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# **Imaging biomarkers of neurodegeneration in Alzheimer's disease: distinct contributions of cortical MRI atrophy and FDG-PET hypometabolism**

Running title: Imaging biomarkers of neurodegeneration

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**ABSTRACT:**

Background: Neurodegeneration biomarkers are routinely used in the diagnosis of Alzheimer's disease (AD).

Objective: To evaluate the respective contributions of two neuroimaging biomarkers, structural MRI and <sup>18</sup>FDG-PET, in the assessment of neurodegeneration in AD dementia.

Methods: Patients with mild AD dementia diagnosed based on clinical and cerebrospinal fluid criteria and cognitively healthy subjects, from the Marseille cohort ADage with cognitive, structural MRI and <sup>18</sup>FDG-PET assessments, were included. Extent of atrophy on MRI and of hypometabolism on <sup>18</sup>FDG-PET were individually evaluated in each patient using a voxel-based analysis on whole-brain approach and compared to healthy subjects. Patients were divided in distinct groups according to their atrophy extent on the one hand and to their hypometabolism extent on the other, then, to their imaging profile combining the extent of the two biomarkers.

Results: Fifty-two patients were included. The MMSE score was significantly lower in the "Extensive hypometabolism" group than in the "Limited hypometabolism" group (respectively 19.5/30 versus 23/30). A lower Innotest Amyloid Tau Index was associated with an extensive hypometabolism (p=0.04). There were more patients with low educational level in the "Extensive atrophy" group, while a higher educational level was more found in the "Limited atrophy" group (p=0.005).

Conclusion: <sup>18</sup>FDG-PET hypometabolism extent is associated with the pathological processes and clinical severity of AD, while MRI atrophy seems to be influenced by the cognitive reserve. In the context of mild AD dementia, these two biomarkers of neurodegeneration are thus not interchangeable and require to be considered in combination rather than in isolation.

KEYWORDS: Alzheimer's disease; Dementia; Neuroimaging biomarkers; Magnetic resonance imaging; Positron emission tomography imaging.

## INTRODUCTION

Alzheimer's disease (AD) is the leading cause of neurodegenerative dementia. The NIA-AA criteria distinguish 3 clinical stages of AD: asymptomatic preclinical stage, amnesic Mild Cognitive Impairment (MCI) due to AD and AD dementia [1-4].

According to the new criteria for AD diagnosis, the biomarkers of the pathophysiological process of the disease play an important role in increasing the diagnosis probability [1,4,5].

Biomarkers are currently divided into 3 categories [6]: 1)  $\beta$ -amyloid biomarkers:

cerebrospinal fluid (CSF) levels of amyloid beta-42 peptide ( $A\beta_{42}$ ) and amyloid PET

(Positron Emission Tomography) imaging; 2) Tau biomarkers: CSF levels of phosphorylated

Tau (P-Tau) and Tau PET; 3) neurodegeneration or neuronal injury biomarkers: CSF levels of

total Tau (T-Tau),  $^{18}$ fluorodeoxyglucose fixation on PET ( $^{18}$ FDG-PET) and structural

Magnetic Resonance Imaging (MRI) [6].

CSF concentrations of  $A\beta_{42}$ , T-Tau and P-Tau are used as reference biomarkers in the

diagnosis of AD [7,8]. Indeed, CSF biomarkers of AD, characterized by a decreased  $A\beta_{42}$

level, and increased T-Tau and P-Tau levels, correlate with post-mortem pathological

analyses in AD [9-11]. The level of P-Tau is the most specific biomarker of AD as it reflects

the formation of neurofibrillary tangles [12] while the level of T-Tau reflects a process of

degeneration and active neuronal death [6,13].

Although they are not specific of AD pathology [5], MRI atrophy and  $^{18}$ FDG-PET

hypometabolism are routinely used as AD biomarkers in memory clinics [14-16].  $^{18}$ FDG-PET

reflects brain metabolism by measuring glucose consumption. It allows differentiating AD

patients from healthy subjects with good sensitivity and specificity [17,18], showing a

decrease in  $^{18}$ FDG fixation in the temporoparietal region. MRI, used in T1 anatomical

sequence, reveals grey matter atrophy in the temporal (medial, basal, lateral) and medial parietal lobes, which correlates with histological neurodegeneration. Thus, it evolves with disease progression according to Braak stages [19].

