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Neural correlates of episodic memory in the Memento cohort

Stephane Epelbaum\textsuperscript{a,b,*},1, Vincent Bouteloup\textsuperscript{c,d,1}, Jean F. Mangin\textsuperscript{e,f}, Valentina La Corte\textsuperscript{g,h}, Raffaela Migliaccio\textsuperscript{a,b}, Hugo Bertin\textsuperscript{e,i,j}, Marie O. Habert\textsuperscript{e,i,j}, Clara Fischer\textsuperscript{e,f}, Chabha Azouani\textsuperscript{e}, Ludovic Fillon\textsuperscript{e}, Marie Chupin\textsuperscript{e}, Bruno Vellas\textsuperscript{k,l}, Florence Pasquier\textsuperscript{m}, Jean F. Dartigues\textsuperscript{e,n}, Fréderic Blanc\textsuperscript{c}, Audrey Gabelle\textsuperscript{b,q}, Mathieu Ceccaldi\textsuperscript{t,s}, Pierre Krolak-Salmon\textsuperscript{a}, Olivier Hanon\textsuperscript{v}, Olivier Rouaud\textsuperscript{w}, Renaud David\textsuperscript{x}, Genevieve Chène\textsuperscript{c,d}, Bruno Dubois\textsuperscript{a,b}, Carole Dufouil\textsuperscript{c,d}, for the Memento Study group**

\textsuperscript{a}Institut de la mémoire et de la maladie d’Alzheimer, Département de neurologie, Hôpital de la Pitié-Salpêtrière, Paris, France
\textsuperscript{b}Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, and Inserm, U 1127, and CNRS UMR 7225, and ICM, Paris, France
\textsuperscript{c}Inserm, Bordeaux Population Health Research Center, UMR 1219, University Bordeaux, ISPED, CIC 1401-EC, Univ Bordeaux, Bordeaux, France
\textsuperscript{d}CHU de Bordeaux, Pole Santé Publique, Bordeaux, France
\textsuperscript{e}CATI Multicenter Neuroimaging platform, http://cati-neuroimaging.com, Gif sur Yvette, France
\textsuperscript{f}Neurospin, DRE, CEA, Paris Saclay University, Gif sur Yvette, France
\textsuperscript{g}Institut de psychologie, Université Paris Descartes, Sorbonne Paris Cité, Paris, France
\textsuperscript{h}Sorbonne Universités, UPMC Univ Paris 06, CNRS, INSERM, Laboratoire d’Imagerie Biomédicale, Paris, France
\textsuperscript{i}Département de Médecine Nucléaire, Hôpital de la Pitié-Salpêtrière, AP-HP, Paris, France
\textsuperscript{j}Gérontopôle, Centre Hospitalier Universitaire de Toulouse, Toulouse, France
\textsuperscript{k}Inserm UMR1027, Université de Toulouse III Paul Sabatier, Toulouse, France
\textsuperscript{l}Univ Lille, Inserm 1171, CHU, Centre Mémoire (CMRR) Distalz, Lille, France
\textsuperscript{m}CHU de Bordeaux, CMRR, Pôle Neurosciences, Bordeaux, France
\textsuperscript{n}Centre Mémoire (CMRR), Hôpital Universitaire de Strasbourg, Département de Gériatrie, Hôpital de Jour Gériatrique, Strasbourg, France
\textsuperscript{o}Department of Neurology and Memory Research and Resources Center, Gui de Chauliac University Hospital, Montpellier, France
\textsuperscript{p}CHRU de Montpellier, Université de Montpellier, Institute of Regenerative Medicine and Bio-therapy (IRMB), INSERM U1183, CCBHM, Laboratoire de Biologie Protéomique Clinique, Montpellier, France
\textsuperscript{q}Université Aix-Marseille, INSERM, Institut des Neurosciences des Systemes (INS) UMR 1106, Marseille, France
\textsuperscript{r}APHM, Hôpitaux de la Timone, Service de Neurologie et de Neuropsychiatrie, Marseille, France
\textsuperscript{s}Clinical and Research Memory Center of Lyon, Hôpital des Charpennes, Hospices Civils de Lyon, Lyon, France
\textsuperscript{t}Centre Mémoire (CMRR) Paris Nord Ile de France, Groupe Hospitalier Lariboisiere FW Saint-Louis, APHP, Université Paris Diderot, Paris, France
\textsuperscript{u}Service de Gériatrie, Université Paris Descartes, Hôpital Broca, Paris, France
\textsuperscript{v}Département de Neurologie, Hôpital universitaire et faculté de médecine, Dijon, France
\textsuperscript{w}Centre Mémoire de Ressources et de Recherche, CHU de Nice, EA COBITok, Université Côte d’Azur, Nice, France

\textsuperscript{1}Both authors contributed equally to the article.
\textsuperscript{**}The Memento Study group is described in the online Supplementary data section.

\textsuperscript{*}Corresponding author. Tel.: +33142167525; Fax: +33142167504.
E-mail address: stephane.epelbaum@aphp.fr

Abstract

Introduction: The free and cued selective reminding test is used to identify memory deficits in mild cognitive impairment and demented patients. It allows assessing three processes: encoding, storage, and recollection of verbal episodic memory.

Methods: We investigated the neural correlates of these three memory processes in a large cohort study. The Memento cohort enrolled 2323 outpatients presenting either with subjective cognitive decline or mild cognitive impairment who underwent cognitive, structural MRI and, for a subset, fluorodeoxyglucose–positron emission tomography evaluations.

Results: Encoding was associated with a network including parietal and temporal cortices; storage was mainly associated with entorhinal and parahippocampal regions, bilaterally; retrieval was associated with a widespread network encompassing frontal regions.
1. Introduction

Episodic memory refers to memory for personal experience with respect to time and context [1]. The three principal processes involved in episodic memory are encoding, storage, and retrieval of information. It can be impaired in various diseases, for example, depression [2], Parkinson disease [3], frontotemporal dementia [4], Alzheimer’s disease (AD) is the most frequent disorder characterized by memory impairment [5]. Indeed, impairments in episodic memory performance are considered as the first clinical sign of typical AD and have been associated with atrophy of the entorhinal cortex and hippocampus [6–8].

A few longitudinal studies of cognition in healthy older adults have shown that a subtle decline in episodic memory often occurs before the emergence of the functional and overt cognitive changes required for a clinical diagnosis of AD dementia [9–14]. These findings led to the amnestic mild cognitive impairment (MCI) [15] concept, a predementia condition in elderly individuals, which is characterized by subjective and objective memory impairments with relatively preserved general cognition and functional abilities. Before this MCI stage of AD, subjective cognitive decline (SCD) can be a symptom of preclinical AD [16,17].

The Free and Cued Selective Reminding Test (FCSRT) has been proposed as a verbal associative episodic memory test [18]. It aims at exploring the three memory processes in a single neuropsychological test and is used in clinical practice of some memory clinics for AD diagnosis [11,19]. Its subscores allow the assessment of serial cognitive processes involved in episodic memory: immediate recall (IR) for encoding, index of sensitivity to cueing (ISC) for storage, and total free recall (FR) for retrieval of memorized stimuli. Previous studies have shown that FCSRT is useful for prognosing MCI patients who will decline to dementia stage of AD [11,20–22] and for diagnosing typical amnestic AD patients among various neurodegenerative conditions [19]. When storage is impaired (i.e., low FR score and low total recall or ISC scores), an amnestic syndrome [23] termed “of the hippocampal (or medial temporal) type” has been defined. However, only a few imaging studies, mainly in a small number of demented patients, have shown a correlation between hippocampal volumes and FCSRT performances [24,25]. In addition, little is known on the link between FCSRT performances and other brain regions known to be implicated in episodic memory such as the working memory network [26] or prefrontal areas [27]. There is a large number of studies that tackled the question of the neural correlates of episodic memory (for a recent review see [28]). However, the experimental paradigms frequently differ from one study to the next, which induced some discrepancies, concerning for instance the laterality of the medial temporal lobe involvement found to be mainly left sided in some studies [29–31] right sided in other [32,33] and sometimes bilateral [34,35].

In this study, we investigated structural and metabolic correlates of the three episodic memory processes assessed by the FCSRT in a large French cohort of participants with standardized cognitive assessment as well as structural and metabolic imaging. Within this framework, we hypothesize that encoding and storage phases would be related to hippocampal and parietal regions, and recollection phase would be related to a widespread brain network, including more anterior brain regions. Our large sample size and standardization allow us to draw unequivocal conclusions from our results, shedding some light on previously described discrepancies [36].

2. Material and methods

2.1. Participants

Memento study consecutively enrolled 2323 nondemented outpatients in 28 French expert memory clinics, from 2011 to 2014. The study procedures and participants’ baseline characteristics are described elsewhere [37]. At inclusion, participants presented either with cognitive impairment, when performing worse than one standard deviation to the mean of a group (with similar age, age/educational norms) in one or more cognitive domains, this deviation being identified for the first time through cognitive tests performed recently (less than 6 months preceding screening phase), or with isolated cognitive complaints, if participants had subjective cognitive complaint (assessed through visual analogic scale), without any objective cognitive deficit as defined previously, while being 60 years and older, and they all had a Clinical Dementia Rating scale [38] score ≤0.5. Main exclusion criteria were contraindication or refusal to perform magnetic resonance imaging (MRI), neurological disease such as treated epilepsy, treated Parkinson’s disease, Huntington disease, or brain tumor, history of head trauma with neurological sequelae, stroke occurring in the past three months, history of schizophrenia, or illiteracy.
All examinations (including neuropsychological battery administration, clinical examinations, brain MRI, and fluorodeoxyglucose [FDG] positron emission tomography [PET]) performed through Memento followed standardized procedures.

The analytic sample consists in participants who underwent a brain MRI and a neuropsychological evaluation, including the FCSRT at their inclusion in the cohort (N = 2157). A subsample that additionally performed the optional FDG-PET was considered in a subsequent analysis (N = 1310).

All participants signed an informed consent to participate in the study that was approved by the ethics committee “Comité de Protection des Personnes Sud-Ouest et Outre Mer III.” The study was conducted following standards of the Good Clinical Practice and the Helsinki Declaration. Although not a clinical trial, the protocol was registered in ClinicalTrials.gov (Identifier: NCT01926249, https://clinicaltrials.gov/ct2/show/NCT01926249).

2.2. Neuropsychological evaluation

A full neuropsychological test battery was administered to participants at baseline [37] including the FCSRT [39] to study the verbal episodic memory. In this associative memory test, the subject has to learn 16 words by groups of four with each corresponding cue provided verbally by the tester (e.g., “fish” is the cue for the word “herring”). In a first step, the subject is asked to recall words just after reading them, four by four (namely IR, scored from 0 to 16). Then, three recall (firstly free and then cued) trials separated from each other by a distractive task (mental calculation during 20 seconds) are successively performed. The FR score ranges from 0 to 16 × 3 = 48. The ISC is computed as 100 * (sum of the three cued recall/[48-FR]). The list of the 16 words and the detailed procedure of execution are available elsewhere [40].

The neuropsychological test battery also included the Rey figure copy [41] that assesses visuospatial and visuoconstructive abilities and was used as a control of the specificity of the morpho-metabolic correlates of the FCSRT subscores.

Using performances at the full neuropsychological tests battery, Petersen criteria [42] were applied to categorize participants’ cognitive status as non-MCI (SCD), pure amnestic MCI, multidomain amnestic MCI, pure nonamnestic MCI, multidomain nonamnestic MCI.

2.3. MRI evaluation

Brain magnetic resonance images were acquired after a standardization of the imaging processes (notably the sequences used) by a dedicated neuroimaging specialist team (CATI for “Centre pour l’Acquisition et le Traitement des Images”, http://cati-neuroimaging.com/). MRI machines of 1.5 and 3 Tesla were used for this study (the complete list of machines is provided in Supplementary Appendix A).

All MRI scans were centralized, quality checked, and postprocessed by the CATI to obtain standardized measurements for each participant. The MRI protocol included 3D-T1 1 mm isometric sequences that were used to assess the whole-brain, gray matter, and white matter volumes with Statistical Parametric Mapping [43], hippocampal volumes with the SACHA software [44,45] and cortical thickness with FreeSurfer in Desikan-Killiany atlas [46,47].

