

Original Research Article

Comparison between Early-Onset and Late-Onset Alzheimer's Disease Patients with Amnestic Presentation: CSF and ¹⁸F-FDG PET Study

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Key Words

Alzheimer's disease · Early onset · Late onset · Precuneus · Cerebrospinal fluid biomarkers

Abstract

Background/Aims: To investigate the differences in brain glucose consumption between patients with early onset of Alzheimer's disease (EOAD, aged ≤65 years) and patients with late onset of Alzheimer's disease (LOAD, aged >65 years). **Methods:** Differences in brain glucose consumption between the groups have been evaluated by means of Statistical Parametric Mapping version 8, with the use of age, sex, Mini-Mental State Examination and cerebrospinal fluid values of Aβ_{1–42}, phosphorylated Tau and total Tau as covariates in the comparison between EOAD and LOAD. **Results:** As compared to LOAD, EOAD patients showed a significant decrease in glucose consumption in a wide portion of the left parietal lobe (BA7, BA31 and BA40). No significant differences were obtained when subtracting the EOAD from the LOAD group. **Conclusions:** The results of our study show that patients with EOAD show a different metabolic pattern as compared to those with LOAD that mainly involves the left parietal lobe.

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder responsible for progressive cognitive decline and dementia [1, 2]. Although it is generally defined as an age-related disorder, cases with early onset are described [3, 4]. These cases represent the early-onset AD (EOAD) group and are defined by a clinical onset of AD before the age of 65 years. EOAD cases are both familial and sporadic and represent about 10% of all AD cases. EOAD can manifest clinically with nonamnesic symptoms in 25–65% of cases, presenting with language deficits, apraxia and visuospatial functional deficits [5, 6]. Such a presentation often overlaps with frontotemporal degeneration syndromes or with psychiatric conditions, causing great diagnostic delay [7, 8]. Although neuropathological studies showed that EOAD and LOAD have the same features and represent a continuum of the same pathological process, differences between EOAD and LOAD are reported [9, 10]. Indeed, EOAD patients often present (in about half of the cases described in the literature) with atypical neuropsychological symptoms and have an atypical MRI and ¹⁸F-FDG PET imaging pattern, with cortical thickness atrophy and hypometabolism, respectively, of the mesial temporal and parietal lobes (i.e. precuneus, lateral parietal and occipital brain regions) with relative hippocampal sparing, with respect to LOAD, where hippocampi are more involved; in addition, EOAD patients tend to have a more aggressive rate of progression with a shorter duration of the disease than LOAD patients [11–13]. These observations led us to suppose that EOAD might represent a definite clinico-pathological entity, characterized by distinct pathophysiological mechanisms and pathological burden responsible for a faster decline as well as for atypical presentation. Several recent studies have investigated cerebrospinal fluid (CSF) biomarkers of EOAD, focusing on atypical presentations, with controversial results [14]. Although differences do not reach statistical significance, EOAD individuals often show lower CSF A β ₄₂ and very high total Tau (t-Tau) levels, features that are compatible with faster cognitive decline in AD. [¹¹C]-labeled Pittsburgh compound B studies showed greater A β accumulation in posterior cortical areas, indicating a possible vulnerability in these individuals for these regions [15, 16]. However, most of the available data uniquely describe EOAD with atypical presentation, and the radiological and laboratory findings presented in the literature often reflect the asymmetric and focal localization features of EOAD. Data on the amnesic presentation of EOAD are, to our knowledge, not available. Here, we present a CSF analysis and an ¹⁸F-FDG PET study of a subgroup of EOAD patients with a typical amnesic presentation and compare them with a group of LOAD patients with an amnesic presentation.

Materials and Methods

Patients

We examined a total of 84 patients with a diagnosis of probable AD according to the NINCDS-ADRDA criteria [17]. The mean age (\pm SD) of the patients was 69 (\pm 7) years. Based on the age at onset, the patients could be divided into an EOAD (\leq 65 years of age) and an LOAD ($>$ 65 years of age) group. The EOAD group consisted of 23 patients, with a mean age of 64 (\pm 2) years, while 65 patients were in the LOAD group, with a mean age of 76 (\pm 3) years. All patients underwent a complete clinical investigation, including a medical history, neurological examination, Mini-Mental State Examination (MMSE), a complete blood screening (including routine examinations, thyroid hormones, level of vitamin B₁₂), a neuropsychological examination [18], a complete neuropsychiatric evaluation and neuroimaging consisting of magnetic resonance imaging (1.5-tesla MRI). Exclusion criteria were the following: patients with isolated deficits and/or unmodified MMSE (\geq 25/30) on revisit (6,