Finally, MRI atrophy and  $^{18}\text{F}$ FDG-PET hypometabolism are temporally associated in the biomarker dynamic model described by Jack et al [20], and are presented as interchangeable, as they both reflect neurodegeneration [5,21,22]. But the question of their real equivalence may be raised. Indeed, some authors have suggested that  $^{18}\text{F}$ FDG-PET may be more sensitive than MRI in the diagnosis of AD [23], while others have found no evidence that  $^{18}\text{F}$ FDG-PET is more sensitive than MRI to the degeneration occurring in preclinical and mild AD [24]. The objective of the study is to evaluate the respective contributions of two neuroimaging biomarkers, structural MRI and  $^{18}\text{F}$ FDG-PET, in assessing neurodegeneration in mild Alzheimer's type dementia patients, diagnosed based on clinical and CSF biomarkers criteria.

The main hypothesis of this paper is that, in a group of AD patients, neurodegeneration could be related to both AD and non-AD processes, and that measures of atrophy on MRI and hypometabolism on  $^{18}\text{F}$ FDG-PET could be proxies of distinct and composite neurodegeneration processes.

## MATERIALS AND METHODS

Patients were enrolled from the Marseille cohort ADAge (PHRC National 2008) in which patients with probable AD according to NIA-AA criteria [1] were included and evaluated between 2008 and 2014. Patients included were at mild dementia stage (Clinical Dementia Rating (CDR) of 1), were symptomatic for one to five years at the time of inclusion, were

aged 45-85 years at disease onset. All were native French speaker and had at least 5 years of formal education. Patients with atypical presentations (primary progressive aphasia, posterior cortical atrophy, behavioural presentation), a sudden onset of cognitive deficits, a history of neurological episodes (stroke, seizure, trauma...), a serious general condition (cancer, diabetes, systemic disease, alcoholism...), fulfilling diagnostic criteria for another neurodegenerative disease, were not included. Patients with a contraindication to MRI or  $^{18}\text{F}$ FDG-PET or presenting with significant vascular lesions on MRI were not included too. Patients were matched for age with healthy control subjects from the ADage cohort.

For each patient, demographic data were collected, including: age at onset, years since onset of disease course, gender and educational level. Global cognitive functions were assessed using the MMSE (Mini-Mental State Evaluation) [25], with a maximal score of 30 points (a low score corresponding to a greater cognitive deficit).

All patients underwent a lumbar puncture to study CSF biomarkers of AD:  $\text{A}\beta_{42}$  ( $\text{N} > 500$  pg/mL), T-Tau ( $\text{N} < 450$  pg/mL), P-Tau ( $\text{N} < 60$  pg/mL). The  $\text{A}\beta_{42}$  / P-Tau ratio ( $\text{A}\beta_{42}/\text{pT}$ ) [26] and the Innostest Amyloid Tau Index (IATI) were calculated. An IATI  $< 0.8$  is suggestive of AD [27].

All patients and control subjects underwent cerebral structural MRI, on a 3T Magnetom Verio MR scanner (Siemens, Erlangen, Germany) and T1-weighted images were obtained with a 3D MPRAGE (magnetization prepared rapid gradient echo) sequence, according to the following parameters: 128 axial slices, slice thickness less than 1.25 mm, 256x256 matrix, repetition time = 1050 ms, echo time = 3.93 ms, inversion time = 310 ms, fractional anisotropy =  $12^\circ$ , passband = 123 Hz/pixel.

Cerebral PET scan was performed in patients and healthy subjects with an integrated PET/CT device (Discovery ST, GE Healthcare, Waukesha, WI) with an axial resolution of 6.2 mm, 47 contiguous transverse sections of the brain of 3.27mm thick. Fluorodeoxyglucose (150 MBq) was injected intravenously at rest, with eyes closed in a calm environment. Image acquisition started 30 minutes after injection for 15 minutes. Images were reconstructed using the ordered subset expectation maximization algorithm with 5 iterations and 32 subsets, and corrected for attenuation by the scanner.

CSF collection, MRI and  $^{18}\text{F}$ FDG-PET were performed over a mean total time interval of 5 months (0.5-28 months).

The research protocol was approved by the local research ethics committee.