2.4. FDG-PET evaluation

As for MRI, the CATI allowed for intercenter reproducibility through harmonization of FDG-PET protocols and postprocessing [48]. Structural MRI images were coregistered to PET images using Statistical Parametric Mapping 8 with visual inspection to detect any coregistration errors. MRI 3D T1-weighted images were segmented and spatially normalized into the Montreal Neurological Institute space using the VBM8 package (http://dbm.neuro.uni-jena.de/vbm/) implemented in Statistical Parametric Mapping 8. MRI matrix transformation was then used to spatially normalize PET images into Montreal Neurological Institute space. Parametric PET images were created for each individual, by dividing each voxel with the mean activity extracted from the reference region, the pons. Finally, gray matter masks extracted from each individual MRI volume were applied to the parametric PET images before Regions Of Interest (ROIs) analysis. Metabolic FDG-PET indexes were calculated in ROIs from the Automated Anatomical Labeling 2 (AAL2) atlas [49] to the exception of the cerebellum.

2.5. APOE genotyping

Apolipoprotein E (APOE) ε2, ε3, or ε4 alleles were determined for all participants by KBiosciences (Hoddesdon, UK; www.kbioscience.co.uk) as described elsewhere [37].

2.6. Statistical methods

Sample characteristics are reported as median (q1; q3) or frequency, as appropriate. Between-group comparisons were performed through the χ² test for discrete variables or analysis of variance tests for continuous variables. Multivariable analyses were undertaken on three outcomes (IR, FR, and ISC scores at inclusion). As more than half of the population scored 16 (maximum score) in the IR subscore, it was dichotomized as equal to 16 versus <16, and logistic regressions were computed for analyses. To account for skewed distributions of FR and ISC subscores, their anatomical and metabolic correlates were modeled through median regression. For each outcome, models were built using brain structure as the “exposure” of interest and gender, age, education, number of ε4 alleles of APOE genotype, and type of MRI/PET as adjustment covariates. Due to multiple comparisons in 34 cortical thicknesses (FreeSurfer) MRI ROIs and in the 47 (AAL2) FDG-PET ROIs, a false discovery rate (FDR) was maintained at 0.05 or less by recomputing P-values.
A $P$-value $\leq .05$ was considered statistically significant. The effect sizes (estimate) of the significant association were then presented graphically on an inflated brain mesh.

Finally, we analyzed jointly the association between the imaging measurements and the three FCSRT subscores, assuming that all three are markers of the episodic memory. As the episodic memory in itself is unmeasured, we used a latent class analysis approach [51]. This method allows linking multiple outcomes of different nature (i.e., binary, ordinal, discrete and continuous) generated by the same underlying latent process and flexible enough to deal with nonlinear associations. We thus can estimate whether imaging measurements are associated with the latent process and, using contrasts, test whether the contribution of the subscores can be considered statistically equivalent or different [52].

Analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC) and R (LCMM package v1.7.8) for latent class analysis.

Finally, to determine whether $APOE\varepsilon4$ genotype could modify the relation between cortical thickness and FCSRT performances, we introduced $APOE\varepsilon4$ genotype*cortical thickness interaction term and was tested in the models. Uncorrected and FDR-corrected $P$-values were computed. For uncorrected $P$-values $< .05$, results of stratified analyses (Non–$APOE\varepsilon4$ and $APOE\varepsilon4$ carriers) were presented.

3. Results

Of the 2323 participants, 2157 (age median and [interquartile range]: 71.6, [65.6–77.1] years) were administered the FCSRT and had a brain MRI. Among them, 1310 underwent FDG-PET scan (Fig. 1). Table 1 shows the analytical sample baseline characteristics according to FDG data availability. Participants who had a FDG-PET were more likely women (67% vs. 59%, $P = .0002$), had less frequently a clinical dementia rating score equal to 0.5 (63% vs. 58%, $P = .018$) and had more frequently an SCD or a nonamnestic MCI profile ($P = .045$). The scatter plots of raw FCSRT subscores are provided in Supplementary Appendix B both globally (whole cohort) and by $APOE$ and cognitive (SCD or MCI) status.

### 3.1. MRI measures and FCSRT subscores

Fig. 2 summarizes results of MRI analyses and FCSRT scores correlations. As expected, greater hippocampal volume was associated with increased odds of having high scores at IR: $1.30 (1.15; 1.46)$ (odds ratio [95% confidence interval {CI}], FR and ISC: $5.53 (4.72; 6.35)$ and $3.72 (2.71; 4.73)$, respectively (differences in median [95% CI]), all FDR corrected $P$ values $< .0001$ associations. Distinct patterns of associations were observed for the three subscores: FCSRT-IR and FCSRT-ISC were mainly associated with entorhinal and parahippocampal regions, bilaterally; FCSRT-FR was associated with a widespread network encompassing frontal regions. No differences were found in these associations between hemispheres. Rey figure copy score was not associated with any medio-temporal regional cortical thickness (data not shown).

| Characteristics          | All participants (N = 2157) | FDG-PET participants (n = 1310) | FDG-PET performed yes versus no ($P$-value) |
|--------------------------|-----------------------------|---------------------------------|------------------------------------------|
| Median age in years, (Q1; Q3) | 71.6 (65.6; 77.1)           | 72 (65.8; 77.0)                 | .55                                      |
| Female gender, n (%)     | 1335 (61.9)                 | 770 (58.8)                      | .0002                                    |
| Educational level > 12 years, n (%) | 1172 (54.5)      | 732 (56.0)                      | .070                                     |
| Number of $APOE\varepsilon4$ allele, n (%) | 40 (70.4)  | 890 (70.4)                      | .99                                      |
| CDR score, n (%)         | 537 (26.2)                  | 332 (26.2)                      | .0018                                    |
| Cognitive status, n (%)  | 70 (3.4)                    | 43 (3.4)                        | .045                                     |
| SCD                      | 343 (15.9)                  | 219 (16.7)                      |                                           |
| Pure aMCI                | 196 (9.1)                   | 112 (8.5)                       |                                           |
| Multi-domain aMCI        | 924 (42.8)                  | 533 (40.7)                      |                                           |
| Pure naMCI               | 366 (17.0)                  | 237 (18.1)                      |                                           |
| Multi-domain naMCI       | 328 (15.2)                  | 209 (16.0)                      |                                           |
| Median MMSE score, (Q1; Q3) | 869 (40.3)  | 554 (42.3)                      | .045                                     |
| FCSRT scores, median (Q1; Q3) | 28 (27; 29)  | 28 (27; 29)                     | .97                                       |

Abbreviations: CDR, clinical dementia rating; MMSE, Mini Mental State Evaluation; FCSRT, Free and Cued Selective Reminding Test; IR, immediate recall; FR, free recall; ISC, index of sensitivity to cueing; SCD, subjective cognitive decline; aMCI, amnestic mild cognitive impairment; naMCI, nonamnestic mild cognitive impairment; FDG-PET, fluorodeoxyglucose-positron emission tomography.

NOTE. Between-group comparisons were performed through $\chi^2$ test for discrete variables or analysis of variance tests for continuous variables.
In the latent class analyses (results provided in Supplementary Appendix C), IR was the subscore most strongly associated with cortical thicknesses in the superior temporal, precentral, lingual, precuneus, and lateral-occipital regions. By contrast, the ISC was not associated with these structural variations, except for cortical thickness in the superior temporal cortex (coefficient $\beta = 0.10$ [95% CI 0.02; 0.17]) as compared to IR (coefficient $\beta = 0.21$ [95% CI 0.10; 0.31]) and FR (coefficient $\beta = 0.19$ [95% CI 0.13; 0.26]).

APOE $\varepsilon 4$ carriers had significantly different associations between FCSRT subscores and regional cortical thicknesses as described in Supplementary Appendices D and E. Most strikingly, the difference in median of the FR associated to the entorhinal cortex thickness was twice as important in APOE $\varepsilon 4$ carriers than in noncarriers. However, none of these differences was significant after FDR correction.

### 3.2. FDG-PET correlates of FCSRT subscores

As there was no difference between the left and right hemisphere associations to FCSRT subscores, symmetrical regions were joined as metaregions of interest to study the associations to each FCSRT subscores in 47 regions (i.e., 94/2 from the AAL2 atlas, excluding the cerebellum).

The regions where the brain metabolism was significantly linked to IR and ISC scores were limited to the posterior cingulate gyri, parietotemporal junction, and medial temporal lobes albeit in a more widespread fashion for ISC than for IR (Fig. 3). Conversely, FR score was significantly related to metabolic measures in a diffuse network comprising prefrontal (medial, dorsolateral, and orbitofrontal), as well as parietal (lateral and medial) and temporal (lateral and medial) regions.

FR and ISC were significantly associated with precuneus, posterior cingulate cortex, associative parietal cortex, and temporal cortex (both left and right sides), whereas for IR, correlations were significant only in the posterior cingulate and temporal cortices, bilaterally.

The latent class analysis (Supplementary Appendix F) did not indicate singular patterns of regional metabolic association to the three FCSRT subscores. However, we found a global effect on episodic memory as a whole of the metabolic measures in 34/47 of the studied AAL regions (with the exception of the putamen, pallidum, and primary motor and sensitive areas).

Compared to noncarriers, APOE $\varepsilon 4$ carriers had higher associations between FCSRT subscores and metabolism in multiple regions encompassing a large occipito-parietotemporal network for IR and FR and the same network with additional frontal and limbic regions for ISC. In contrast to the same analysis for cortical thicknesses, most of these differences remained significant after the FDR correction and are described in Supplementary Appendices G and H.

### 4. Discussion

We explored the structural (MRI) and metabolic (FDG-PET) correlates of the three main processes of episodic memory, using a cued memory test, the FCSRT, in a large cohort of elderly participants with cognitive profile ranging...
find any similar association between the Rey’s figure copy score, chosen as a nonmemory/nonlanguage cognitive process control, and the imaging markers in temporomedial regions (data not shown).

Current structural and metabolic correlates of memory exhibited some similarities. However, some regions were rather associated to a memory process on MRI (such as temporopolar regions for encoding) or FDG-PET (such as posterior cingulate cortex for storage). This is probably due both to differences in imaging acquisition and processing and to physiopathological discrepancies in MRI versus FDG-PET. The hippocampal paradox in AD (i.e., compensated metabolism that remains normal in atrophied hippocampus) is an example of such discrepancies [56]. The processing of the images relied on the use of validated pipelines and atlases that differed between the two imaging modalities, namely FreeSurfer [46] for the MRI cortical thickness ROIs and AAL2 [49] for FDG-PET ROIs. However, the macroscopic differences evidenced in our study cannot be attributed solely to the use of these different atlases. As FDG-PET was optional and performed only in a subsample, one could argue that this is the cause of the evidenced discrepancies. However, the Appendix analysis on the subsample having both MRI and FDG-PET showed the same results as in the whole group excluding a selection bias (Supplementary Appendices I and J).

A limitation in the delineation of the neural correlates of episodic memory in our study is that the FCSRT is an associative memory test with semantic cueing. Hence, some of the associated structural or metabolic regions are likely to support semantic rather than episodic processes [57]. This memory process is largely independent of attention and executive functions, which are impaired, for example, in pure brain vascular disease, such as in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy [53]. In Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, storage impairment is both rare and occurs at a later course of the disease [54].

Interestingly, the absence of differential associations according to hemispheric side for both hippocampal volumes and medial temporal lobe cortical thicknesses on FCSRT subscores is in line with previous studies [28]. In young healthy subjects, episodic memory rather involves the left hemisphere [55], but in the elderly, it involves both hemispheres. This might reflect a compensatory mechanism necessary to memorize stimuli in aging.

Our results concerning the FCSRT association with brain structures and metabolism are specific. Indeed, we did not from SCD to MCI. We found that the three different processes involved in episodic memory are associated with different brain networks.

4.1. Validity of the FCSRT to study episodic memory

Our findings are in line with the “Attention to memory” model proposed by Cabeza and collaborators [26]. This model stipulates that the parietal cortex is involved in voluntary (top-down) retrieval of information, which is the case in the FCSRT. First, IR (which reflects the registration process) was mostly associated with metabolism in posterior brain areas. These posterior regions are associated with attentional and working memory performances [26]. Second, FR is associated with cortical thickness and metabolism in most of the brain regions and most notably in anterior brain regions. Actually, FR measures the ability to actively recollect information and is linked to executive functions. Finally, the ISC, a subscore representative of storage, is mostly associated with the cortical thickness in temporal regions [28]. This memory process is largely independent of attention and executive functions, which are impaired, for example, in pure brain vascular disease, such as in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy [53]. In Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, storage impairment is both rare and occurs at a later course of the disease [54].

