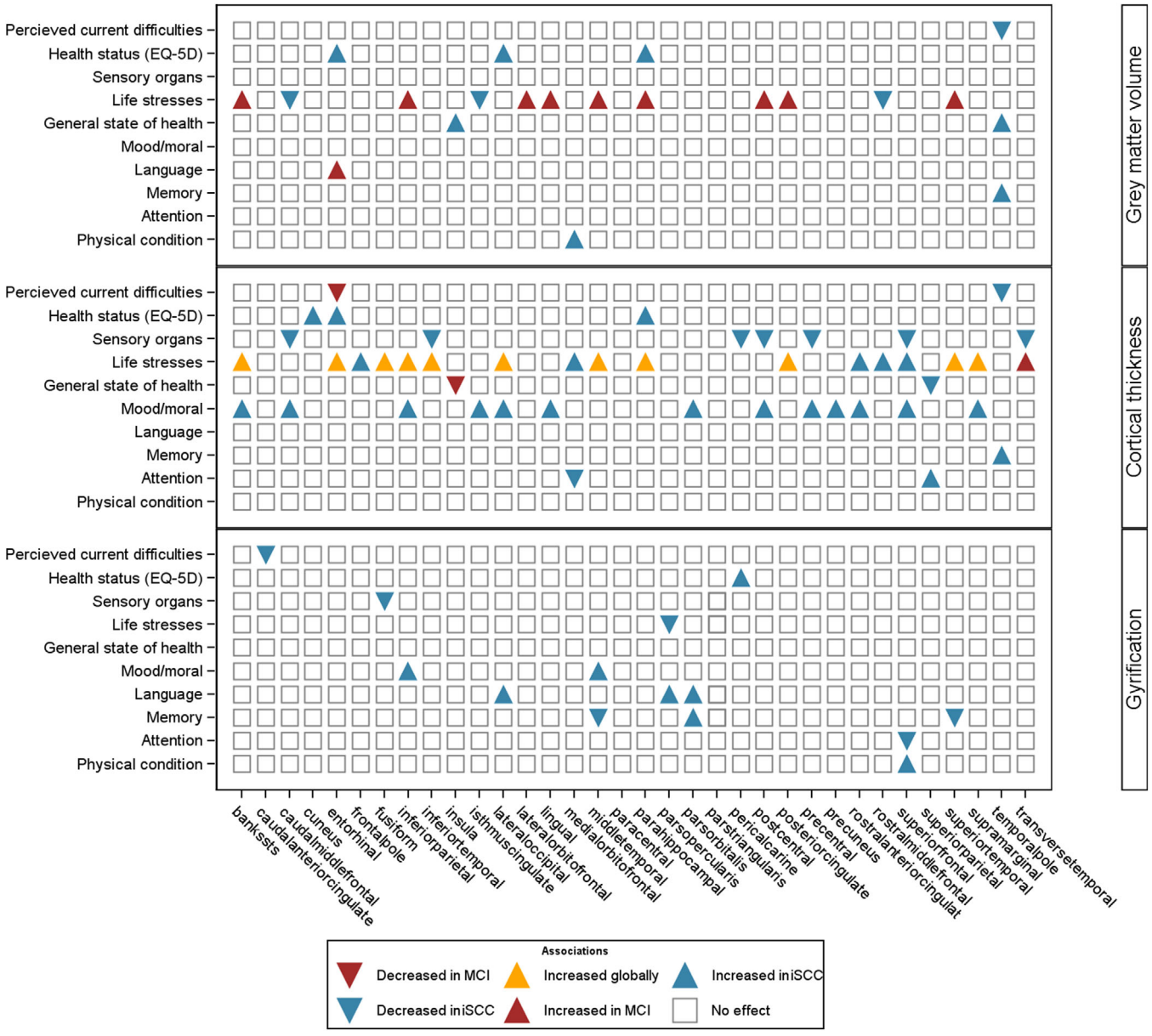


FIGURE 3 Associations between magnetic resonance imaging (MRI) biomarker gray matter volume, cortical thickness, and gyrification index (GI) by regions of interest (ROIs) and the different subjective complaint domains (interaction with isolated subjective cognitive complaint [iSCC] or mild cognitive impairment [MCI] status). Figure 3 shows the impact of MRI biomarkers (for +1 SD) on the level of cognitive complaint. A white square indicates no association, whereas an up-triangle indicates an increased and a down-triangle a decreased level of complaint. An interaction with the iSCCs or MCI was systematically explored, and for a $P < .05$, the figure shows whether the level of complaint was higher/lower in MCI (in red) or in iSCC (in blue). For a non-significant interaction, associations were presented globally (in yellow)

be less aware of impairment and have already brain alterations that interfere with the subjective complaints report.[18,40] In the study of Edmonds et al., there was also an inverse association between CFS biomarkers and subjective cognitive complaints in individuals with MCI compared to individuals who were cognitively normal. Nevertheless, the lack of sensibility of the subjective complaint in MCI to detect brain alterations cannot be generalized in all domains of complaints, as in our study, the cognitive status did not modulate the association between subjective memory complaint and discomfort in daily life scores and brain biomarkers.

The strengths of the current study include the consecutive recruitment of participants (non-convenient sampling) that reduces selection bias, the large spectrum of subjective complaints assessed, and the large panel of brain MRI biomarkers available. Although previous studies have often restricted their analyses to whole-brain and gray-matter volume or pre-specified ROIs recognized to be altered in AD patients (eg, medial temporal structures), the current study takes an original approach with the exploration of the possible significance of subjective cognitive and non-cognitive complaints by addressing the question with whole-brain biomarkers, supplemented by an analysis of brain