#### *Data analysis*

We performed individual analyses of  $^{18}\text{F}$ FDG-PET and MRI images. Images were realigned, reoriented and spatially normalized into the Montreal Neurological Institute space. They were smoothed to 8mm full-width at half-maximum with a Gaussian filter, to obtain images that could be compared to each other with a voxel size equal to 2x2x2 mm.

Extent of atrophy on MRI and hypometabolism on  $^{18}\text{F}$ FDG-PET were assessed for each patient and compared to healthy subjects. A voxel-based comparison on a whole brain approach with a grey matter mask, using SPM12 software, were carried out (Wellcome Department of Cognitive Neurology, University College, London, UK, [fil.ion.ucl.ac.uk/spm](http://fil.ion.ucl.ac.uk/spm)). A two-sample t-test, adjusted for age, was used at the significance threshold of 3.16 T-score, corresponding to a p-value threshold of 0.001 [28], based on a previous study using this data for comparisons of groups [29], and a cluster size greater than 97 voxels for PET images and 34 voxels for MRI images, were considered as significant for the comparison between patients and healthy

subjects. This cluster threshold for SPM(T) maps corresponds to the expected threshold provided by SPM simulations to avoid type II errors. This cluster threshold is derived from the probability density function of cluster size based on the random field theory [30-32]. Cluster that were larger than these threshold values defined extents of hypometabolism and atrophy respectively.

The median was calculated as the value of atrophy or hypometabolism volumes sharing all their values in two equal parts. Limited atrophy was defined by values less than or equal to the median atrophy. Extensive atrophy was defined by values greater than the median atrophy. Limited hypometabolism was defined by values less than or equal to the median hypometabolism. Extensive hypometabolism was defined by values greater than the median hypometabolism. Consequently, patients were divided into two groups according to the extent of atrophy and into two groups according to the extent of hypometabolism. These features were then combined and allowed dividing patients into four groups according to their imaging profile: group 1 (G1): limited atrophy and limited hypometabolism; group 2 (G2): limited atrophy and extensive hypometabolism; group 3 (G3): extensive atrophy and limited hypometabolism; group 4 (G4): extensive atrophy and extensive hypometabolism.

Demographic, global cognitive function and CSF biomarkers features were first compared between the groups divided according the hypometabolism extent, then between the groups divided according to the atrophy extent and finally between the groups of combined profile.

Statistical analyses and graphs were computed with R statistical software [33]. Numerical results are presented as a median (1st-3rd quartiles).

The difference between groups for quantitative variables was analysed using the Kruskal-Wallis non-parametric test, followed by a signed Wilcoxon ranks test adjusted with the Bonferroni method in case of significance. Qualitative variables were compared using a Fisher's exact test. We used non-parametric tests because of sample sizes and normality issue. A p-value  $\leq 0.05$  was considered significant.

## RESULTS

Fifty-two patients (32 women and 20 men) were compared to 52 cognitively healthy control subjects. Characteristics of patients and controls are presented in Table 1. In patients, the following CSF levels of biomarkers were found:  $A\beta_{42} = 377.6$  pg/mL (297.2-437.5), T-Tau = 475.5 pg/mL (354.8-642.5), P-Tau = 101.1 pg/mL (65-108.5), IATI = 0.46 (0.35-0.6), and the  $A\beta_{42}/pT$  ratio was 4 (3-5). The median atrophy and hypometabolism values were respectively  $545 \text{ mm}^3$  (148-1818) and  $2020 \text{ mm}^3$  (337-3,630) in patients.

### • *Analysis according to hypometabolism extent*

The 52 patients were divided into two comparable groups of 26 patients each, according to their hypometabolism extent.

Their demographics, neuropsychological and CSF biomarker values are presented in Table 2.

No significant difference in educational level was observed between both groups ( $p = 0.84$ ).

The MMSE score was significantly lower in the "Extensive hypometabolism" group than in the "Limited hypometabolism" group (respectively 19.5/30 (16.5-22) versus 23/30 (20-25)).

A lower IATI was significantly associated with an extensive hypometabolism ( $p = 0.04$ ).

### • *Analysis according to atrophy extent*

The 52 patients were divided into two comparable groups of 26 patients each, according to their atrophy extent.