Fig. 3. Regional pattern of association between FCSRT subscores and mean regional FDG uptake values (n = 1310). Abbreviations: FCSRT, free and cued selective reminding test; FDG, fluorodeoxyglucose; ISC, index of sensitivity to cueing; FR, free recall; IR, immediate recall.
cognitive marker of AD than the more specific storage deficit.

When looking at the association between storage and retrieval and the regional cortical thickness, AD physiopathology distribution comes to mind.

In typical AD patients, the disease progression is stereotyped: amyloid β lesions are initially neocortical and will diffuse centripetally, and tau neurofibrillary tangles are first evidenced in the medial temporal regions before spreading in a centrifuge way [61].

The medial temporal regions underlying storage is reminiscent of the early Braak stages that can be demonstrated neuropathologically [62] or more recently by way of tau tracer PET imaging [63]. This medial temporal involvement associated with the storage explains the specificity of the ISC (and of the sum of the total recall) for AD even at an early (prodromal) stage and among multiple neurodegenerative conditions [19]. Conversely, the retrieval process neural substrates encompass both the medial temporal regions (affected early on during AD by the tauopathy as mentioned previously) and the regions in which amyloid deposition begins in AD (medial and dorsal prefrontal, precuneus, anterior and posterior cingulate, parietotemporal junction) [64,65]. This interpretation is in line with recent evidence suggesting that the FR score declines on average 2 years before the total recall score in cognitively healthy elderly individuals but having a positive amyloid PET scan [66].

Two conditions are considered at high risk for AD: the status of MCI and the status of APOE ε4 carrier. In our study, the metabolic correlates of the storage process are the same regions as those found to be hypometabolic both in MCI who rapidly progress to AD [67] and in asymptomatic APOE ε4 carriers [68]. This strongly suggests that FCSRT can be considered as a valuable surrogate marker of neurodegeneration in subjects at risk for AD. The fact that episodic and semantic memory processes are tested in the FCSRT explains why this test is so sensitive to early AD as both episodic and semantic impairment can be observed in this affection [69].

In AD, MRI and FDG-PET are considered valuable prognostic tools [5]. In our analytical sample, APOE ε4 had an impact on the degree of association between FCSRT subscores, metabolism and, to a lesser extent, cortical thickness. The stronger associations observed between structure or metabolism and FCSRT subscores in APOE ε4 carriers in our study is an argument to support the claim that this cognitive test can be considered, in this population of elderly SCD or MCI, as a neuropsychological prognostic marker of AD.

Among the three subscores, FR correlates to cortical thickness and metabolism in the largest cortical network (fronto-parieto-temporal associative cortices). Thus, FR is likely to decrease if any part of its associated neural network is injured. This explains why this subscore is the most sensitive in early AD. By contrast, the ISC, which is associated with cortical thickness and metabolism in the medial temporal areas is probably a more specific but less-sensitive marker. As amyloid PET imaging will be soon available for a sample of several hundred of Memento participants, it will be possible to test the hypothesis of an early cognitive impact of brain amyloidosis on the retrieval process of episodic memory. In summary, our results strengthen Wolk and Dickerson’s claim that multiple measures of memory tests, underlined by different brain structures, are required to address the full spectrum of impairment that can affect AD patients [70]. These authors’ work on the longitudinal follow-up of cognitively normal elderly Alzheimer’s Disease Neuroimaging Initiative participants [71] confirms that cortical thickness is an early sign of AD and not only linked with cross-sectional memory impairment as demonstrated by our study but also with longitudinal cognitive decline.

The relation between FCSRT neural substrates and early-stage AD pathological patterns has direct implication for clinical care and trials. It can explain why some trials in amnestic MCI defined with the FCSRT will show some evidence of efficacy, such as the slowing of hippocampal atrophy and cortical thickness with Donepezil [72,73], whereas other trials in which MCI is not defined with the FCSRT do not, despite being more powered and longer [74,75]. Our study supports the use of the FCSRT as an important neuropsychological enrichment factor for AD in SCD and MCI trials. The FCSRT can also be used as a clinically meaningful endpoint as in the recently published INSIGHT-PreAD study [76] in which the total recall subscore dramatic decrease is used as a proxy to address the “preclinical” to “clinical” stages transition. This approach is aimed at increasing the specificity of early clinical AD detection (at the prodromal stage) to enrich clinical trial inclusions. Other studies, such as a large U.S. prevention trial Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease [77,78] and the French Multidomain Alzheimer Preventive Trial [79] have used the FCSRT as a clinical endpoint not by itself but among other tests in cognitive composite scores, namely the “Preclinical Alzheimer Cognitive Composite” score and the “MAPT-PACC” score, respectively. Although the use of composite scores allow to reduce type one error in statistical analyses, their clinical value and neural underpinnings are not as clear as individual cognitive tests (although most individual tests, and the FCSRT among them, are not purely related to one cognitive domain. In the case of the FCSRT, as mentioned previously, episodic and semantic memory processes are implicated).

4.3. Validity of the methodology

Strengths of our findings are related to the size of the cohort, its multimodality, and the quality of data collected for the Memento cohort, including a high degree of standardization of acquired data in all domains, from neuropsychological tests to imaging. This was organized before,
during, and after (postprocessing) acquisition of data, which allowed optimal intercenter reproducibility as already described for PET imaging [48].

We acknowledge that the approach we used cannot bring the same refined information as functional MRI (fMRI) studies, which can for instance indicate which part of the hippocampus is involved in different memorization processes [36]. Our approach is complementary to fMRI delineation of the structural underpinning of memory processes and is likely to yield more robust, if less precise, results. The small number of participants included in most fMRI studies can be seen as a factor of discrepancies observed across studies (i.e., no hippocampal involvement in the retrieval of personal episodic autobiographical memory events [80] versus left hippocampal involvement [29]). The fMRI methodologies (particularly concerning the statistical analysis of results) also vary from one fMRI study to the next, and the inferences derived must be taken with caution [81]. In our study, the added value of a homogeneous population, standardized acquisition process over a relatively short interval of time, standardized quality checking, and postprocessing of data by a unique team (at the CATI [82]) and ultimately, statistical analysis taking into account both the multiple comparisons and adjustment factors allow us to draw valid conclusions from our findings. Also, the choice to study the associations of cognitive tests with predefined cortical areas derived from published atlas greatly decreases the number of statistical tests performed relatively to voxel-based comparisons while the analyzed regions remain pertinent on an anatomical and functional point of view. In any case, both types of studies are bound to provide complementary results, fMRI providing a finer delineation of subtle episodic memory functioning while our innovative methodology gives a more general and robust understanding of the major regions structurally and functionally underlying the cognitive processes of memory in aging.

This type of study has to be considered in the broader spectrum of standardized MRI postprocessing for routine clinical care. Numerous software programs are becoming available to the radiologists to help clinicians in their assessment of brain (particularly neurodegenerative) diseases [83]. This approach yet remains to be studied, but the Memento cohort seems to have the optimal design to validate it further as the participants will be followed longitudinally, allowing to determine the best marker of combination of markers to identify incipient AD or other brain diseases.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.trci.2018.03.010.

RESEARCH IN CONTEXT

1. Systematic review: We searched the literature (PubMed) for the following terms: episodic memory AND magnetic resonance imaging OR Positron emission tomography (PET) OR structural correlates OR functional correlates revealing that there was no single study nor any meta-analysis with such a large number of participants used to analyze the structural and functional correlates of episodic memory with such a high degree of clinical and imaging standardization.

2. Interpretation: Our study revealed that the free and selective reminding test and a simple and rapid association memory tests can be used to finely analyze the anatomical and functional underpinnings of episodic memory. The stronger association between regional metabolism on fluorodeoxyglucose-PET and memory performances in APOE ε4 carriers strengthens the diagnostic value of FCSRT for Alzheimer’s disease.

3. Future directions: As amyloid PET imaging will be soon available for a sample of several hundred of Memento participants, it will be possible to test the hypothesis of an early cognitive impact of brain amyloidosis on the retrieval process of episodic memory.

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| Number of sites | Participants | %  |
|-----------------|--------------|----|
| **3T MRI (n=1854)** |              |    |
| GE MR Discovery 3T | 4            | 162 | 7.5 |
| GE Signa 3T       | 6            | 127 | 5.9 |
| Philips Achieva 3T | 8            | 475 | 22.0|
| Philips Ingenia 3T | 2            | 102 | 4.7 |
| Siemens Skyra 3T  | 3            | 199 | 9.2 |
| Siemens Trio 3T   | 2            | 78  | 3.6 |
| Siemens Verio 3T  | 9            | 711 | 33.0|
| **1.5T MRI (n=303)** |              |    |
| GE Signa 1.5T     | 1            | 79  | 3.7 |
| Philips Achieva 1.5T | 1        | 28  | 1.3 |
| Philips Intera 1.5T | 1          | 51  | 2.4 |
| Siemens Avanto 1.5T | 2          | 65  | 3.0 |
| Siemens Symphonytim Avanto 1.5T | 1 | 80 | 3.7 |
Appendix B. FCSRT sub-scores distribution
Appendix C: Latent class analysis of the associations between MRI measurements and episodic memory in the Memento Cohort

| MRI features       | Overall effect on episodic memory | FDR-corrected p values | Test of effect homogeneity (FDR-corrected p-value) | IR  | FR  | ISC |
|--------------------|-----------------------------------|------------------------|--------------------------------------------------|-----|-----|-----|
| entorhinal         | 0.31 [0.24;0.37]                  | <0.0001                | 0.61                                             |     |     |     |
| parahippocampal    | 0.18 [0.12;0.24]                  | <0.0001                | 0.49                                             |     |     |     |
| fusiform           | 0.16 [0.10;0.23]                  | <0.0001                | 0.050                                            |     |     |     |
| temporalpole       | 0.14 [0.08;0.20]                  | <0.0001                | 0.22                                             |     |     |     |
| supramarginal      | 0.15 [0.09;0.21]                  | <0.0001                | 0.050                                            |     |     |     |
| parsorbitalis      | 0.07 [0.01;0.13]                  | 0.041                  | 0.141                                            |     |     |     |
| insula             | 0.13 [0.07;0.19]                  | <0.0001                | 0.43                                             |     |     |     |
| superiortemporal   | 0.17 [0.10;0.23]                  | <0.0001                | 0.036                                            | 0.21 [0.10;0.31] | 0.19 [0.13;0.26] | 0.10 [0.02;0.17] |
| medialorbitofrontal| 0.10 [0.04;0.16]                  | 0.0017                 | 0.69                                             |     |     |     |
| inferiorparietal   | 0.13 [0.07;0.19]                  | <0.0001                | 0.050                                            |     |     |     |
| middletemporal     | 0.13 [0.07;0.19]                  | 0.0011                 | 0.050                                            |     |     |     |
| precentral         | 0.11 [0.04;0.17]                  | 0.0028                 | 0.027                                            | 0.16 [0.06;0.26] | 0.13 [0.07;0.19] | 0.03 [-.04;0.10] |
| superfrontal       | 0.07 [0.01;0.13]                  | 0.046                  | 0.50                                             |     |     |     |
| caudalmiddlefrontal| 0.09 [0.03;0.15]                  | 0.0057                 | 0.47                                             |     |     |     |
| lateralorbitofrontal| 0.08 [0.02;0.14]             | 0.020                  | 0.43                                             |     |     |     |
| isthmuscingulate   | 0.10 [0.04;0.15]                  | 0.0031                 | 0.050                                            |     |     |     |
| lingual            | 0.06 [-.00;0.12]                  | 0.077                  | 0.0048                                           | 0.12 [0.03;0.22] | 0.08 [0.02;0.14] | -03 [-.10;0.04] |
| posteriorcingulate | 0.03 [-.03;0.09]                  | 0.30                   | 0.126                                            |     |     |     |
| transversetemporal | 0.08 [0.02;0.14]                  | 0.023                  | 0.076                                            |     |     |     |
| frontalpole        | 0.06 [0.00;0.12]                  | 0.050                  | 0.88                                             |     |     |     |
| precuneus          | 0.12 [0.06;0.18]                  | 0.0004                 | 0.029                                            | 0.19 [0.09;0.29] | 0.13 [0.07;0.19] | 0.05 [-.03;0.12] |
| parsopercularis    | 0.04 [-.01;0.10]                  | 0.18                   | 0.064                                            |     |     |     |
| inferiortemporal   | 0.11 [0.05;0.17]                  | 0.0013                 | 0.149                                            |     |     |     |
| lateralloccipital  | 0.09 [0.03;0.15]                  | 0.0080                 | 0.029                                            | 0.14 [0.05;0.23] | 0.11 [0.05;0.17] | 0.02 [-.05;0.08] |
| rostralmiddlefrontal| 0.07 [0.01;0.13]                | 0.042                  | 0.94                                             |     |     |     |
| MRI features          | Overall effect on episodic memory | FDR-corrected p values | Test of effect homogeneity (FDR-corrected p-value) | IR  | FR  | ISC  |
|-----------------------|----------------------------------|------------------------|---------------------------------------------------|-----|-----|------|
| postcentral           | 0.09 [0.03;0.15]                 | 0.0049                 | 0.050                                             |     |     |      |
| paracentral           | 0.04 [-0.02;0.10]                | 0.24                   | 0.050                                             |     |     |      |
| parstriangularis      | 0.02 [-0.04;0.07]                | 0.63                   | 0.131                                             |     |     |      |
| caudalanteriorcingulate | 0.01 [-0.05;0.06]            | 0.84                   | 0.84                                              |     |     |      |
| cuneus                | 0.04 [-0.02;0.10]                | 0.20                   | 0.131                                             |     |     |      |
| superiorparietal      | 0.06 [0.00;0.12]                 | 0.054                  | 0.050                                             |     |     |      |
| rostralanteriorcingulate | 0.02 [-0.03;0.08]        | 0.44                   | 0.69                                              |     |     |      |
| pericalcarine         | 0.02 [-0.04;0.08]                | 0.48                   | 0.050                                             |     |     |      |
| bankssts              | 0.07 [0.01;0.13]                 | 0.042                  | 0.066                                             |     |     |      |

