Cognitive and Brain Profiles Associated with Current Neuroimaging Biomarkers of Preclinical Alzheimer's Disease

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Neuroimaging biomarkers, namely hippocampal volume loss, temporoparietal hypometabolism, and neocortical β -amyloid ($A\beta$) deposition, are included in the recent research criteria for preclinical Alzheimer's disease (AD). However, how to use these biomarkers is still being debated, especially regarding their sequence. Our aim was to characterize the cognitive and brain profiles of elders classified as positive or negative for each biomarker to further our understanding of their use in the preclinical diagnosis of AD. Fifty-four cognitively normal individuals (age = 65.8 ± 8.3 years) underwent neuropsychological tests (structural MRI, FDG-PET, and Florbetapir-PET) and were dichotomized into positive or negative independently for each neuroimaging biomarker. Demographic, neuropsychological, and neuroimaging data were compared between positive and negative subgroups. The MRI-positive subgroup had lower executive performances and mixed patterns of lower volume and metabolism in AD-characteristic regions and in the prefrontal cortex. The FDG-positive subgroup showed only hypometabolism, predominantly in AD-sensitive areas extending to the whole neocortex, compared with the FDG-negative subgroup. The amyloid-positive subgroup was older and included more APOE $\epsilon 4$ carriers compared with the amyloid-negative subgroup. When considering MRI and/or FDG biomarkers together (i.e., the neurodegeneration-positive), there was a trend for an inverse relationship with $A\beta$ deposition such that those with neurodegeneration tended to show less $A\beta$ deposition and the reverse was true as well. Our findings suggest that: (1) MRI and FDG biomarkers provide complementary rather than redundant information and (2) relatively young cognitively normal elders tend to have either neurodegeneration or $A\beta$ deposition, but not both, suggesting additive rather than sequential/causative links between AD neuroimaging biomarkers at this age.

Key words: Alzheimer's disease; amyloid; biomarkers; FDG; MRI; PET

Significance Statement

Neuroimaging biomarkers are included in the recent research criteria for preclinical Alzheimer's disease (AD). However, how to use these biomarkers is still being debated, especially regarding their sequence. Our findings suggest that MRI and FDG-PET biomarkers should be used in combination, offering an additive contribution instead of reflecting the same process of neurodegeneration. Moreover, the present study also challenges the hierarchical use of the neuroimaging biomarkers in preclinical AD because it suggests that the neurodegeneration observed in this population is not due to β -amyloid deposition. Rather, our results suggest that β -amyloid- and tau-related pathological processes may interact but not necessarily appear in a systematic sequence.

Introduction

In 2011, the National Institute on Aging–Alzheimer's Association (NIA-AA) workgroup defined new guidelines criteria for the clinical diagnosis of Alzheimer's disease (AD) (McKhann et al., 2011). These guidelines integrated neuroimaging biomarkers, including MRI-based hippocampal volume, FDG-PET temporoparietal metabolism in typical AD brain regions, and cortical β -amyloid ($A\beta$) deposition detected with PET.

Consistent with the amyloid cascade hypothesis, three stages have been defined for the preclinical phase of AD (Sperling et al., 2011): stage 1 corresponds to the presence of $A\beta$ deposition alone, stage 2 to $A\beta$ deposition with neurodegeneration (low hippocampal volume and/or temporoparietal hypometabolism), and stage 3 to $A\beta$ deposition, neurodegeneration, and subtle cognitive decline. However, evidence for the presence of neurodegeneration without, before, or independently from $A\beta$ deposition (Jagust et al., 2012; Reiman et al., 2012; Jack et al., 2013) has led to reconsideration of this sequential view. Unlike autosomal-dominant AD (Bateman et al., 2012; Fleisher et al., 2015), for which the primary and causal role of $A\beta$ is indisputable (mutations altering $A\beta$ processing lead to dementia with complete penetrance), sporadic AD might be multifactorial. More specifically, $A\beta$ and neurodegeneration may interact but not necessarily appear in a systematic sequence (Small and Duff, 2008; Fjell and Walhovd, 2012; Chételat, 2013a, 2013b). Therefore, alternative scenarios have been proposed in which volume loss and/or hypometabolism may appear independently from, and sometimes before, $A\beta$ deposition even if both processes likely interact to promote the AD neuropathological process (Chételat, 2013a, 2013b). In this context, the way to use AD-neuroimaging biomarkers remains unclear (Sperling et al., 2011; Dubois et al., 2014).