There were more patients with a primary education level in the “Extensive atrophy” group, while there were more patients with a higher educational level in the “Limited atrophy” group ( $p = 0.0005$ ).

Intergroup comparisons are presented in Table 3. No significant difference in CSF biomarker levels was observed between both atrophy groups.

- *Combination of atrophy and hypometabolism extents*

The extents of atrophy and hypometabolism were combined and four imaging profiles were individualized (Figure 1) as follows: G1: limited atrophy ( $86 \text{ mm}^3$  [0-286]) and limited hypometabolism ( $168 \text{ mm}^3$  [0-552]) including 17 patients; G2: limited atrophy ( $177 \text{ mm}^3$  [139-367]) and extensive hypometabolism ( $3621 \text{ mm}^3$  [2529-4936]) including 9 patients; G3: extensive atrophy ( $942 \text{ mm}^3$  [633-1224]) and limited hypometabolism ( $850 \text{ mm}^3$  [628-1158]) including 9 patients; and G4: extensive atrophy ( $3332 \text{ mm}^3$  [1370-4549]) and extensive hypometabolism ( $3656 \text{ mm}^3$  [2695-5476]) including 17 patients. Demographics for each group are presented in Table 4.

Patients with a primary education level were mainly in G3 and G4 (Extensive atrophy) while those with a higher educational level were in G1 and G2 (Limited atrophy).

The IATI was significantly higher in G3 than in G4 ( $p = 0.042$ ) (Table 4).

Although differences were not significant between the four groups concerning the other biomarkers, the CSF T-Tau levels tended to be higher in G2 than in the other groups (Table 4). Similarly, the  $A\beta_{42}/pT$  ratio was higher in G3 and lower in G2 (Table 4).

The MMSE scores were not significantly different between the 4 groups ( $p = 0.06$ ). However, they tended to differ between G3 (23/30 [20-24]) and G4 (19/30 [16-22]), the only difference

between these groups being their extent of hypometabolism, with MMSE of G3 similar to that of G1 (23/30 [20-24]) and MMSE of G4 similar to that of G2 (20/30 [18-25]), from which they respectively differed only by their extent of atrophy.

## DISCUSSION

Neurodegeneration imaging data, from a cohort of patients with mild AD, were investigated in an individual analysis of whole-brain MRI grey matter volume atrophy and  $^{18}\text{F}$ FDG-PET volume hypometabolism to be compared to CSF biomarkers of AD.

### • *Hypometabolism on $^{18}\text{F}$ FDG-PET imaging*

In the present study, no correlation was found between hypometabolism and each CSF biomarker taken individually ( $\text{A}\beta_{42}$ , P-Tau and T-Tau), but extensive hypometabolism was associated with a lower IATI, this latter combining levels of  $\text{A}\beta_{42}$  and T-Tau proteins according to the following formula:  $\text{A}\beta_{42} / (240 + 1.18 * \text{Tau})$  [7]. The IATI is correlated with the AD diagnosis. IATI <0.8 has a sensitivity of 95% to diagnose AD compared to other neurodegenerative pathology; IATI > 1.2 eliminates an AD with a specificity of 95% [27].  $^{18}\text{F}$ FDG-PET reflects brain metabolism by measuring glucose consumption by cortical neurons, that is an index of synaptic function and density. Previous studies have shown correlations between the typical hypometabolism pattern of AD and a high CSF level of P-Tau and T-Tau in MCI patients [34], at the moderate dementia stage of AD [35], and in patients at risk of AD with a memory complaint [36]. Jagust et al have found an association between  $^{18}\text{F}$ FDG hypometabolism and the CSF  $\text{A}\beta_{42}$  level [37]. Some imaging studies have identified a strong inverse correlation between the glucose metabolism on  $^{18}\text{F}$ FDG-PET and the amyloid load on PET in AD-specific areas such as the precuneus and parietal regions at the dementia stage

[38], whereas others have found a lack of correlation or a low correlation between  $^{18}\text{F}$ FDG-PET and Amyloid PET levels [36]. No correlation was found at the MCI stage [38].

Conversely, correlations between focal hypometabolism on  $^{18}\text{F}$ FDG-PET and the retention of Tau PET ligand in areas of interest (usually clinically affected areas) have been found at baseline in several studies [39-41]. However, a longitudinal study [42] has shown that there was no change in Tau PET imaging between baseline and the follow-up, while hypometabolism was significantly decreased on  $^{18}\text{F}$ FDG-PET. The relationship between FDG-PET and imaging disease biomarkers remains therefore to be fully defined.