* p-values were FDR-corrected for cortical thickness.

FCSRT: Free and Cued Selective Reminding Test, IR: Immediate Recall, FR: Free Recall, ISC: Index of Sensitivity to Cueing, WMH: White Matter Hyperintensities.
Appendix D. APOE interaction with cortical thickness

Method: To determine whether APOE eps4 status could modify the relation between cortical thickness and FCSRT performance, we introduce APOE as an interaction term, and tested it to 0. For p-values < 0.05, we presented both estimations in Non APOE and APOE carriers. FDR-corrected p-values were also presented.

Part A. Immediate Recall

| Region      | Global Effect | APOE interaction | APOE interaction Corrected | No APOEeps4   | APOE eps4 +  |
|-------------|---------------|------------------|----------------------------|---------------|--------------|
| middletemporal | 1.14 [1.02; 1.26] | 0.025            | 0.63                       | 1.23 [1.08; 1.39] | 0.97 [0.81; 1.16] |
| superiorparietal | 1.11 [1.00; 1.23] | 0.017            | 0.57                       | 1.21 [1.07; 1.37] | 0.94 [0.79; 1.12] |
| precuneus    | 1.14 [1.03; 1.26] | 0.041            | 0.70                       | 1.23 [1.08; 1.39] | 1.00 [0.84; 1.18] |
| lingual      | 1.07 [0.97; 1.18] | 0.037            | 0.70                       | 1.13 [1.00; 1.28] | 0.91 [0.76; 1.08] |
| pericalcarine| 1.05 [0.95; 1.16] | 0.049            | 0.72                       | 1.13 [1.00; 1.27] | 0.92 [0.77; 1.09] |
| cuneus       | 1.01 [0.92; 1.12] | 0.011            | 0.56                       | 1.10 [0.98; 1.24] | 0.85 [0.71; 1.01] |

Part B. Free Recall

| Region     | Global Effect | APOE interaction | APOE interaction Corrected | No APOEeps4   | APOE eps4 +  |
|------------|---------------|------------------|----------------------------|---------------|--------------|
| entorhinal | 4.27 [3.46; 5.08] | 0.0043          | 0.44                       | 3.41 [2.40; 4.43] | 6.41 [4.49; 8.34] |
Appendix E. Summary of interaction between cortical thickness and APOE in association with FCSRT subscores (RIM = Immediate recall, RL = Free recall, ISI = Index of sensitivity to cueing)
Appendix F: Latent class analysis of the associations between FDG-PET Mean Uptake Values and episodic memory in the Memento Cohort

| Anatomical description | Overall effect on episodic memory | FDR-corrected p values | Test of effect homogeneity (FDR-corrected p-value) |
|------------------------|----------------------------------|------------------------|--------------------------------------------------|
| CENTRAL                |                                  |                        |                                                  |
| Precentral             | 0.07 [-.00;0.15]                 | 0.084                  | 1.00                                             |
| Postcentral            | 0.02 [-.06;0.11]                 | 0.61                   | 1.00                                             |
| Rolandic_Oper          | 0.08 [0.01;0.16]                 | 0.043                  | 0.73                                             |
| FRONTAL               |                                  |                        |                                                  |
| Frontal_Sup_2          | 0.07 [0.00;0.14]                 | 0.058                  | 0.89                                             |
| Frontal_Mid_2          | 0.09 [0.03;0.15]                 | 0.0063                 | 0.70                                             |
| Frontal_Inf_Oper       | 0.10 [0.04;0.17]                 | 0.0032                 | 0.64                                             |
| Frontal_Inf_Tri        | 0.10 [0.04;0.16]                 | 0.0027                 | 0.70                                             |
| Frontal_Sup_Medial     | 0.06 [-0.00;0.13]                | 0.069                  | 0.70                                             |
| Supp_Motor_Area        | 0.03 [-.03;0.10]                 | 0.37                   | 1.00                                             |
| Paracentral_lobule     | 0.03 [-.04;0.10]                 | 0.40                   | 0.70                                             |
| Frontal_Med_Orb        | 0.12 [0.05;0.18]                 | 0.0017                 | 0.64                                             |
| Frontal_Inf_Orb_2      | 0.07 [0.01;0.14]                 | 0.040                  | 0.64                                             |
| Rectus                 | 0.15 [0.08;0.22]                 | 0.0002                 | 0.93                                             |
| OFCmed                 | 0.14 [0.07;0.22]                 | 0.0009                 | 0.64                                             |
| OFCant                 | 0.07 [0.01;0.13]                 | 0.029                  | 0.64                                             |
| OFCpost                | 0.11 [0.03;0.18]                 | 0.0074                 | 0.64                                             |
| Anatomical description | Overall effect on episodic memory | FDR-corrected p values | Test of effect homogeneity (FDR-corrected p-value) |
|------------------------|----------------------------------|------------------------|------------------------------------------------|
| OFClat                 | 0.02 [-0.03;0.07]                | 0.46                   | 0.64                                           |
| Olfactory              | 0.20 [0.10;0.29]                 | 0.0002                 | 0.64                                           |
| TEMPORAL               |                                   |                        |                                                |
| Temporal_Sup           | 0.10 [0.02;0.17]                 | 0.017                  | 0.70                                           |
| Heschl                 | 0.10 [0.04;0.15]                 | 0.0027                 | 0.89                                           |
| Temporal_Mid           | 0.15 [0.07;0.22]                 | 0.0006                 | 0.64                                           |
| Temporal_Inf           | 0.16 [0.07;0.24]                 | 0.0009                 | 0.70                                           |
| PARIETAL               |                                   |                        |                                                |
| Parietal_Sup           | 0.12 [0.05;0.18]                 | 0.0017                 | 1.00                                           |
| Parietal_Inf           | 0.11 [0.05;0.17]                 | 0.0010                 | 0.80                                           |
| Angular                | 0.16 [0.10;0.22]                 | <0.0001                | 0.64                                           |
| SupraMarginal          | 0.12 [0.05;0.19]                 | 0.0018                 | 0.70                                           |
| Precuneus              | 0.11 [0.05;0.16]                 | 0.0012                 | 0.93                                           |
| OCCIPITAL              |                                   |                        |                                                |
| Occipital_Sup          | 0.04 [-0.03;0.10]                | 0.27                   | 1.00                                           |
| Occipital_Mid          | 0.08 [0.02;0.15]                 | 0.020                  | 1.00                                           |
| Occipital_Inf          | 0.04 [-0.02;0.10]                | 0.23                   | 0.73                                           |
| Cuneus                 | 0.04 [-0.02;0.10]                | 0.20                   | 1.00                                           |
| Calcarine              | 0.04 [-0.01;0.09]                | 0.150                  | 0.72                                           |
| Lingual                | 0.05 [-0.02;0.11]                | 0.16                   | 1.00                                           |
| Fusiform               | 0.11 [0.02;0.20]                 | 0.023                  | 0.93                                           |
| Anatomical description          | Overall effect on episodic memory | FDR-corrected p values | Test of effect homogeneity (FDR-corrected p-value) |
|--------------------------------|----------------------------------|------------------------|-----------------------------------------------|
| LIMBIC                         |                                  |                        |                                               |
| Temporal_Pole_Sup             | 0.12 [0.02;0.23]                 | 0.033                  | 0.70                                          |
| Temporal_Pole_Mid             | 0.11 [0.00;0.22]                 | 0.067                  | 0.70                                          |
| Cingulate_Ant                 | 0.14 [0.06;0.22]                 | 0.0012                 | 0.64                                          |
| Cingulate_Mid                 | 0.12 [0.05;0.18]                 | 0.0012                 | 0.93                                          |
| Cingulate_Post                | 0.15 [0.10;0.20]                 | <0.0001                | 0.64                                          |
| Hippocampus                   | 0.41 [0.25;0.57]                 | <0.0001                | 0.65                                          |
| ParaHippocampal               | 0.35 [0.22;0.47]                 | <0.0001                | 0.70                                          |
| Insula                        | 0.14 [0.05;0.22]                 | 0.0027                 | 0.70                                          |
| Sub cortical grey nuclei      |                                  |                        |                                               |
| Amygdala                      | 0.26 [0.12;0.41]                 | 0.0014                 | 0.64                                          |
| Caudate                       | 0.12 [0.06;0.19]                 | 0.0009                 | 0.64                                          |
| Putamen                       | 0.05 [-0.01;0.10]                | 0.123                  | 0.71                                          |
| Pallidum                      | 0.04 [0.00;0.08]                 | 0.043                  | 1.00                                          |
| Thalamus                      | 0.10 [0.04;0.16]                 | 0.0032                 | 0.64                                          |
### Appendix G. APOE interaction with 18-FDG TEP