The aim of this study was to characterize the neuroimaging and cognitive profiles of cognitively normal elders selected based on each neuroimaging biomarker to further our understanding of their use in the preclinical diagnosis of AD.

Materials and Methods

Participants

Fifty-four healthy elderly (HE) subjects between 50 and 84 years of age (mean $\pm$ SD = 65.8 $\pm$ 8.3) from the IMAP (Multimodal Imaging of Early-Stage Alzheimer's Disease) project (La Joie et al., 2012; Arenaza-Urquijo et al., 2013; Mevel et al., 2013) recruited from the community were included in this study. All individuals were screened by a neuropsychologist (S.E.) who administered a standardized battery of neuropsychological tests assessing multiple domains of cognition (verbal and visual episodic memory, semantic memory, language skills, executive functions, visuospatial functions, and praxis; see below). Performances were carefully reviewed and compared with age-adjusted (and, when available, sex- and education-adjusted) references; only these individuals with nonpathological performances (>fifth percentile or z-score >

Table 1. Characteristics of the study sample of HEs

N	54
Age, mean $\pm$ SD (min-max)	65.8 $\pm$ 8.3 (50–84)
Female, n (%)	27 (50)
Education level, mean $\pm$ SD	11.7 $\pm$ 3.7
MMSE, mean $\pm$ SD (min-max)	29 $\pm$ 0.9 (27–30)
APOE ϵ 4 carriers, n (%) ^a	15/53 (28)
Cognitive z scores, median (IQR)	
Global	0.08 (–0.6, 0.8)
Verbal memory	–0.03 (–0.6, 0.7)
Visual memory	0 (–0.5, 0.7)
Executive function	0.01 (–0.7, 0.5)
Processing speed	0.05 (–0.8, 0.8)
Semantic memory	–0.1 (–0.6, 0.6)
Total	–0.1 (–0.7, 0.7)

IQR, Interquartile range.

^aAPOE ϵ 4 status was not available for one individual.

–1.65) were included in our study. All participants were right handed, had at least 7 years of education, and had no history of alcoholism, drug abuse, head trauma, or psychiatric disorders. Written informed consent was obtained from all participants. Demographic and clinical characteristics of the sample are summarized in Table 1.

Neuropsychological data

The participants took part in a comprehensive neuropsychological assessment as described in detail previously (Mevel et al., 2013). For all tests, individual scores showing no ceiling or floor effects were z-scored and averaged to compute six individual composite scores: global cognition, verbal episodic memory, visual episodic memory, executive function, processing speed, and semantic memory. Global cognition included the Mini Mental State Examination (MMSE) (Folstein et al., 1975) and the Mattis Dementia Rating scale (Matthis, 1976). The verbal episodic memory score included the immediate and delayed free recalls of the Free and Cued Selective Reminding Test (FCSRT) (Grober, 1987) and of the “encoding, storage, retrieval” paradigm (Eustache et al., 1998; Chételat et al., 2003; Fouquet et al., 2012). The visual episodic memory score included the free recalls from two lists of eight graphic signs, 12 of which were derived from the BEM-144 memory battery (Signoret, 1991). The executive function score was derived from the letter verbal fluency (Lezak, 1995), the digit span test (Wechsler, 1997), the Trail Making Test (TMT; time difference between parts B and A; Arnett James A, 1995), and the Stroop test (Lezak et al., 2004). The processing speed score included the times to perform TMT part A and the color naming part of the Stroop test. The semantic memory score included performances in animal fluency and in a semantic (names) autobiographical memory task (Dritschel et al., 1992; Piolino, 2003). Finally, a total individual summary score was calculated for each subject by averaging the z-scores of the six composite scores.

Neuroimaging data acquisition and preprocessing

All participants performed a high-resolution anatomical T1-weighted MRI, as well as an FDG and a Florbetapir PET scans, within a few days or weeks at the same neuroimaging center (Cyceron, Caen, France).