Nevertheless, based on AD biomarkers in the CSF,  $^{18}\text{F}$ FDG hypometabolism could be a good proxy for AD pathological processes.

Moreover, we found that the hypometabolism extent was associated with lower MMSE score, indicating a greater cognitive impairment when the hypometabolism extent was larger. This finding is consistent with the literature data where a strong relationship has been described between the MMSE score and  $^{18}\text{F}$ FDG hypometabolism measured in averaged regions of interest [37] or in the left temporo-parieto-occipital areas [43]. In AD patients,  $^{18}\text{F}$ FDG-PET hypometabolism is strongly correlated with the clinical severity of the disease which is itself related to the extent of neurodegeneration induced by AD pathology [44,45]. Therefore, in patients with mild AD dementia,  $^{18}\text{F}$ FDG hypometabolism could be a good marker of neurodegeneration directly driven by AD pathological processes.

- *MRI atrophy*

In the present study, we found no statistical correlation between extent of grey matter atrophy on whole-brain MRI and levels of CSF AD biomarkers, and no link between the extent of atrophy and the severity of the cognitive decline. This could be explained by the small size of

our groups. Few studies have investigated the link between the whole brain volume and level of CSF biomarkers [46-48]. In line with our results, Li et al also found no correlation between total grey matter volume and CSF biomarkers levels in an Alzheimer's dementia subgroup [47]. However, two studies have shown an inverse correlation between the total brain volume and CSF levels of T-Tau or P-Tau in very mild-to-mild [46] or severe [48] Alzheimer's dementia.

An alternative hypothesis could be that the whole grey matter brain volume could be influenced by other factors than AD pathological processes. Chetelat et al found a significantly larger brain volume on MRI in healthy subjects and a greater atrophy in MCI or subject with dementia, for the same amyloid deposition level (high deposition) [49]. Thus, atrophy could be dependent on a mechanism other than amyloidopathy and a larger grey matter volume could preserve from cognitive disorder onset [49]. Otherwise, several studies have reported an association between atrophy and educational level [50-54].

Education can act through a passive brain reserve mechanism related to the cortical brain volume. Indeed, in cognitively healthy subjects, a high educational level (secondary or higher) was significantly associated with a larger whole brain volume than a low educational level (short period of schooling) [50].

Conversely, in Alzheimer's dementia patients, the volume of cortical atrophy is more severe in patients with a high educational level than in less educated patients, for a similar cognitive deficit level in the whole brain evaluation [54] or in more AD-specific cerebral regions [51-54]. Indeed, in patients with a greater cognitive reserve, atrophy is tolerated for much longer in the absence of cognitive disorder expression, as if these patients could better cope with pathological changes in the brain through compensatory mechanisms (more synapses that

remain available or more efficient recruitment of alternative brain networks) [55-57], according to the active cognitive reserve hypothesis [56].

In the present study, the extent of the cortical atrophy volume also appeared to be dependent on the initial education level but, unlike volume of local atrophy, the cortical atrophy was less extended in subjects with a high educational level than in subjects with lower educational levels, as opposed to the hypometabolism volume for which this difference was not found in this study. Thus, in patients with mild AD dementia, cortical atrophy could not only be a marker of AD-induced neurodegeneration but also be strongly related to premorbid factors such as the cognitive reserve.

Conversely, there was no evidence of relationship between hypometabolism extent and the different educational levels in this study. However, others have found that in cognitively asymptomatic AD patients [58], in prodromal AD patients [59] or in AD mild dementia [60], hypometabolism was more marked in patients with a higher educational level as they could compensate for this deficit for a longer period through the use of their cognitive reserve. This discrepancy could be explained by the fact that patients of our study were more severe than in the above-mentioned studies, and had a lower MMSE. It could also be explained by the fact that these papers have used a different methodology: our study investigated the hypometabolism extent while the other two studies have focused on the severity of hypometabolism.”