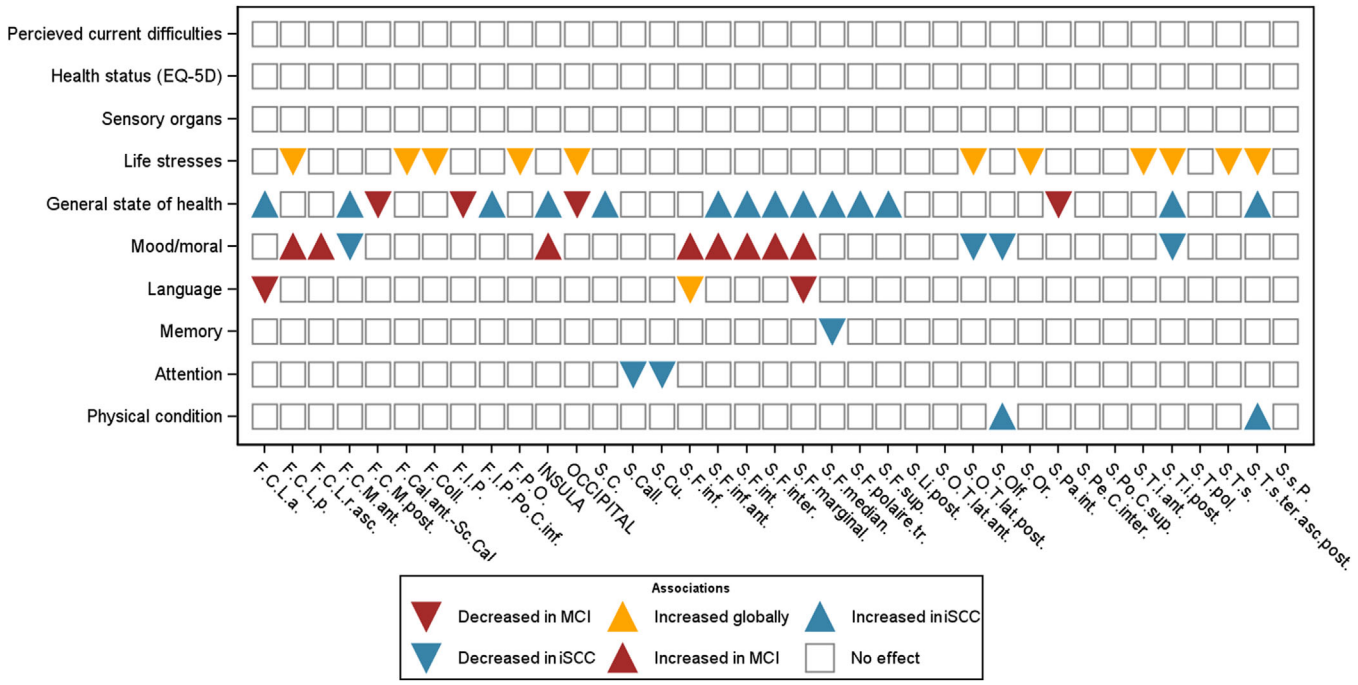


FIGURE 4 Associations between magnetic resonance imaging (MRI) biomarker sulcus spans by regions of interest (ROIs) and different subjective complaint domains (interaction with isolated subjective cognitive complaint (iSCC) or mild cognitive impairment [MCI] status). Figure 4 shows the impact of MRI biomarker sulcus span (for +1 SD) on the level of cognitive complaint. A white square indicates no association, whereas an up-triangle indicates an increased and a down-triangle a decreased level of complaint. An interaction with the iSCC or MCI status was systematically explored, and for a $P < .05$, the figure shows whether the level of complaint was higher/lower in MCI (in red) or in iSCC (in blue). For a non-significant interaction, associations were presented globally (in yellow)

structure by 34 ROIs and over 100 sulci. Cortical thickness, GI, and sulcus spans were also analyzed, as they may help identify specific areas. In addition, the subjective complaints were assessed more comprehensively to broaden the exploration of complaints as they relate to brain MRI biomarkers. In addition, we considered the subjective complaints as a continuous phenomenon, whereas previous studies have often considered them as dichotomous. Although categorization of participants with or without subjective cognitive complaints appears important in clinical practice to identify at-risk patients for whom specific intervention and support may be provided, the dichotomization may also represent a limitation. Furthermore, measuring the intensity of the complaints provides an opportunity to assess the presence of a continuum between these complaints, brain alterations, and memory impairment. We chose to use the level of complaint not to its natural scale (ie, 0 to 10) but with an intra-individual rescaling with standardized score. Because the different complaint domains are not independent, we assume that considering a specific domain taking into account the overall complaint level is a relevant approach and emphasize the analysis on what the patient reported to be the most disturbing for him/herself. The clinical interpretation of the results is not easy to appreciate (as is it the case for numerous statistical approach), but the significance and the direction of the effects are valuable information to better understand the relationship between subjective complaint and brain structures.