MRI scans were acquired on a Philips Achieva 3T scanner using a 3D fast-field echo sequence (sagittal; repetition time = 20 ms; echo time = 4.6 ms; flip angle = 10°; 180 slices; slice thickness = 1 mm; field of view = 256 $\times$ 256 mm²; matrix = 256 $\times$ 256). Images were segmented, normalized into the MNI space, and modulated using the VBM5.1 toolbox (<http://dbm.neuro.uni-jena.de>) implemented in Statistical Parametric Mapping SPM5 software (Wellcome Trust Centre for Neuroimaging, London) to obtain standardized maps of gray matter volume corrected for brain size. Resultant images were smoothed using a 10 mm full-width at half-maximum (FWHM) Gaussian kernel.

Both FDG and Florbetapir PET scans were acquired on a GE Healthcare Discovery RX VCT 64 PET-CT device (resolution = 3.76 $\times$ 3.76 $\times$ 4.9 mm; field of view = 157 mm; voxel size = 1.95 $\times$ 1.95 $\times$ 3.27 mm). A transmission scan was performed for attenuation correction before each PET acquisition. For FDG PET, participants were fasted for at least

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Figure 1. Definition of AD-signature ROIs. For MRI (**A**) and FDG (**B**), AD-signature ROIs were derived from the group comparison between independent samples of 23 AD patients versus 106 HEs from the ADNI (including age, sex, years of education, and APOE $\epsilon 4$ status as covariates) using a statistical threshold that allowed us to include only the most representative areas: the hippocampi for volume loss ($p < 0.0001$ FWE, k800) and the posterior cingulate and temporoparietal cortex for hypometabolism ($p < 0.00001$ FWE, k100). The A β AD-signature ROI (**C**) was defined anatomically as described previously (La Joie et al., 2012). All AD-signature ROIs were masked to include only gray matter voxels from the IMAP population of the present study. The corresponding gray matter mask was obtained from the mean across all IMAP participants of the normalized gray matter segments.

6 h and remained in a quiet, dark environment for 30 min before injection of the radiotracer. Fifty minutes after the intravenous injection of 180 MBq of FDG, a 10 min PET acquisition began. For florbetapir PET, a 20 min PET scan was acquired 50 min after the intravenous injection of 4 MBq/kg Florbetapir. FDG and Florbetapir PET images were corrected for partial volume effects (PMOD Technologies), coregistered onto their corresponding MRI, and spatially normalized into the MNI space using the deformation parameters from the MRI VBM procedure described above. Each PET image was then scaled using the cerebellum gray matter mean activity to obtain the standardized uptake value ratio (SUVr) and smoothed using a 12 mm FWHM Gaussian kernel.

Dichotomization of participants based on each neuroimaging biomarker status

For each HE, MRI and FDG biomarker values of volume and metabolism were extracted from specific regions of interest (ROIs) corresponding to the areas of greatest changes in AD (including the hippocampus for MRI and the posterior cingulate and temporoparietal region for FDG) defined from an independent sample [i.e., the Alzheimer's Disease Neuroimaging Initiative (ADNI) database;] and masked to include only gray matter voxels from the IMAP population of the present study (see Fig. 1 for details). For the A β biomarker, we used a binary mask corresponding to the entire gray matter except the cerebellum, occipital and sensory motor cortices, hippocampi, amygdala, and basal nuclei, as described previously (La Joie et al., 2012; Fig. 1).

HEs were then classified as biomarker positive or negative independently for the MRI, FDG, and A β biomarkers. For the MRI and FDG biomarkers, values extracted within the AD-signature ROIs in each HE of the study were adjusted for age. Then, the positivity threshold was defined as the 90th percentile of the biomarker residuals estimated in an independent group of 24 patients from the IMAP project fulfilling clinical criteria for probable AD (McKhann et al., 1984; AD_{IMAP}; 12 females; age = 70 ± 8.4 ; education level = 10.21 ± 3.6 ; MMSE = 20.8 ± 4.3 ; 78% APOE $\epsilon 4$ carriers). HEs with age-adjusted values below the positivity threshold were classified as negative and those above were classified as positive (Fig. 2). Because A β is thought to accumulate around the fifth decade (Morris et al., 2010; Villemagne et al., 2013), the positivity threshold for the A β biomarker was defined as the 90th percentile of the Florbetapir PET values estimated in an independent group of 26 healthy controls age < 50 years from the IMAP project (8 females; age = 31 ± 8.4 ; education level = 13.6 ± 2.5 ; MMSE = 29.4 ± 0.64 ; 29% APOE $\epsilon 4$ carriers), corresponding to a Florbetapir SUVr of 1.005. HEs with values above this threshold were considered positive for the A β biomarker and those below as negative (Fig. 2).