- *Combination of hypometabolism and atrophy extents*

The Jack et al’s hypothetical model of dynamic AD biomarkers showed that the FDG functional imaging was able to detect the earlier phases of neuronal dysfunction that precede structural atrophy at the MCI stage [61]. Thus, earlier changes in PET metabolism than in

MRI atrophy can predict AD dementia conversion in MCI patients [62]. Moreover, our study showed that, at the later stage of dementia, when the curves converged in Jack's model, <sup>18</sup>F-DG-PET also had an additional interest that was independent of MRI.

Indeed, our results suggest that at the mild dementia stage, whole brain atrophy and hypometabolism extents are not “interchangeable” and could be proxies of distinct and composite processes leading to neurodegeneration.

In this line, some authors have previously observed discrepancies between hypometabolic/hypoperfused and atrophic regions, in AD. Thus, medial temporal areas showed greater grey matter atrophy than hypometabolism, whereas posterior cingulate gyri, precuneus and associative parietal cortex showed more hypometabolism than atrophy [63,64]. This suggests that there might be different underlying mechanisms and different sequences between atrophy and hypometabolism, in different brain regions [65]. Several studies have shown that combining PET and MRI imaging using various methods provides a better diagnosis of AD than each technique used separately [64,66,67]. Our results provide interesting information on the respective contributions of both neuroimaging methods in the assessment of patients with mild AD dementia.

The “extensive atrophy - limited hypometabolism” group was the group in which CSF biomarkers were the less pathological, with an A $\beta$ <sub>42</sub> level decrease, a T-Tau and P-Tau levels increase that were less marked, and a higher IATI. Conversely, the “limited atrophy - extensive hypometabolism” group was the group in which the underlying pathological activity was the most marked. In patients with clinical AD dementia, a combined analysis of whole brain atrophy and hypometabolism volumes might be a better marker of neurodegeneration, integrating the effects of both premorbid factors such as the cognitive reserve and specific AD pathological processes.

- *Study limitations*

The major limitation of this study is the small sample size in each group, especially in those with combined imaging profiles, which could explain the non-significant differences observed.

Furthermore, control subjects had a higher educational level than patients, and thus possibly a larger cerebral volume. This initial difference could explain a more extensive atrophy volume in patients with a lower educational level.

Finally, the analysis of metabolism was not corrected according to atrophy which could have overestimated metabolic deficits. However, as the groups were defined according to the extent of atrophy, we hypothesized that this effect was relatively equivalent within groups and between groups of equivalent extent of atrophy.

- *Conclusion*

The  $^{18}\text{F}$ FDG-PET hypometabolism extent is associated with AD pathological processes and clinical severity, while atrophy as assessed by MRI seems to be influenced by the cognitive reserve. In the context of AD at the mild dementia stage, these two biomarkers of neurodegeneration do not seem interchangeable, but should rather be considered in combination. The most favourable association was observed when atrophy was limited and hypometabolism was extended.

Further studies are needed to confirm these assumptions in a larger sample of dementia patients, but also in earlier-stage AD patients, in order to determine the respective contributions of neurodegenerative biomarkers in the prodromal stages of the disease.

## CONFLICT OF INTEREST

Mathieu Ceccaldi occasionally received expertise honoraria from Lilly, GE Healthcare and Piramal Imaging GmbH.

Eric Guedj occasionally received expertise honoraria from Lilly, GE Healthcare and Piramal Imaging GmbH.

The other authors have no conflict of interest to report.

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## TABLES

**Table 1: Patient and healthy control demographic and neuropsychological characteristics**

	Patients	Controls
Age at inclusion (in years) **	70 (61-77)	70 (61-75)
Age at onset (in years) **	68 (58-74)	-
Gender (female) *	32 (61.5%)	35 (67.3%)
Gender (male) *	20 (38.5%)	17 (32.7%)
Disease duration (in years) **	3 (2-4)	-
Formal education (in years) **	9.5 (7-12)	12 (11-15)
MMSE score (/30) **	22 (18-24)	29 (29-30)

\*: in number of individuals (%)

\*\*: median (1st-3rd quartiles)

**Table 2: Demographics, clinical and biological features according to the extent of hypometabolism (on <sup>18</sup>FDG-PET)**