#### Part 1. Immediate Recall

| Region         | Global Effect | APOE Interaction | APOE Interaction Corrected | No APOE eps4 | APOE eps4 + |
|----------------|---------------|------------------|----------------------------|--------------|-------------|
| CENTRAL        |               |                  |                            |              |             |
| Precentral     | 0.97 [0.87; 1.07] | 0.50             | 0.61                       |              |             |
| Postcentral    | 0.98 [0.88; 1.09] | 0.19             | 0.31                       |              |             |
| Rolandic_Oper  | 1.07 [0.96; 1.18] | 0.24             | 0.37                       |              |             |
| FRONTAL        |               |                  |                            |              |             |
| Frontal_Sup_2  | 1.00 [0.92; 1.10] | 0.38             | 0.50                       |              |             |
| Frontal_Mid_2  | 1.02 [0.94; 1.11] | 0.31             | 0.44                       |              |             |
| Frontal_Inf_Oper | 1.07 [0.98; 1.17] | 0.24             | 0.37                       |              |             |
| Frontal_Inf_Tri | 1.06 [0.97; 1.15] | 0.139            | 0.25                       |              |             |
| Frontal_Sup_Medial | 1.01 [0.93; 1.11] | 0.38             | 0.51                       |              |             |
| Supp_Motor_Area | 0.95 [0.87; 1.04] | 0.35             | 0.48                       |              |             |
| Paracentral_Lobule | 0.97 [0.88; 1.06] | 0.78             | 0.83                       |              |             |
| Frontal_Med_Orb | 1.10 [1.01; 1.21] | 0.110            | 0.23                       |              |             |
| Frontal_Inf_Orb_2 | 1.02 [0.93; 1.11] | 0.070            | 0.15                       |              |             |
| Rectus         | 1.15 [1.04; 1.26] | 0.070            | 0.15                       |              |             |
| OFCmed         | 1.08 [0.97; 1.19] | 0.0091           | 0.042                      | 0.98 [0.87; 1.10] | 1.30 [1.08; 1.57] |
| OFCant         | 1.02 [0.94; 1.10] | 0.027            | 0.088                      | 0.96 [0.88; 1.06] | 1.17 [1.00; 1.36] |
| OFCpost        | 1.06 [0.96; 1.17] | 0.032            | 0.094                      | 0.99 [0.88; 1.11] | 1.23 [1.03; 1.47] |
| OFClat         | 0.95 [0.88; 1.02] | 0.044            | 0.118                      | 0.90 [0.83; 0.99] | 1.05 [0.92; 1.21] |
| Olfactory      | 1.16 [1.02; 1.32] | 0.45             | 0.57                       |              |             |
| TEMPORAL       |               |                  |                            |              |             |
| Temporal_Sup   | 1.11 [1.00; 1.23] | 0.063            | 0.150                      |              |             |
| Heschl         | 1.07 [0.99; 1.16] | 0.20             | 0.32                       |              |             |
| Temporal_Mid   | 1.13 [1.02; 1.25] | 0.0028           | 0.024                      | 1.01 [0.89; 1.14] | 1.38 [1.15; 1.64] |
| Temporal_Inf   | 1.13 [1.02; 1.27] | 0.0037           | 0.027                      | 1.01 [0.89; 1.16] | 1.41 [1.16; 1.71] |
| PARITIAL       |               |                  |                            |              |             |
| Parietal_Sup   | 1.03 [0.94; 1.14] | 0.014            | 0.057                      | 0.96 [0.86; 1.07] | 1.25 [1.04; 1.50] |
| Parietal_Inf   | 1.07 [0.99; 1.16] | 0.021            | 0.073                      | 1.00 [0.91; 1.10] | 1.22 [1.06; 1.40] |
| Angular        | 1.12 [1.04; 1.21] | 0.0029           | 0.024                      | 1.04 [0.95; 1.13] | 1.31 [1.14; 1.50] |
| SupraMarginal  | 1.14 [1.03; 1.25] | 0.019            | 0.070                      | 1.05 [0.94; 1.17] | 1.33 [1.12; 1.59] |
| Precuneus      | 1.06 [0.98; 1.15] | 0.013            | 0.065                      | 0.99 [0.90; 1.09] | 1.22 [1.06; 1.41] |
| OCCIPITAL      |               |                  |                            |              |             |
| Occipital_Sup  | 1.01 [0.93; 1.11] | 0.022            | 0.077                      | 0.95 [0.86; 1.06] | 1.18 [1.00; 1.38] |
| Occipital_Mid  | 1.07 [0.98; 1.17] | 0.019            | 0.070                      | 0.99 [0.89; 1.10] | 1.23 [1.05; 1.44] |
| Occipital_Inf  | 1.01 [0.93; 1.10] | 0.0054           | 0.030                      | 0.92 [0.83; 1.02] | 1.19 [1.02; 1.38] |
| Cuneus         | 1.04 [0.95; 1.12] | 0.0071           | 0.036                      | 0.97 [0.88; 1.06] | 1.22 [1.05; 1.42] |
| Calcarine      | 1.01 [0.94; 1.09] | 0.057            | 0.138                      |              |             |
| Region               | Global Effect | APOE Interaction | APOE Interaction Corrected | No APOE eps4 | APOE eps4 + |
|----------------------|--------------|------------------|---------------------------|--------------|-------------|
| LIMBIC               |              |                  |                           |              |             |
| Lingual             | 1.01 [ 0.92; 1.11] | 0.103             | 0.21                      |              |             |
| Fusiform            | 1.11 [ 0.98; 1.25] | 0.018             | 0.069                      | 1.00 [ 0.86; 1.16] | 1.36 [ 1.09; 1.70] |
| Temporal_Pole_Sup  | 1.20 [ 1.03; 1.39] | 0.29              | 0.43                      |              |             |
| Temporal_Pole_Mid   | 1.12 [ 0.96; 1.30] | 0.018             | 0.069                      | 0.98 [ 0.82; 1.18] | 1.41 [ 1.09; 1.83] |
| Cingulate_Ant       | 1.11 [ 1.00; 1.23] | 0.119             | 0.23                      |              |             |
| Cingulate_Mid       | 1.09 [ 1.00; 1.19] | 0.083             | 0.18                      |              |             |
| Cingulate_Post      | 1.14 [ 1.07; 1.21] | 0.030             | 0.090                      | 1.09 [ 1.01; 1.17] | 1.25 [ 1.12; 1.40] |
| Hippocampus         | 1.46 [ 1.18; 1.80] | 0.24              | 0.37                      |              |             |
| ParaHippocampal     | 1.36 [ 1.15; 1.61] | 0.070             | 0.15                      |              |             |
| Insula              | 1.10 [ 0.98; 1.23] | 0.70              | 0.79                      |              |             |
| SCGN                |              |                  |                           |              |             |
| Amygdala            | 1.44 [ 1.19; 1.74] | 0.47              | 0.59                      |              |             |
| Caudate             | 1.05 [ 0.97; 1.15] | 0.59              | 0.71                      |              |             |
| Putamen             | 0.99 [ 0.91; 1.06] | 0.85              | 0.89                      |              |             |
| Pallidum            | 1.00 [ 0.95; 1.05] | 0.121             | 0.23                      |              |             |
| Thalamus            | 1.03 [ 0.94; 1.12] | 0.56              | 0.67                      |              |             |

Part 2. Free Recall

| Region               | Global Effect | APOE Interaction | APOE Interaction Corrected | No APOE eps4 | APOE eps4 + |
|----------------------|--------------|------------------|---------------------------|--------------|-------------|
| CENTRAL              |              |                  |                           |              |             |
| Postcentral          | 0.86 [ 0.06; 1.66] | 0.051             | 0.129                     |              |             |
| Precentral           | 0.98 [ 0.14; 1.81] | 0.086             | 0.18                      |              |             |
| Rolandic_Oper        | 1.11 [ 0.47; 1.75] | 0.18              | 0.31                      |              |             |
| Supp_Motor_Area      | 0.63 [-0.12; 1.37] | 0.089             | 0.19                      |              |             |
| Frontal_Inf_Oper     | 1.19 [ 0.49; 1.89] | 0.048             | 0.124                      | 1.06 [ 0.20; 1.91] | 2.74 [ 1.33; 4.15] |
| OFClat               | 1.29 [ 0.68; 1.89] | 0.057             | 0.138                     |              |             |
| Frontal_Sup_2        | 1.30 [ 0.61; 1.99] | 0.048             | 0.124                      | 0.87 [ 0.14; 1.60] | 2.51 [ 1.00; 4.02] |
| Frontal_Sup_Medial   | 1.40 [ 0.75; 2.04] | 0.23              | 0.37                      |              |             |
| Frontal_Inf_Orb_2    | 1.42 [ 0.69; 2.14] | 0.42              | 0.54                      |              |             |
| Frontal_Mid_2        | 1.55 [ 0.93; 2.17] | 0.017             | 0.065                      | 1.27 [ 0.55; 1.99] | 3.16 [ 2.00; 4.31] |
| Frontal_Inf_Tri      | 1.58 [ 0.87; 2.29] | 0.113             | 0.23                      |              |             |
| OFCant               | 1.69 [ 1.00; 2.38] | 0.30              | 0.44                      |              |             |
| Frontal_Med_Orb      | 1.79 [ 1.09; 2.49] | 0.121             | 0.23                      |              |             |
| OFCpost              | 2.11 [ 1.35; 2.87] | 0.15              | 0.27                      |              |             |
| Rectus               | 2.26 [ 1.56; 2.96] | 0.32              | 0.45                      |              |             |
| Region                     | Global Effect | APOE interaction | APOE interaction Corrected | No APOE eps4 | APOE eps4 + |
|----------------------------|--------------|------------------|-----------------------------|--------------|------------|
| OFCmed                     | 2.30 [ 1.50; 3.11] | 0.029 | 0.089 | 1.62 [ 0.55; 2.69] | 4.17 [ 2.46; 5.88] |
| Olfactory                  | 2.44 [ 1.43; 3.45] | 0.44 | 0.56 |
| Paracentral_lobule         | -0.15 [-0.83; 0.53] | 0.083 | 0.18 |
| **TEMPORAL**               |              |                  |                             |              |            |
| Heschl                     | 0.65 [ 0.09; 1.22] | 0.42 | 0.54 |
| Temporal_Sup               | 0.94 [ 0.15; 1.74] | 0.028 | 0.088 | 0.21 [-0.66; 1.09] | 2.37 [ 0.62; 4.11] |
| Temporal_Mid               | 1.63 [ 0.74; 2.51] | 0.0016 | 0.020 | 0.64 [-0.32; 1.61] | 4.05 [ 2.32; 5.78] |
| Temporal_Inf               | 2.09 [ 1.20; 2.99] | 0.0002 | 0.011 | 1.13 [ 0.13; 2.14] | 4.40 [ 2.74; 6.05] |
| **PARIETAL**               |              |                  |                             |              |            |
| SupraMarginal              | 1.44 [ 0.71; 2.18] | 0.025 | 0.082 | 1.11 [ 0.19; 2.03] | 3.31 [ 1.75; 4.87] |
| Parietal_Sup               | 1.63 [ 0.83; 2.43] | 0.0004 | 0.011 | 0.79 [-0.03; 1.60] | 4.14 [ 2.66; 5.63] |
| Parietal_Inf               | 1.63 [ 0.98; 2.27] | 0.0057 | 0.031 | 1.15 [ 0.48; 1.81] | 3.48 [ 2.24; 4.71] |
| Precuneus                  | 1.77 [ 1.15; 2.40] | 0.0034 | 0.027 | 1.05 [ 0.28; 1.83] | 3.50 [ 2.00; 5.00] |
| Angular                    | 1.79 [ 1.10; 2.47] | 0.0003 | 0.011 | 1.28 [ 0.57; 2.00] | 4.03 [ 2.92; 5.14] |
| **OCCIPITAL**              |              |                  |                             |              |            |
| Occipital_Inf              | 0.65 [-0.02; 1.32] | 0.0004 | 0.011 | -0.09 [-0.87; 0.69] | 2.79 [ 1.33; 4.25] |
| Occipital_Sup              | 0.69 [-0.07; 1.44] | 0.0003 | 0.011 | -0.10 [-0.97; 0.78] | 3.62 [ 1.92; 5.32] |
| Lingual                    | 0.72 [-0.12; 1.56] | 0.015 | 0.060 | -0.00 [-0.92; 0.92] | 2.17 [ 0.62; 3.72] |
| Calcarine                  | 0.83 [ 0.20; 1.46] | 0.015 | 0.060 | 0.29 [-0.35; 0.94] | 2.70 [ 1.00; 3.20] |
| Cuneus                     | 0.98 [ 0.27; 1.69] | 0.0013 | 0.020 | 0.37 [-0.38; 1.12] | 3.28 [ 1.74; 4.83] |
| Occipital_Mid              | 1.15 [ 0.33; 1.96] | 0.0024 | 0.023 | 0.50 [-0.24; 1.24] | 3.31 [ 1.76; 4.85] |
| Fusiform                   | 1.40 [ 0.19; 2.61] | 0.028 | 0.088 | 0.80 [-0.31; 1.92] | 3.74 [ 1.87; 5.60] |
| **LIMBIC**                 |              |                  |                             |              |            |
| Cingulate_Mid              | 1.47 [ 0.79; 2.15] | 0.120 | 0.23 |
| Temporal_Pole_Mid          | 1.52 [ 0.28; 2.76] | 0.0018 | 0.022 | 0.71 [-0.65; 2.06] | 4.71 [ 2.66; 6.76] |
| Temporal_Pole_Sup          | 1.70 [ 0.47; 2.93] | 0.056 | 0.137 |
| Insula                     | 1.76 [ 0.81; 2.71] | 0.94 | 0.96 |
| Cingulate_Ant              | 1.80 [ 0.97; 2.63] | 0.96 | 0.97 |
| Cingulate_Post             | 2.29 [ 1.59; 2.99] | 0.022 | 0.075 | 1.44 [ 0.71; 2.16] | 3.09 [ 1.76; 4.42] |
| Hippocampus                | 3.23 [ 1.53; 4.93] | 0.72 | 0.80 |
| ParaHippocampal            | 3.70 [ 2.05; 5.34] | 0.0014 | 0.020 | 2.39 [ 0.93; 3.85] | 7.26 [ 4.74; 9.78] |
| **SCGN**                   |              |                  |                             |              |            |
| Pallidum                   | 0.40 [ 0.01; 0.79] | 0.64 | 0.74 |
| Putamen                    | 0.63 [ 0.04; 1.21] | 0.93 | 0.96 |
| Caudate                    | 1.55 [ 0.90; 2.20] | 0.38 | 0.50 |
| Thalamus                   | 1.80 [ 1.19; 2.41] | 0.62 | 0.73 |
| Amygdala                   | 2.32 [ 0.94; 3.69] | 0.28 | 0.41 |