Between-group comparison analyses

First, for each biomarker separately, the positive HEs were compared with their negative counterparts on clinical, cognitive, and neuroimaging data (MRI, FDG-PET, and Florbetapir-PET).

Second, because MRI and FDG biomarkers are sometimes considered together as markers of neurodegeneration (Sperling et al., 2011), the HEs

who were positive for at least one of these two biomarkers (i.e., “the neurodegeneration-positive”) were compared with those negative for both biomarkers (the “neurodegeneration-negative”).

For neuroimaging data, the aim was to assess whether HEs classified according to a specific imaging biomarker (e.g., hippocampal volume) would have alterations elsewhere in the brain for the same imaging modality (i.e., lower volume in brain regions outside the hippocampus) and would have alterations with the other imaging modalities (i.e., hypometabolism and/or A β deposition), especially within AD-specific areas (the AD-signature ROIs).

Statistics

Clinical and neuropsychological analyses. All between-group comparisons were performed using nonparametric Mann–Whitney tests for continuous variables (age, education level, MMSE, and cognitive performances) and proportional χ^2 tests for categorical data (sex and APOE $\epsilon 4$ status). All results were considered significant at $p < 0.05$.

Voxelwise analyses. For each group comparison, voxelwise analyses were performed throughout the whole brain cortex using two sample t tests in SPM5. Voxelwise results were displayed at uncorrected $p < 0.005$ (extent threshold $k = 1600 \text{ mm}^3$) unless otherwise specified.

Results

Each biomarker considered independently

Among the 54 HEs, 26 (48%) were classified as positive for at least one biomarker and 28 (52%) were considered negative for the three biomarkers. Among the positive HEs, 1 was positive for the three biomarkers, 4 for 2 biomarkers (3 for both the MRI and the FDG biomarkers and 1 for both the MRI and the A β biomarkers), and 21 for only one biomarker (7 for the MRI, 8 for the FDG, and 6 for the A β biomarkers).

Clinical and neuropsychological data

As illustrated in Table 2, no difference was found on age, sex, education level, or APOE $\epsilon 4$ status between the positive and the negative HEs when classified based on the MRI or the FDG biomarker. When HEs were classified using the A β biomarker, the positive group was older than the negative one and included significantly more APOE $\epsilon 4$ carriers. Concerning cognitive performances, the MRI-positive HEs showed lower performance in the executive function composite score ($p = 0.024$) compared with the MRI-negative HEs.

Voxelwise analysis

Compared with their negative counterparts, MRI-positive HEs showed significant lower volume in both hippocampi (as expected), but also in frontoinsula, ventromedial, prefrontal, and lateral temporal cortex bilaterally (Fig. 3). They also showed significant hypometabolism in the left parietotemporal area and

Figure 2. Classification of HE into positive or negative for each biomarker. Aligned plots with individual data points for the MRI, FDG, and $A\beta$ biomarkers. Red dotted line in each panel indicates the 90th percentile of the reference sample (AD for MRI and FDG and young controls for $A\beta$) and corresponds to the biomarker positivity threshold. For MRI and FDG biomarkers, all HEs below the red dotted line were considered as positive. For the $A\beta$ biomarker, all HEs above the red dotted line were considered as positive.

the dorsal prefrontal cortex (Fig. 3). There was no significant between-group difference in $A\beta$ load and no difference in the reverse comparisons (i.e., lower volume or metabolism in the negative compared with the positive HEs; data not shown). To further confirm the presence or lack of difference within AD-signature ROIs, complementary analyses were repeated using a very permissive (uncorrected) $p < 0.05$ threshold while restricting the analyses to the AD-signature ROIs to limit the risk of type I (false-positive) errors. The presence of lower hippocampal volume and hypometabolism in AD-signature ROIs in MRI-positive HEs compared with MRI-negative HEs was confirmed (Fig. 3); in addition, the negative HEs tended to show higher $A\beta$ deposition in insular, frontal, and temporal areas (Fig. 4).