The main limitation of the study is its cross-sectional design, which has hampered our ability to assess the temporal relationship between complaints and brain alterations. Moreover, the manner in which participants were recruited (from memory clinics) should also be considered in the interpretation of these findings. Indeed, a previous study has shown that the risk of progression to MCI or dementia could be higher in memory clinics than in the general population.[41] This implies that study participants may present more brain alterations than in the general population. However, the hypothesis could not be verified and we do not have any reason to suspect that cohort's design could have an impact on the direction of the relationships that were investigated in this analysis. The questionnaire to assess the subjective complaints has not yet been validated, except the perceived health status; nevertheless the intensity of the complaints was measured using VAS, which is widely used in clinical practice and research to measure subjective symptoms.

5 | CONCLUSION

Subjective complaints not limited to memory but also related to discomfort in daily life were associated with markers of brain degeneration, independent of the cognitive status. The presence of *APOE* ε4 modulated the relationships between subjective memory complaints and brain alterations. The follow-up of the MEMENTO cohort will allow us to study whether higher initial complaint scores are predictive of progression to advanced stage of neurocognitive disorders due to AD. Future research investigating the link between subjective complaints

and risk of AD should be expanded to include subjective complaints in non-cognitive domains such as discomfort in daily life.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

FINANCIAL DISCLOSURE

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SUPPORTING INFORMATION

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

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