Part 3. Index of Sensitivity to Cueing
| Location          | Global Effect | APOE interaction | APOE interaction Corrected | No APOE eps4 | APOE eps4 + |
|-------------------|---------------|------------------|----------------------------|--------------|-------------|
| CENTRAL           |               |                  |                            |              |             |
| Postcentral       | 0.67 [-0.09; 1.43] | 0.115            | 0.23                       |              |             |
| Precentral        | 0.77 [ 0.08; 1.46] | 0.135            | 0.25                       |              |             |
| Rolandic_Oper     | 0.99 [ 0.15; 1.83] | 0.040            | 0.114 0.25 [-0.53; 1.03]   | 2.22 [ 0.59; 3.85] |
| FRONTAL           |               |                  |                            |              |             |
| Paracentral_lobe   | 0.00 [-0.59; 0.60] | 0.46             | 0.58                       |              |             |
| Supp_Motor_Area   | 0.31 [-0.22; 0.84] | 0.118            | 0.23                       |              |             |
| OFClat            | 0.55 [-0.06; 1.15] | 0.0050           | 0.030 0.09 [-0.48; 0.66]   | 1.93 [ 0.72; 3.15] |
| Frontal_Sup_Medial| 0.60 [ 0.01; 1.18] | 0.043            | 0.118 0.21 [-0.43; 0.85]   | 1.69 [ 0.36; 3.02] |
| Frontal_Sup_Orb   | 0.70 [ 0.10; 1.30] | 0.0023           | 0.023 0.28 [-0.34; 0.90]   | 2.45 [ 1.18; 3.72] |
| OFCant            | 0.74 [ 0.20; 1.29] | 0.0084           | 0.041 0.36 [-0.25; 0.98]   | 1.99 [ 0.87; 3.10] |
| Frontal_Sup_2     | 0.79 [ 0.25; 1.33] | 0.0072           | 0.036 0.42 [-0.29; 1.12]   | 2.36 [ 0.97; 3.75] |
| Frontal_Mid_2     | 0.84 [ 0.23; 1.44] | 0.0004           | 0.011 0.38 [-0.24; 1.00]   | 2.36 [ 1.32; 3.41] |
| OFCpost           | 0.93 [ 0.18; 1.69] | 0.0021           | 0.023 0.28 [-0.49; 1.05]   | 2.69 [ 1.24; 4.14] |
| Supp_Motor_Area   | 0.31 [-0.22; 0.84] | 0.118            | 0.23                       |              |             |
| FrontoMed          | 1.04 [ 0.03; 2.05] | 0.26             | 0.39                       |              |             |
| Frontal_Sup_Medial| 1.05 [ 0.37; 1.73] | 0.0004           | 0.011 0.46 [-0.33; 1.25]   | 3.00 [ 1.66; 4.35] |
| OFCmed             | 1.30 [ 0.47; 2.13] | 0.0009           | 0.016 0.46 [-0.37; 1.30]   | 3.16 [ 1.72; 4.60] |
| Rectus             | 1.36 [ 0.64; 2.09] | 0.0043           | 0.029 0.55 [-0.23; 1.33]   | 2.92 [ 1.46; 4.38] |
| TEMPORAL           |               |                  |                            |              |             |
| Heschl            | 0.97 [ 0.35; 1.59] | 0.25             | 0.38                       |              |             |
| Temporal_Sup      | 1.09 [ 0.31; 1.87] | 0.033            | 0.095 0.48 [-0.44; 1.39]   | 2.28 [ 0.87; 3.69] |
| Temporal_Mid      | 1.33 [ 0.51; 2.15] | 0.0007           | 0.015 0.39 [-0.45; 1.23]   | 3.01 [ 1.59; 4.44] |
| Temporal_Inf      | 1.58 [ 0.77; 2.39] | 0.011            | 0.047 0.83 [-0.22; 1.88]   | 3.23 [ 1.80; 4.67] |
| PARIETAL          |               |                  |                            |              |             |
| Precuneus         | 0.99 [ 0.35; 1.63] | 0.041            | 0.114 0.46 [-0.24; 1.16]   | 2.04 [ 0.68; 3.39] |
| Parietal_Sup      | 1.10 [ 0.34; 1.86] | 0.0065           | 0.035 0.48 [-0.25; 1.22]   | 3.01 [ 1.32; 4.70] |
| SupraMarginal     | 1.17 [ 0.37; 1.97] | 0.0095           | 0.043 0.43 [-0.38; 1.24]   | 2.56 [ 1.10; 4.02] |
| Parietal_Inf      | 1.22 [ 0.62; 1.82] | 0.046            | 0.124 0.64 [-0.03; 1.31]   | 2.11 [ 0.85; 3.37] |
| Angular           | 1.47 [ 0.88; 2.06] | 0.0037           | 0.027 0.75 [ 0.04; 1.45]   | 2.68 [ 1.51; 3.86] |
| OCCIPITAL         |               |                  |                            |              |             |
| Calcarine         | 0.55 [-0.01; 1.11] | 0.031            | 0.092 0.26 [-0.36; 0.88]   | 1.52 [ 0.35; 2.69] |
| Lingual           | 0.72 [ 0.04; 1.39] | 0.126            | 0.23                       |              |             |
| Cuneus            | 0.79 [ 0.19; 1.40] | 0.067            | 0.15                       |              |             |
| Occipital_Sup     | 0.88 [ 0.19; 1.58] | 0.0067           | 0.035 0.27 [-0.58; 1.12]   | 2.35 [ 0.93; 3.77] |
| Occipital_Inf     | 0.97 [ 0.33; 1.61] | 0.0046           | 0.030 0.29 [-0.49; 1.06]   | 2.38 [ 1.04; 3.73] |
| Occipital_Mid     | 1.04 [ 0.38; 1.71] | 0.055            | 0.136                       |              |             |
| Fusiform          | 1.30 [ 0.42; 2.18] | 0.0043           | 0.029 0.50 [-0.40; 1.39]   | 3.43 [ 1.73; 5.12] |
| LIMBIC            |               |                  |                            |              |             |
| Cingulate_Ant     | 0.97 [ 0.20; 1.73] | 0.17             | 0.29                       |              |             |
| Region          | Global Effect | APOE interaction | APOE interaction Corrected | No APOE eps4 | APOE eps4 + |
|-----------------|---------------|------------------|----------------------------|--------------|-------------|
| Insula          | 1.04 [ 0.18; 1.90] | 0.44             | 0.56                       |              |             |
| Cingulate_Post  | 1.15 [ 0.62; 1.68] | 0.0029           | 0.024                      | 0.68 [ 0.13; 1.24] | 2.14 [ 1.30; 2.98] |
| Cingulate_Mid   | 1.17 [ 0.50; 1.83] | 0.023            | 0.079                      | 0.53 [-0.26; 1.33] | 2.19 [ 0.90; 3.48] |
| Temporal_Pole_Sup | 1.65 [ 0.59; 2.72] | 0.0024           | 0.023                      | 0.43 [-0.74; 1.60] | 3.78 [ 2.01; 5.54] |
| Temporal_Pole_Mid | 1.98 [ 0.88; 3.08] | 0.0005           | 0.013                      | 0.50 [-0.83; 1.82] | 4.39 [ 2.58; 6.20] |
| ParaHippocampal | 2.59 [ 1.42; 3.77] | 0.0015           | 0.020                      | 1.13 [-0.32; 2.57] | 5.44 [ 3.19; 7.68] |
| SCGN Hippocampus | 2.90 [ 1.03; 4.76] | 0.0096           | 0.043                      | 1.22 [-0.78; 3.22] | 5.41 [ 2.36; 8.47] |
| Putamen         | 0.33 [-0.18; 0.85] | 0.34             | 0.47                       |              |             |
| Pallidum        | 0.34 [-0.05; 0.72] | 0.0037           | 0.027                      | 0.08 [-0.32; 0.48] | 1.43 [ 0.64; 2.22] |
| Thalamus        | 0.58 [-0.09; 1.24] | 0.64             | 0.74                       |              |             |
| Caudate         | 0.80 [ 0.09; 1.50] | 0.31             | 0.44                       |              |             |
| Amygdala        | 1.91 [ 0.23; 3.59] | 0.0053           | 0.030                      | 0.48 [-1.00; 1.96] | 4.89 [ 2.18; 7.61] |
Appendix H. Summary of interaction between regional metabolism and APOE in association with FCSRT subscores (RIM = Immediate recall, RL = Free recall, ISI = Index of sensitivity to cueing)
Appendix I: Visual comparison of the regional patterns of association between FCSRT subscores (RIM = Immediate recall, RL = Free recall, ISI = Index of sensitivity to cueing) and cortical thickness in the whole group (N=2157) and the MRI+FDG-PET subsample cohort (n=1310). Regions name are explicated in Appendix J.
Appendix J: Freesurfer regions in which the cortical thickness was measured
Bertrand, Accart, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Geneviève, Achdjibachdian, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Isabelle, Addra, CIC-1401 Clinical Epidemiology, CHU Bordeaux, Bordeaux, France
Sarah, Adjal, Memory Resource and Research Centre of Bordeaux, CHU Bordeaux, Bordeaux, France
Timothée, Albasser, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Michèle, Allard, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux France
Sandrine, Andrieu, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Cédric, Annweiller, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France
Pierre, Anthony, Memory Resource and Research Centre of Colmar, Colmar, France
Elise, Antoine, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Jean-Paul, Armspach, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Christine, Astier, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Vanessa, Auberti, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Christelle, Audrain, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France

Alexandre, Augier, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France

Sophie, Auriacombe, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France

John, Avet, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France

Romain, Bachelet, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France

Olivier, Bailon, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France

Hélène, Bansard, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France

Laurent, Baranti, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France

Fabrice-Guy, Barral, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France

Jean, Barré, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France

Yoan, Barsznica, Memory Resource and Research Centre of Besançon, Besançon, France