When classified on the FDG biomarker, no difference in cortical volume between the positive and negative HEs was found, even in the AD-signature ROIs at $p < 0.05$ (Fig. 5). Significant hypometabolism was found, as expected, in the FDG-positive HEs compared with the negative, predominantly in the in AD-signature ROIs (the PCC and bilateral temporoparietal cortex), but also in frontal areas and extend-

ing almost to the entire cortex (Fig. 5). No difference was found in $A\beta$ load except when using an exploratory $p < 0.05$ threshold in which negative HEs tended to show higher $A\beta$ load compared with positive HEs in frontal, parietal, and posterior temporal areas (Fig. 4).

Finally, except for the expected higher $A\beta$ burden in the $A\beta$ -positive HEs compared with their negative counterparts, no other difference in brain volume or hypometabolism was found, even at a permissive threshold in the AD-signature ROIs (Figs. 4, 6).

Neurodegeneration biomarker

Among the 54 HEs, 20 (37%) were classified as positive for the neurodegeneration biomarker.

Clinical and neuropsychological data

No significant difference was found in any of the demographic, clinical, or neuropsychological variables between the neurodegeneration-negative versus neurodegeneration-positive HEs (Table 2).

Table 2. Characteristics of the HE subsamples dichotomized based on the MRI, FDG, and amyloid biomarkers

Characteristics	MRI biomarker		FDG biomarker		Neurodegeneration biomarker		Amyloid biomarker	
	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
<i>n</i> (%)	42 (78)	12 (22)	42 (78)	12 (22)	34 (63)	20 (37)	46 (85)	8 (15)
Age, mean $\pm$ SD (min-max)	65.5 $\pm$ 8.3 (50–84)	67 $\pm$ 8.6 (54–81)	66 $\pm$ 8.7 (50–84)	65 $\pm$ 7.3 (54–81)	65.9 $\pm$ 9.05 (50–84)	65.6 $\pm$ 7.16 (54–81)	64.5 $\pm$ 8 (50–81)*	73.1 $\pm$ 6.9 (62–84)*
Female, <i>n</i> (%)	19 (45)	8 (67)	22 (52)	5 (42)	16 (47)	11 (55)	21 (46)	6 (75)
Education level, mean $\pm$ SD	12 $\pm$ 3.7	10.8 $\pm$ 3.8	11.8 $\pm$ 3.8	11.4 $\pm$ 3.5	12.1 $\pm$ 3.6	11.1 $\pm$ 3.8	11.9 $\pm$ 3.7	11 $\pm$ 3.7
MMSE, mean $\pm$ SD (min-max)	29 $\pm$ 1 (27–30)	29.1 $\pm$ 0.7 (28–30)	29.1 $\pm$ 0.8 (28–30)	28.8 $\pm$ 1.2 (27–30)	29.1 $\pm$ 0.8 (28–30)	28.9 $\pm$ 1 (27–30)	29 $\pm$ 0.9 (27–30)	29.3 $\pm$ 0.7 (28–30)
APOE ϵ 4 carriers, <i>n</i> (%) ^a	13/41 (32)	2/12 (17)	12/42 (29)	3/11 (27)	11/34 (32)	4/19 (21)	10/45 (22)*	5/8 (63)*
Cognitive domain z-scores, median (IQR)								
Global	−0.07 (−0.6, 0.9)	0.2 (−0.5, 0.6)	−0.07 (−0.6, 0.8)	0.2 (−0.8, 0.7)	−0.06 (−0.53, 0.91)	0.2 (−0.7, 0.6)	0.08 (−0.6, 0.8)	0.08 (−1.3, 0.8)
Verbal memory	−0.04 (−0.8, 0.8)	0.01 (−0.2, 0.4)	−0.03 (−0.5, 0.7)	0.02 (−0.7, 0.9)	−0.1 (−1, 0.7)	0.03 (−0.5, 0.3)	−0.03 (−0.5, 0.8)	−0.1 (−1.1, 0.4)
Visual memory	−0.07 (−0.5, 0.9)	0.1 (−0.4, 0.5)	0.06 (−0.5, 0.7)	−0.07 (−1, 0.8)	−0.06 (−0.5, 0.9)	0 (−0.5, 0.7)	0.12 (−0.5, 0.9)	−0.2 (−0.7, −0.2)
Executive function	0.3 (−0.3, 0.5)*	−0.5 (−1.1, 0.2)*	0 (−0.7, 0.5)	0.05 (−0.7, 0.5)	0.3 (−0.5, 0.8)	−0.1 (−0.8, 0.3)	0.05 (−0.5, 0.5)	−0.7 (−0.8, 0.8)
Processing speed	0.2 (−0.9, 0.8)	−0.1 (−0.7, 0.4)	0.05 (−0.8, 0.8)	0.01 (−1, 0.9)	0.2 (−0.9, 0.8)	−0.1 (−0.7, 0.5)	0.1 (−0.8, 0.8)	−0.5 (−0.8, 0.2)
Semantic memory	−0.1 (−0.6, 0.7)	−0.3 (−0.7, 0.5)	−0.2 (−0.6, 0.8)	−0.03 (−0.6, 0.4)	−0.03 (−0.7, 0.7)	−0.06 (−0.6, 0.15)	−0.06 (−0.6, 0.6)	−0.5 (−0.7, −0.02)
Total	0.06 (−0.6, 0.7)	−0.3 (−0.7, 0.5)	−0.2 (−0.7, 0.7)	0.2 (−0.9, 0.7)	0 (−0.6, 0.9)	−0.18 (−0.6, 0.5)	−0.1 (−0.6, 0.7)	−0.2 (−1, 0.5)