	Limited hypometabolism	Extensive hypometabolism	p-value
<i>Demographics</i>			
Age at onset (in years) **	70.5 (59.25-75.5)	67 (57-73)	0.43 ☒
Gender (female) *	18 (69.2)	14 (53.8)	0.39 ☒☒
Gender (male) *	8 (30.8)	12 (46.2)	
Disease duration (in years) **	2.5 (2-4)	3 (2-4)	0.94 ☒
Formal education (in years) **	10.5 (7.5-12)	9 (7-12)	0.51 ☒
- primary *	3 (11.5)	4 (15.4)	0.84 ☒☒
- secondary *	17 (65.4)	18 (69.2)	
- higher *	6 (23.1)	4 (15.4)	
<i>General neuropsychological evaluation</i>			
MMSE score (/30) **	23 (20-25)	19.5 (16.5-22)	0.02 ☒
<i>CSF Biomarkers</i>			
CSF level of A $\beta$ <sub>42</sub> (in pg/mL)**	396 (315.25-451.75)	336 (293.75-420.5)	0.22 ☒
CSF level of T-Tau (in pg/mL)**	468.5 (348.25-566.75)	517 (374.25-739.75)	0.34 ☒
CSF level of P-Tau (in pg/mL)**	80.5 (65.25-99.5)	93 (65.75-121.5)	0.17 ☒
CSF A $\beta$ <sub>42</sub> /pT ratio **	4 (3.25-6)	3.5 (2-5)	0.07 ☒
CSF IATI **	0.48 (0.40-0.66)	0.41 (0.27-0.56)	0.04 ☒

Limited hypometabolism group (corresponds to hypometabolism values less than or equal to the median hypometabolism, 2020 mm<sup>3</sup>)

Extensive hypometabolism group (corresponds to hypometabolism values greater than the median hypometabolism, 2020 mm<sup>3</sup>)

\*: in number of individuals (%)

\*\* : median (1st-3rd quartiles)

☒: Kruskal-Wallis test (significant when p <0.05)

☒☒: Fisher's exact test (significant when p <0.05)

**Table 3: Demographics, clinical and biological features according to the extent of atrophy (on MRI)**

	Limited atrophy	Extensive atrophy	p- value	
<i>Demographics</i>				
Age at onset (in years) **	67.5 (58-74)	68.5 (59.25-74.25)	0.96	⊘
Gender (female) *	17 (65.4)	15 (57.7)	0.78	⊘⊘
Gender (male) *	9 (34.6)	11 (42.3)		
Disease duration (in years) **	2 (2-4)	3 (2-4)	0.73	⊘
Formal education (in years) **	11 (7.5-14)	9 (6-12)	0.05	⊘
- primary *	1 (3.8)	6 (23.1)		
- secondary *	16 (61.5)	19 (73.1)	0.0005	⊘⊘
- higher *	9 (34.6)	1 (3.8)		
<i>General neuropsychological evaluation</i>				
MMSE score (/30) **	23 (19-25)	21 (18-23)	0.06	⊘
<i>CSF Biomarkers</i>				
CSF level of Aβ <sub>42</sub> (in pg/mL)**	371.5 (315.25-451.75)	364.5 (287.5-419.75)	0.36	⊘
CSF level of T-Tau (in pg/mL)**	487 (366-645)	447.5 (326.5-632.5)	0.68	⊘
CSF level of P-Tau (in pg/mL)**	87 (69.25-115.75)	80 (63.5-107.25)	0.43	⊘
CSF Aβ <sub>42</sub> /pT ratio **	4 (3-5)	4 (3-5)	0.67	⊘
CSF IATI **	0.46 (0.36-0.60)	0.46 (0.34-0.6)	0.88	⊘

Limited atrophy group (corresponds to atrophy values less than or equal to the median atrophy, 545 mm<sup>3</sup>)

Extensive atrophy group (corresponds to atrophy values greater than the median atrophy, 545 mm<sup>3</sup>)

\*: in number of individuals (%)

\*\* : median (1st-3rd quartiles)

⊘: Kruskal-Wallis test (significant when p <0.05)

⊘⊘: Fisher's exact test (significant when p <0.05)