Annick, Barthelaix, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France
Laurie, Barthelemy, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France
Fanny, Barthelemy, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Anthony, Bathsavanis, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Vanessa, Baudiffier, Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Poitiers, France
Sophie, Bayer, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Catherine, Bayle, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Mélinda, Beaudenon, Memory Resource and Research Centre of Angers, CHU d'Angers, Angers, France
Emilie, Beaufils, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France
Yannick, Bejot, Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Dijon, France
Sandrine, Belkadi, Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Poitiers, France
Julie, Bellet, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Marwa, Ben, Yacoub, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Habib, Benali, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France
Karim, Bennys, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France
Nadine, Bensoussan, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Géraldine, Bera, Laboratoire d'Imagerie Biomédicale, Sorbonne Universités, UPMC Univ Paris 06, Inserm U 1146, CNRS UMR 7371, F-75006 Paris, France NeuroSpin, I2BM, Commissariat à l'Energie Atomique, France
Eric, Berger, Memory Resource and Research Centre of Besançon, Besançon, France
Juliette, Berger, Memory Resource and Research Centre of Clermont-Ferrand, CHU de Clermont-Ferrand, Clermont-Ferrand, France
Marc, G, Berger, Memory Resource and Research Centre of Clermont-Ferrand, CHU de Clermont-Ferrand, Clermont-Ferrand, France
Georgette, Berlier, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Laëtitia, Berly, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Hassan, Berrissoul, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France
Marie-Camille, Berthel, Memory Resource and Research Centre of Colmar, Colmar, France
Véronique, Berthier, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
François, Bertin-Hugault, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
François-Xavier, Bertrand, Memory Resource and Research Centre of Nantes, CHU de Nantes, Nantes, France
Guillaume, Bertrand, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Anaïck, Besozzi, Memory Resource and Research Centre of Nancy, CHU de Nancy, Nancy, France
Christelle, Betogliati-Filleau, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Catherine, Beze, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France
Mathias, Bilger, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Sandrine, Bioux, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France
Elisa, Bittard, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Ludovic, Blanchard, Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Poitiers, France
Odile, Blanchet, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France
Maryline, Blanchon, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Evangéline, Bliaux, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France
Pierre, Bohn, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France
Stéphanie, Bombois, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Alain, Bonafe, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France
Marie, Bonnet, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Hélène, Bonnot, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Martine, Bordessoules, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Nathalie, Bortone, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Amandine, Bossant, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Elodie, Bouaziz, Phar, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Yasmina, Boudali, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Laurie, Boukadida, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-
Justine, Boulanghien, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France

Clemence, Boullly, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France

Isabelle, Bourdel-Marchasson, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France

Marie-France, Bourin, Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Poitiers, France

Christophe, Bouvier, Coordinating Centre, CIC-1401 Clinical Epidemiology, Bordeaux, France

Serge, Bracard, Memory Resource and Research Centre of Nancy, CHU de Nancy, Nancy, France

Antoine, Brangier, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France

Laëtitia, Breuilh, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France

Lysiane, Brick, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France

Marie-Laure, Brickert, Memory Resource and Research Centre of Colmar, Colmar, France

Pierre-Yves, Brillet, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France

Signe, Brinck, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Caroline, Buisson, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Francine, Bury, Memory Resource and Research Centre of Colmar, Colmar, France
Laurence, Cadet, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Julien, Cahors, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Laure, Caillard, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Maria, Callejo, Plazas, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Fabienne, Calvas, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Sabine, Camara, Memory Resource and Research Centre of Colmar, Colmar, France
Aurore, Camoreyt, Memory Resource and Research Centre of Colmar, Colmar, France
Sandra, Campagne, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Agnès, Camus, Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Dijon, France
Vincent, Camus, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France
Sandrine, Canaple, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France
Edith, Carneiro, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Sabine, Caron, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Antoine, Carpentier, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Elise, Carré, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Isabelle, Carrie, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Pascaline, Cassagnaud, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Françoise, Cattin, Memory Resource and Research Centre of Besançon, Besançon, France
Valérie, Causse-Lemercier, Laboratoire d'Imagerie Biomédicale, Sorbonne Universités, UPMC Univ Paris 06, Inserm U 1146, CNRS UMR 7371, F-75006 Paris, France
NeuroSpin, I2BM, Commissariat à l'Energie Atomique, France
Anne, Cavey, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Matthieu, Chabel, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Ludivine, Chamard, Memory Resource and Research Centre of Besançon, Besançon, France
Stéphane, Chanalet, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Thierry, Chaptal, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France
Annik, Charnallet, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Hélène, Chartrel, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France
Mathieu, Chastan, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France
Rose-May, Chaudat, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Sophie, Chauvelier, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Valérie, Chauvire, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France
Samia, Cheriet, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Sylvie, Chiron, Memory Resource and Research Centre of Colmar, Colmar, France
Gilles, Chopard, Memory Resource and Research Centre of Besançon, Besançon, France
Emilie, Chrétien, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Dominique, Clamens, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France
Anthony, Clotagatide, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Emmanuel, Cognat, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Lora, Cohen, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France

Olivier, Colliot, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France

Jean-Marc, Constans, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France

Elodie, Cordier, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France

Marie-Hélène, Coste, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France

Jean-Philippe, Cottier, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France

François, Cotton, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France

Pierre, Malick, Coulibaly, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France

Isabelle, Couret, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France

Françoise, Courtin, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France

Olivier-François, Couturier, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France
Marie-Claude, Daudon, Memory Resource and Research Centre of Saint-Etienne,
CHU de Saint-Etienne, Saint-Etienne, France
Francesca, De, Anna, Memory Resource and Research Centre of Marseille, CHU de
Marseille, Marseille, France
Virginie, de, Beco, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Xavier, de, Petigny, Memory Resource and Research Centre of Strasbourg, CHRU de
Strasbourg, Strasbourg, France
Delphine, De, Verbizier-Lonjon, Memory Resource and Research Centre of
Montpellier, CHU de Montpellier, Montpellier, France
Marielle, Decousus, Memory Resource and Research Centre of Saint-Etienne, CHU de
Saint-Etienne, Saint-Etienne, France
Isabelle, Defouilloy, Memory Resource and Research of Amiens, CHU Amiens
Picardie, Amiens, France
Cécile, Delaunay-Bretaut, Memory Resource and Research Centre of Angers, CHU
d’Angers, Angers, France
Xavier, Delbeuck, Memory Resource and Research Centre of Lille, CHRU de Lille,
Lille, France
Melissa, Delhommeau, Memory Resource and Research Centre of Nice, CHU de
Nice, Nice, France
Christine, Delmaire, Memory Resource and Research Centre of Lille, CHRU de Lille,
Lille, France
Floriane, Delphin-Combe, Memory Resource and Research Centre of Lyon, Hospices
Civils de Lyon, Lyon, France
Julien, Delrieu, Memory Resource and Research Centre of Toulouse, CHU de
Toulouse, Toulouse, France
Catherine, Demuyinck, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France

Vincent, Deramecourt, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France

Hervé, Deramond, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France

Virginie, Derenaucourt, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France

Thomas, Desmidt, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France

Marie-Dominique, Desruet, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France

Julien, Detour, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France

Audrey, Deudon, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France

Viviane, Derreux, Coordinating Centre, CIC-1401 Clinical Epidemiology, Administrative Assistant, France

Agnès, Devendeville, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France

Laure, Di, Bitonto, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France

Sally, Dia, Memory Resource and Research Centre of Colmar, Colmar, France

Mira, Didic, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Maritchu, Doireau, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Marie-Thérèse, Dorier, Memory Resource and Research Centre of Besançon, Besançon, France
Antonio, Dos, Santos, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France
Patrice, Douillet, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France
Déborah, Drai, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Foucaud, Du, Boisgueheneuc, Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Poitiers, France
Delphine, Dubail, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Sandrine, Duchez, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Nathalie, Dufay, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Sophie, Dulhoste, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Julien, Dumont, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Julien, Dumurgier, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Mélanie, Dupin, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Diane, Dupuy, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France
Emmanuelle, Durand, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Emmanuelle, Duron, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Inna, Dygai-Cochet, Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Dijon, France
Véronique, Eder, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Emmanuelle, Ehrhard, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Hanane, El, Haouari, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Elise, Enderlin, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Stéphane, Epelbaum, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France
Julie, Erraud, CIC-1401 Clinical Epidemiology, CHU de Bordeaux, Bordeaux, France
Frédérique, Etcharry-Bouyx, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France
Magali, Eyriey, Memory Resource and Research Centre of Colmar, Colmar, France
Daniel, Fagret, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Isabelle, Faillenot, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Catherine, Faisant, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Karim, Farid, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Véronique, Fasquel, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France
Marion, Fatisson, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Denis, Fédérico, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Olivier, Felician, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Philippe, Fernandez, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Sabrina, Ferreira, Memory Resource and Research Centre of Besançon, Besançon, France
Camille, Ferté, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Patrick, Gelé, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France

Emmanuel, Gerardin, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France

Pascale, Gerardin, Memory Resource and Research Centre of Nancy, CHU de Nancy, Nancy, France

Loïc, Gerlier, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France

Claire, Gervais, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France

Jean-Claude, Getenet, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France

Cindy, Giaume, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France

Carole, Girard, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France

Nadine, Girard, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France

Béatrice, Giroz, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France

Chantal, Girtanner, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France

Valérie, Gissot, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France
Rémy, Guillevin, Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Poitiers, France

Anne, Guyard, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France

Jacques, Guyard, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France

Lilia, Habbessi, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France

Sophie, Haffen, Memory Resource and Research Centre of Besançon, Besançon, France

Sarah, Hammami, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France

Didier, Hannequin, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France

Véronique, Hannier, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France

Anne-Marie, Hanser, Memory Resource and Research Centre of Colmar, Colmar, France

Saoussen, Haouas, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France

Anaïs, Heurtebise, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France

Sophie, Hierry, Memory Resource and Research Centre of Colmar, Colmar, France

Anne, Hitzel, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Claude, Hossein-Foucher, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Fabrice, Hubele, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Sabrina, Iannuzzi, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Danielle, Ibarrola, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Sandrine, Indart, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Agnès, Jacquin-Piques, Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Dijon, France
Sophie, Jaeger, Memory Resource and Research Centre of Colmar, Colmar, France
Séverine, Jallier, Coordinating Centre, CIC-1401 Clinical Epidemiology, Bordeaux, France
Betty, Jean, Memory Resource and Research Centre of Clermont-Ferrand, CHU de Clermont-Ferrand, Clermont-Ferrand, France
Joanne, Jenn, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Laure, Joly, Memory Resource and Research Centre of Nancy, CHU de Nancy, Nancy, France
Thérèse, Jonveaux, Memory Resource and Research Centre of Nancy, CHU de Nancy, Nancy, France
Séverine, Jourdain, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France
Adrien, Julian, Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Poitiers, France
Barbara, Jung, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Alexandra, Juphard, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Nora, Karaoun, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Anisse, Karoun, CIC-1401 Clinical Epidemiology, CHU de Bordeaux, Bordeaux, France
Aurélie, Kas, Laboratoire d'Imagerie Biomédicale, Sorbonne Universités, UPMC Univ Paris 06, Inserm U 1146, CNRS UMR 7371, F-75006 Paris, France NeuroSpin, I2BM, Commissariat à l'Energie Atomique, France
Anna, Kearney-Schwartz, Memory Resource and Research Centre of Nancy, CHU de Nancy, Nancy, France
Sandrine, Keignart, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Antony, Kelly, Memory Resource and Research Centre of Clermont-Ferrand, CHU de Clermont-Ferrand, Clermont-Ferrand, France
Anne, Klebaur, Memory Resource and Research Centre of Colmar, Colmar, France
Catherine, Kleitz, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Lejla, Koric, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Alexandre, Krainik, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Stéphane, Kremer, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Florian, Labourée, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Franck, Lacoeuille, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France
Valérie, Lafont, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Marie-Claude, Lagneau, Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Dijon, France
Sophie, Lagouarde, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Francoise, Lala, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Frédéric, Lamare, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Sophie, Lamarque, CIC-1401 Clinical Epidemiology, CHU de Bordeaux, Bordeaux, France
Franck, Lamberton, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Chantal, Lamy, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France
Pauline, Lapalus, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Jean-Louis, Laplanche, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Delphine, Lassus-Sangosse, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Caroline, Latger-Florence, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Cyrille, Launay, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France
Caroline, Laurent, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Mathilde, Laye, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Didier, Le, Bars, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Séverine, Le, Dily, Memory Resource and Research Centre of Nantes, CHU de Nantes, Nantes, France
Liliane, Le, Guay, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Lisa, Le, Scouarnec, CIC-1401 Clinical Epidemiology, CHU de Bordeaux, Bordeaux, France
Isabelle, Le, Taillandier, de, Gabory, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Emmanuelle, Lebars, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France
Cécile, Lebrun-Givois, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Eugénie, Leclerc, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Jihyun, Lee, Roy, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Jean-François, Legrand, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Stéphane, Lehericy, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France
Sylvain, Lehmann, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France
Mathieu, Leininger, Memory Resource and Research Centre of Nancy, CHU de Nancy, Nancy, France
Justine, Lemaire, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Hermine, Lenoir, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Marylin, Leny, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Elsa, Leone, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Mélanie, Leroy, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France

Mylène, Lesage, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France

Marcel, Levy, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France

Stéphanie, Libercier, Memory Resource and Research Centre of Colmar, Colmar, France