IQR, Interquartile range.

^aAPOE ϵ 4 status was not available for one individual.*Significant difference between positive and negative subgroups ($p < 0.05$).**Whole brain analysis ($p < 0.005$)** **AD-signature ROI analysis ($p < 0.05$)** **Figure 3.** Voxelwise differences between the MRI-negative and positive HE in the expected direction (i.e., higher volume and metabolism and lower A β deposition in negative compared with positive HE). Colorscales (T scores) are adapted to the range of significance for each comparison.**Voxelwise analysis**

The neurodegeneration-positive group showed significantly lower volume in the bilateral hippocampus and lower metabolism in the AD-signature ROIs (bilateral temporoparietal, precuneus, and posterior cingulum cortices) extending bilaterally to the frontal cortex compared with the neurodegeneration-negative group (Fig. 7). No other between-group difference was observed at this threshold. When lowering the threshold in the AD-signature ROIs, the neurodegeneration-positive group showed, as expected, lower volume and metabolism in these ROIs, but no area of higher A β deposition, compared with the negative HEs (Fig. 7). Instead, the neurodegeneration-negative group tended to show higher A β deposition in temporal, temporoparietal, insular, and frontal regions compared with the neurodegeneration-positive HEs (Fig. 4).

Discussion

Our aim was to characterize groups of elders defined based on each biomarker both independently and when combining MRI (hippocampal volume) and/or FDG (posterior cingulate and temporoparietal hypometabolism) biomarkers to highlight their role in early AD diagnosis.

The proportions of HEs who were classified positive for MRI (22%), FDG (22%), or at least one biomarker (48%) in this study are consistent with other cohorts (Jack et al., 2012; Wirth et al., 2013c). Similarly, HEs classified as stage 0 (neurodegeneration-negative, A β -negative 52%) or “SNAP” (suspected non-Alzheimer pathology; i.e., neurodegeneration-positive, A β -negative, 33%; Sperling et al., 2011; Jack et al., 2012) are also close to those reported previously (Jack et al., 2012; Wirth et al., 2013c; Mormino et al., 2014). In

Figure 4. Voxelwise differences restricted to AD-signature regions between the negative and positive HE in the reverse direction (i.e., higher volume and metabolism and lower A β deposition in negative compared with positive HE). Areas of significantly lower volume (left), hypometabolism (middle), and A β deposition (right) in negative compared with positive HEs, classified using the MRI (**A**), FDG (**B**), A β (**C**), and neurodegeneration (**D**) biomarkers. Note that a very permissive threshold ($p < 0.05$, uncorrected) was used in these analyses to detect potential subtle differences; to counterbalance the risk of type I (false positive) errors, analyses were restricted to AD-signature regions (shown on Fig. 1).

Whole brain analysis ($p < 0.005$)

AD-signature ROI analysis ($p < 0.05$)

Figure 5. Voxelwise differences between the FDG-negative and FDG-positive HEs in the expected direction (i.e., higher volume and metabolism and lower A β deposition in negative compared with positive HEs). Colorscales (T scores) are adapted to the range of significance for each comparison.