**Table4: Demographics, clinical and biological and imaging features of patients according to their imaging profile**

	G1	G2	G3	G4	p-value
Patient distribution *	17 (32.7)	9 (17.3)	9 (17.3)	17 (32.7)	
<i>Demographics</i>					
Gender (female) *	11 (64.7)	6 (66.7)	7 (77.8)	8 (47.1)	0.48 $\alpha\alpha$
Gender (male) *	6 (35.3)	3 (33.3)	2 (22.2)	9 (52.9)	
Age at onset (in years) **	71 (64-76)	65 (56-68)	70 (59-72)	68 (61-75)	0.64 $\alpha$
- onset <65 years old *	8 (47.1)	5 (55.6)	4 (44.4)	6 (35.3)	0.77 $\alpha\alpha$
- onset >65 years old *	9 (52.9)	4 (44.4)	5 (55.6)	11 (64.7)	
Disease duration (in years) **	2 (2-4)	2 (1-4)	3 (2-4)	3 (2-4)	0.93 $\alpha$
Formal education (in years) **	11 (9-14)	11 (7-14)	9 (6-12)	9 (6-12)	0.29 $\alpha$
- primary *	1 (5.9)	0 (0)	2 (22.2)	4 (23.5)	
- secondary *	10 (58.8)	6 (66.7)	7 (77.8)	12 (70.6)	0.09 $\alpha\alpha$
- higher *	6 (35.3)	3 (33.3)	0 (0)	1 (5.9)	
<i>General neuropsychological evaluation</i>					
MMSE score (/30) **	23 (20-24)	20 (18-25)	23 (20-24)	19 (16-22)	0.06 $\alpha$
<i>CSF Biomarkers</i>					
CSF level of A $\beta$ <sub>42</sub> (in pg/mL)**	363 (313-442)	380 (327-484)	401 (379-461)	335 (249-400)	0.25 $\alpha$
CSF level of T-Tau (in pg/mL)**	472 (390-514)	662 (307-933)	368 (242-636)	465 (396-622)	0.69 $\alpha$
CSF level of P-Tau (in pg/mL)**	83 (69-100)	106 (86-122)	70 (49-85)	83 (65-108)	0.32 $\alpha$
CSF A $\beta$ <sub>42</sub> /pT ratio **	4 (3-4)	3 (2-5)	5 (4-10)	4 (2-5)	0.12 $\alpha$
CSF IATI **	0.46 (0.37-0.59)	0.42 (0.29-0.68)	0.67 (0.45-0.69)	0.4 (0.26-0.5)	0.04 $\alpha$
<i>Imaging</i>					
Atrophy volume (in mm <sup>3</sup> ) **	86 (0-286)	177 (139-367)	942 (633-1224)	3332 (1370-4549)	4.892E-11 $\alpha$
Hypometabolism volume (in mm <sup>3</sup> ) **	168 (0-552)	3621 (2529-4936)	850 (628-1158)	3656 (2695-5476)	4.892E-11 $\alpha$

G1: limited atrophy-limited hypometabolism; G2: limited atrophy-extensive hypometabolism; G3: extensive atrophy-limited hypometabolism; G4: extensive atrophy-extensive hypometabolism

\*: in number of individuals (%); \*\*: median (1st-3rd quartiles)

α: Kruskal-Wallis test (significant when  $p < 0.05$ )

A signed Wilcoxon ranks test adjusted with the Bonferroni method was used in case of significance in the Kruskal Wallis test:

For atrophy extent: between G3-G1 ( $p=0.00024$ ), between G4-G1 ( $p=0.0000041$ ), between G3-G2 ( $p=0.00025$ ), between G4-G2 ( $p=0.0000038$ ), between G4-G3 ( $p=0.00541$ ).

For hypometabolism extent: between G2-G1 ( $p=0.00023$ ), between G4-G1 ( $p=0.0000039$ ), between G3-G2 ( $p=0.00025$ ), between G4-G3 ( $p=0.0000038$ ).

For IATI: between G2-G1, G3-G1, G4-G1, G3-G2, G4-G2 (not significant); between G4-G3 ( $p=0.042$ )

αα: Fisher's exact test (significant when  $p < 0.05$ )

FIGURES

**Figure 1: Distribution of individuals in the 4 imaging profiles, divided according to the extents of atrophy and hypometabolism**

- G1: limited atrophy and limited hypometabolism (17 patients)
- G2: limited atrophy and extensive hypometabolism (9 patients)
- G3: extensive atrophy and limited hypometabolism (9 patients)
- G4: extensive atrophy and extensive hypometabolism (17 patients)