Julie, Lidier, CIC-1401 Clinical Epidemiology, CHU de Bordeaux, Bordeaux, France

Nadine, Longato, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France

Paulo, Loureiro, de, Sousa, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France

Marie, Luce, Royère, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France

Juliette, Ly, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France

Marie-Anne, Mackowiak-Cordoliani, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France

Eloi, Magnin, Memory Resource and Research Centre of Besançon, Besançon, France
Serge, Maia, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France
Didier, Maillet, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Zaza, Makaroff, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Oldès, Mansour, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Athina, Marantidou, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Isabelle, Marcet, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Olivier, Marcy, CIC-1401 Clinical Epidemiology, CHU de Bordeaux, Bordeaux, France
Cécilia, Marelli, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France
Sophie, Marilier, Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Dijon, France
Fanny, Marmet, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Laurent, Marquine, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Corinne, Marrer, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Idalie, Martin, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Sandrine, Martin, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France
Olivier, Martinaud, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France
Catherine, Martin-Hunyadi, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Isabelle, Mathieu, Memory Resource and Research Centre of Colmar, Colmar, France
Fabien, Maurel, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Sylvie, Maymon, Memory Resource and Research Centre of Colmar, Colmar, France
Joachim, Mazère, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Aïcha, Medjoul, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Isabelle, Meiss, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Aurélie, Méozoone, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Isabelle, Merlet, Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Poitiers, France
Catherine, Mertz, Memory Resource and Research Centre of Besançon, Besançon, France
Danielle, Mestas, Memory Resource and Research Centre of Clermont-Ferrand, CHU de Clermont-Ferrand, Clermont-Ferrand, France
Catherine, Metzger, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Sabine, Meurrens, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Marc-Etienne, Meyer, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France
Jean-Marc, Michel, Memory Resource and Research Centre of Colmar, Colmar, France
Agnès, Michon, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France
Isabelle, Migeon-Duballet, Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Poitiers, France
Carole, Miguet-Alfonsi, Memory Resource and Research Centre of Besançon, Besançon, France
Karl, Mondon, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France
Laëtitia, Monjoin, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Pascale, Morel, Memory Resource and Research Centre of Colmar, Colmar, France
Sébastien, Moreno, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Clément, Morgat, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Charline, Morillon, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France
Nicolas, Noiret, Memory Resource and Research Centre of Besançon, Besançon, France
Fati, Nourhashemi, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Francis, Nyasse, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France
Estelle, Occelli, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Hélène, Oesterle, Memory Resource and Research Centre of Colmar, Colmar, France
Justine, Oosterlinck, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Claudie, Ornon, Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Poitiers, France
Galdric, Orvoen, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Pierre, Jean, Ousset, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Anne, Pachart, Memory Resource and Research Centre of Colmar, Colmar, France
Florian, Palabaud, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Juliette, Palisson, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Amandine, Pallardy, Memory Resource and Research Centre of Nantes, CHU de Nantes, Nantes, France
Sylvie, Papacatzis, Memory Resource and Research Centre of Grenoble, CHU de
Grenoble Alpes, Grenoble, France
Claire, Paquet, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris,
France
Pierre-Yves, Pare, Memory Resource and Research Centre of Angers, CHU d’Angers,
Angers, France
Guillaume, Pariscoat, Memory Resource and Research Centre of Montpellier, CHU de
Montpellier, Montpellier, France
Anne, Pasco, Memory Resource and Research Centre of Angers, CHU d’Angers,
Angers, France
Pierre, Payoux, Memory Resource and Research Centre of Toulouse, CHU de
Toulouse, Toulouse, France
Cécile, Pays, Memory Resource and Research Centre of Montpellier, CHU de
Montpellier, Montpellier, France
Julie, Pelat, Memory Resource and Research Centre of Marseille, CHU de Marseille,
Marseille, France
Katell, Peoch, Phar, Memory Resource and Research Centre of Paris Nord, AP-HP,
Paris, France
Rémy, Perdrisot, Memory Resource and Research Centre of Poitiers, CHU de Poitiers,
Poitiers, France
Raphaël, Pereira, Memory Resource and Research Centre of Lyon, Hospices Civils de
Lyon, Lyon, France
Bertille, Perin, Memory Resource and Research of Amiens, CHU Amiens Picardie,
Amiens, France
Christine, Perret-Guillaume, Memory Resource and Research Centre of Nancy, CHU de Nancy, Nancy, France
Sophie, Pérusat, Coordinating Centre, CIC-1401 Clinical Epidemiology, Clinical Project Manager, France
Yolande, Petegnief, Memory Resource and Research Centre of Besançon, Besançon, France
Grégory, Petyt, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Lorène, Philibert, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Nathalie, Philippi, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Clélie, Phillipps, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Julie, Piano, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Michèle, Pierre, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Johan, Pietras, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Mélanie, Pigot, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France
Fanny, Pineau, Memory Resource and Research Centre of Colmar, Colmar, France
Geneviève, Pinganaud, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Pierre, Pitet, Memory Resource and Research Centre of Grenoble, CHU de Grenoble, Alpes, Grenoble, France
Matthieu, Plichart, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Catherine, Poisson, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France
Elodie, Pongan, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Gabriel, Pop, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Dorothée, Pouliquen, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France
Cyril, Poupon, Institute of Memory and Alzheimer's Disease (IM2A), France and Brain and Spine Institute (ICM), France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris, France
Stéphane, Pouponneau, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France
Bruno, Pozetto, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Sophie, Pradier, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Thierry, Prangère, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Magali, Prévot, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Evelyne, Provost, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Michèle, Puel, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Mathieu, Queneau, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Muriel, Quillard-Muraine, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France
Valérie, Quipourt, Memory Resource and Research Centre of Dijon, CHU Dijon Bourgogne, Dijon, France
Chloé, Rachez, Memory Resource and Research Centre of Clermont-Ferrand, CHU de Clermont-Ferrand, Clermont-Ferrand, France
Aline, Rahnema, Memory Resource and Research Centre of Nancy, CHU de Nancy, Nancy, France
Muriel, Rainfray, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Nadine, Raoux, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Anatta, Razafimanantsoa, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Micheline, Razzouk-Cadet, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Maria, Rego-Lopes, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Solveig, Relland, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Marie, Revillon, Institute of Memory and Alzheimer's Disease (IM2A, France and Brain and Spine Institute (ICM, France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, France
Sylvie, Richard, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Virginie, Richard, Coordinating Centre, CIC-1401 Clinical Epidemiology, Data Manager, France
Eliane, Riera, Memory Resource and Research Centre of Colmar, Colmar, France
Anne-Sophie, Rigaud, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Marie-Claire, Riocreux, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Philippe, Robert, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Hélène, Robin-Ismer, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Laëtitia, Rocher, Memory Resource and Research Centre of Nantes, CHU de Nantes, Nantes, France
Fabienne, Rochette, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Mathieu, Rodallec, Memory Resource and Research Centre of Paris Nord, AP-HP, Paris, France
Yves, Rolland, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Adeline, Rollin-Sillaire, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Fabien, Rondepierre, Memory Resource and Research Centre of Clermont-Ferrand, CHU de Clermont-Ferrand, Clermont-Ferrand, France
Stéphanie, Roseng, Coordinating Centre, CIC-1401 Clinical Epidemiology, Clinical Research Associate, France
Mélanie, Rossitto, Memory Resource and Research Centre of Nancy, CHU de Nancy, Nancy, France
Caroline, Roubaud, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Isabelle, Rouch, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Olivier, Roulant, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Martine, Roussel, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France
Annie, Routier, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France
Julie, Roux, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Perrine, Roy, Institute of Memory and Alzheimer's Disease (IM2A, France and Brain and Spine Institute (ICM, France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, France
Séverine, Roy, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Ilham, Ryff, Memory Resource and Research Centre of Besançon, Besançon, France
Guillaume, Sacco, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Djamel, Saidi, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Anne-Sophie, Salabert, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
François, Salmon, Memory Resource and Research Centre of Poitiers, CHU de Poitiers, Poitiers, France
Maria-Joao, Santiago-Ribeiro, Memory Resource and Research Centre of Tours, CHRU de Tours, Tours, France
Joëlle, Sapin, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Nadine, Sapin, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Alain, Sarciron, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Nathalie, Sastres, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Amandine, Saubion, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Mathilde, Sauvée, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Sophie, Schahl, Memory Resource and Research Centre of Colmar, Colmar, France
Christian, Scheiber, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Aude, Schlecht, Memory Resource and Research Centre of Colmar, Colmar, France
Anne-Marie, Schneider, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Floraly, Sejalon, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Christian, Sergent, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Amélie, Serra, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Marie-Laure, Seux, Memory Resource and Research Centre of Paris Broca, AP-HP, Paris, France
Romain, Simon, Memory Resource and Research Centre of Angers, CHU d’Angers, Angers, France
Valérie, Simon, Institute of Memory and Alzheimer's Disease (IM2A, France and Brain and Spine Institute (ICM, France UMR S 1127, Department of Neurology, AP-HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, France
Rémi, Sitta, Coordinating Centre, CIC-1401 Clinical Epidemiology, France
Nathalie, Thiery, Coordinating Centre, CIC-1401 Clinical Epidemiology, France
François, Tison, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Hélène, Ton, Van, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Lucie, Toulemonde, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Virginie, Tourbier, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France
Bertrand, Toussaint, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Eve, Tramoni, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Candice, Trocmé, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Irène, Troprès, Memory Resource and Research Centre of Grenoble, CHU de Grenoble Alpes, Grenoble, France
Anne-Cécile, Troussière, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Anne, Turazzi, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Renata, Ursu, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Emilie, Vaillant, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Nathalie, Vayssière, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Pierre, Vera, Memory Resource and Research Centre of Rouen, CHU de Rouen, Rouen, France
Olivier, Vercruysse, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Antoine, Verger, Memory Resource and Research Centre of Nancy, CHU de Nancy, Nancy, France
Maximilien, Vermandel, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Philippe, Viau, Memory Resource and Research Centre of Nice, CHU de Nice, Nice, France
Marie-Neige, Videau, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Jean-Louis, Vincent, Memory Resource and Research Centre of Lille, CHRU de Lille, Lille, France
Vincent, Visneux, Memory Resource and Research Centre of Saint-Etienne, CHU de Saint-Etienne, Saint-Etienne, France
Isabelle, Vivier, Memory Resource and Research Centre of Bordeaux, CHU de Bordeaux, Bordeaux, France
Christelle, Vlaemynck, Memory Resource and Research Centre of Clermont-Ferrand, CHU de Clermont-Ferrand, Clermont-Ferrand, France
Natacha, Vogt, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Thierry, Voisin, Memory Resource and Research Centre of Toulouse, CHU de Toulouse, Toulouse, France
Elodie, Vulliez, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Nathalie, Wagemann, Memory Resource and Research Centre of Nantes, CHU de Nantes, Nantes, France
Caroline, Wagner, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Aziza, Waissi-Sediq, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Sandrine, Wannepain, Memory Resource and Research of Amiens, CHU Amiens Picardie, Amiens, France
Marie-Joséphine, Waryn, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France
Brigitte, Weidmann, Memory Resource and Research Centre of Colmar, Colmar, France
Emilie, Wenish, Memory Resource and Research Centre of Marseille, CHU de Marseille, Marseille, France
Léocadie, Werle, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Gabrielle, Woehrel, Memory Resource and Research Centre of Strasbourg, CHRU de Strasbourg, Strasbourg, France
Jing, Xie, Memory Resource and Research Centre of Lyon, Hospices Civils de Lyon, Lyon, France
Nathanaëlle, Yeni, Laboratoire d'Imagerie Biomédicale, Sorbonne Universités, UPMC Univ Paris 06, Inserm U 1146, CNRS UMR 7371, F-75006 Paris, France NeuroSpin, I2BM, Commissariat à l'Energie Atomique, France
Michel, Zanca, Memory Resource and Research Centre of Montpellier, CHU de Montpellier, Montpellier, France
Rupestre, Zannou, Coordinating Centre, CIC-1401 Clinical Epidemiology, Clinical Research Associate, France
Jean, Zinszner, Memory Clinic of Avicenne, Hôpital Avicenne, Bobigny, France