Whole brain analysis ($p < 0.005$) **AD-signature ROI analysis ($p < 0.05$)**

Figure 6. Voxelwise differences between the $A\beta$ -negative and $A\beta$ -positive HEs in the expected direction (i.e., higher volume and metabolism and lower $A\beta$ deposition in negative compared with positive HE). Colorscales (T scores) are adapted to the range of significance for each comparison.

Whole brain analysis ($p < 0.005$) **AD-signature ROI analysis ($p < 0.05$)**

Figure 7. Voxelwise differences between the neurodegeneration-negative and neurodegeneration-positive HE in the expected direction (i.e., higher volume and metabolism and lower $A\beta$ deposition in negative compared with positive HEs). Colorscales (T scores) are adapted to the range of significance for each comparison.

addition, we found 15% $A\beta$ -positive cases in our sample, which is consistent with the frequency of 10–30% usually reported in HEs (Chételat et al., 2013). Our study also highlight that the individuals detected as positive using one biomarker were mostly different from those detected as positive using another biomarker (only five of the 54 elderly were positive for two biomarkers or more, whereas 21 were positive for one biomarker only). This suggests that the biomarkers are more complementary than redundant and that they may not reflect the same pathological processes.

When assessed voxelwise, the pattern of alteration of a group selected according to one biomarker did not match with that of another biomarker. The comparison between, for example,

FDG-positive versus FDG-negative HEs did not reveal a typical AD-like pattern of decreased volume or increased $A\beta$ deposition. In addition, HEs selected on a particular biomarker in a particular brain region (corresponding to the most altered regions in AD) were not altered only in this specific region. Therefore, lower volume was not restricted to the hippocampus in MRI-positive HEs, but extended to the medial prefrontal and temporal neocortex. The same HEs were also found to show a mixed pattern of hypometabolism including both AD-characteristic (posterior cingulate and temporoparietal) and prefrontal areas. The involvement of the prefrontal cortex is expected in later phases of AD (Nestor et al., 2003) and may be related to non-AD processes

such as normal aging (Kalpouzos et al., 2009) or the behavioral variant of frontotemporal dementia (FTD; Whitwell and Josephs, 2011; Bohnen et al., 2012). Note that the same group also showed lower executive function performance (compared with the MRI-negative HE), which fits both with the involvement of the prefrontal cortex (Stuss and Alexander, 2000; Koechlin and Summerfield, 2007) and the possible involvement of normal aging or FTD, both known to be associated with executive function deficits (Park et al., 2002; Boxer and Boeve, 2007; Jagust, 2013). Overall, the MRI biomarker allows the identification of a mixed population of AD and non-AD etiologies, consistent with the fact that lower hippocampal volume is not specific to AD but is also observed in many other conditions (Geuze et al., 2005; Fotuhi et al., 2012) and that neurodegeneration is a multifactorial process (Barkhof et al., 2007; de Souza et al., 2013). Finally, the MRI-positive HEs were not found to have higher A β deposition than their negative counterparts, which suggests that their lower volume was not specifically due to A β deposition.

With regard to HEs who were classified FDG positive, the voxelwise comparison revealed highly significant hypometabolism, not only, as expected, in the posterior cingulate and temporoparietal regions where it predominated, but also in almost the whole cortex and especially the frontal cortex. This suggests that, in HEs, hypometabolism in AD-typical regions is associated with more global, and especially frontal, hypometabolism, potentially reflecting non-AD-related processes as well. In addition, the FDG-positive HEs did not show higher A β deposition or lower hippocampal volume compared with the FDG-negative HEs (even at $p < 0.05$). This echoes previous reports showing that the reduction of glucose metabolism in AD-sensitive areas is not related to A β deposition (Jagust et al., 2012) and can also be observed in A β -negative cognitively normal elders (Jack et al., 2013; Wirth et al., 2013c). The lack of hippocampal volume loss may appear as surprising because it has been shown that, in AD, part of the posterior cingulate cortex and temporoparietal hypometabolism is due to disconnection from the atrophied hippocampus (Chételat et al., 2008; Villain et al., 2008; Villain et al., 2010). However, this link has been shown to be indirect (i.e., through the cingulum bundle atrophy) and it is thought to be one of the processes underlying hypometabolism, but other mechanisms are likely involved (Chételat et al., 2009).

As mentioned above, the fact that HEs who were classified as FDG-positive and MRI-positive were not the same, together with the fact that they showed distinct profiles of brain alterations, further reinforces the view that these biomarkers reflect at least partly distinct pathological processes and are more complementary than redundant. This finding is consistent with a recent study showing a limited agreement between biomarkers of neurodegeneration (Alexopoulos et al., 2014). Together, this suggests that the neurodegeneration biomarkers should be used in combination because they provide an additive contribution instead of reflecting the same process of neurodegeneration (Chételat, 2013a).

Finally, HEs who were classified as A β -positive were older and more frequently APOE ϵ 4 carriers, which is consistent with the fact that age and APOE ϵ 4 are the strongest predictors of A β deposition (Chételat et al., 2013; Fouquet et al., 2014). In addition, they did not show any evidence of lower volume or metabolism compared with the A β -negative HEs, even when lowering the threshold to $p < 0.05$ in specific AD-signature ROIs. This lack of a direct link between A β deposition and neurodegeneration is consistent with the discrepant reports of previous cross-sectional studies arguing for no, subtle, or complex relationships (Jagust et

al., 2012; Chételat et al., 2013). It might also reflect the fact that A β may induce neurodegeneration with a temporal delay.

The MRI-positive and FDG-positive HEs were grouped together to assess the so-called neurodegeneration-positive HEs described in several previous studies (Jack et al., 2012; Jack et al., 2013; Wirth et al., 2013a; Wirth et al., 2013b) and as indicated in the recommendations for preclinical AD (Sperling et al., 2011).

First, the comparison between neurodegeneration-positive and neurodegeneration-negative HEs revealed that hypometabolism clearly predominates in the former group. This may be related to the fact that hypometabolism is very significant in FDG-positive HEs and that MRI-positive HEs also tend to show hypometabolism in the same AD-sensitive brain areas, so there is a cumulative effects for hypometabolism from both the MRI-positive and FDG-positive HEs.

Second, neurodegeneration-positive HEs did not have higher A β deposition, which, as mentioned above, indicates that neurodegeneration is not due to A β in this group of relatively young cognitively normal elders. Instead, these individuals tended to show lower A β deposition than the neurodegeneration-negative HEs, suggesting that neurodegeneration and A β deposition might be additive rather than sequential. In other words, in our cohort, HEs tended to be positive for either A β or neurodegeneration, but not both. Two independent studies reported that neurodegeneration and A β work synergistically to accelerate cognitive decline in HEs (Wirth et al., 2013b; Mormino et al., 2014). This might explain why individuals with both types of positive biomarkers are rarely found within a group of strictly selected cognitively normal elderly. Alternatively, this might be related to the age of our sample. Jack et al. (2014) reported that the prevalence of individuals positive for both types of biomarkers within cognitively normal elders was low in relatively young elders (1% in 60–64 year olds; 4% in 65–69 year olds) and seriously increased in older individuals (30% in 80–84 year olds; 34% in 85–89 year olds). Our data are consistent with these results because, in our sample (mean age = 65.8), two HEs (4%) were positive for both A β and at least one of the neurodegenerative biomarkers.

The main limitation of the present study is the limited size of some of the subgroups used in the comparison analyses. However, this is partly counterbalanced by the homogeneity and quality of the data because all participants were scanned on the same scanners and all scans were checked one-to-one both before and after preprocessing. Another limitation relevant to the field in general is the lack of standardized methods to determine biomarkers' positivity with regard to both the brain regions and the threshold. We used a methodology that appears to be the most rigorous: selecting the regions of greatest volume loss and hypometabolism in AD using an independent population. Previous studies used similar (Wirth et al., 2013a; Wirth et al., 2013b) or slightly different approaches such as meta-ROIs or "a priori" ROIs based on the literature (Jagust et al., 2009; Landau et al., 2011; Jack et al., 2012), but the regions were always highly comparable to those used in the present study.

Cognitively normal individuals in our cohort of relatively young elders tend to have either neurodegeneration or A β deposition, but not both, suggesting additive effects rather than sequential/causative links between the different biomarkers. Further studies are needed to optimize the use of current neuroimaging biomarkers for the preclinical identification of AD.

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