Table 1. Outline of the AD population examined

	Population (n = 84)	U65 (n = 23)	O65 (n = 61)	p value
Mean age ± SD, years	69±7	60.5±2	76±3	<0.01
MMSE score	18.52±6.481	18.18±7.292	18.65±6.209	0.5466
t-Tau, pg/ml	678.8±322.5	768.9±363	644.9±302.2	0.1118
p-Tau, pg/ml	81.29±47.19	82.70±34.56	80.75±51.40	0.2831
Aβ ₁₋₄₂ , pg/ml	321.2±127.1	300.5±133	329.0±125	0.4281

Table 2. Neuropsychological evaluation of the EOAD and LOAD groups

	EOAD	LOAD	p
MMSE score	18.9±1.3	19.2±0.7	n.s.
Rey Auditory Verbal Learning Test, immediate recall	15.9±1.6	22.5±0.9	0.0032
Rey Auditory Verbal Learning Test, delayed recall	1.57±0.4	2.19±0.3	n.s.
Rey Complex Figure Test, copy	16.35±2.3	17.52±1.3	n.s.
Rey Complex Figure Test, delayed recall	4.34±1.1	7.45±0.7	0.05
Raven's Colored Progressive Matrices	15.8±1.4	20.27±0.7	n.s.
Phonological Word Fluency Test	19.47±2.4	22.15±1.3	n.s.

12 and 18 months of follow-up) and patients with clinically manifest acute stroke in the previous 6 months showing a Hachinski scale score >4 and radiological evidence of subcortical lesions. None of the patients revealed pyramidal and/or extrapyramidal signs at the neurological examination. At the time of enrolment, in the 30 days before participating in this study, none of the patients had been treated with drugs that might have modulated cerebral cortex excitability, such as antidepressants, or any other neuroactive drugs (i.e. benzodiazepines, antiepileptic drugs or neuroleptics), and they had not been treated with cholinesterase inhibitors.

The study was performed according to the Declaration of Helsinki and was approved by the Ethics Committee of the Tor Vergata University in Rome. All AD patients showed a cognitive profile consistent with mild dementia, as assessed by a neuropsychological evaluation including the MMSE and a standardized neuropsychological battery [19]. On the MMSE, AD patients scored a mean of 18.5 ± 6.4, and the Clinical Dementia Rating score was 1.3 ± 1.21. A general overview of the AD population examined is provided in table 1. All participants or their legal guardians gave their written informed consent after receiving extensive information on the study. The Local Ethics Committee approved the study procedures.

Cognitive Evaluation

At the time of enrollment, all recruited patients were administered a neuropsychological battery (table 2) including the following cognitive domains: general cognitive efficiency (MMSE) [20]; verbal episodic long-term memory (Rey Auditory Verbal Learning Test, long-term memory, 15-word list immediate and 15-min delayed recall) [21]; visuospatial abilities and visuospatial episodic long-term memory (Rey Complex Figure Test, copy and 10-min delayed recall) [22]; executive functions (Phonological Word Fluency Test) [19], and analogic reasoning (Raven's Colored Progressive Matrices) [19]. For all tests employed, we used the

Italian normative data for both score adjustment (gender, age and education) and to define cutoff scores of normality, determined as the lower limit of the 95% tolerance interval. For each test, normative data are reported in the corresponding references.

CSF Sampling

In our study, we performed lumbar puncture and CSF sampling to improve the diagnostic accuracy in the AD patients. The first 12 ml of CSF were collected in a polypropylene tube and directly transported to the local laboratory for centrifugation at 2,000 *g* at +4°C for 10 min. The supernatant was pipetted off, gently stirred and mixed to avoid potential gradient effects, and aliquoted in 1-ml portions in polypropylene tubes that were stored at –80°C pending biochemical analyses, without being thawed and re-frozen. In the AD patients, CSF t-Tau and phosphorylated Tau (p-Tau, Thr181) concentrations were determined using a sandwich ELISA (Innotest[®] hTAU-Ag, Innogenetics, Gent, Belgium). CSF Aβ_{1–42} levels were determined using a sandwich ELISA [Innotest β-amyloid(1–42), Innogenetics] specifically constructed to measure Aβ containing both the first and 42nd amino acid, as previously described [23].

Control Group

Fifty-eight chemotherapy-naïve subjects (males, 33; females, 25; mean age, 67 ± 9 years) undergoing an ¹⁸F-FDG PET/CT and found to be completely negative for various diseases were enrolled in the study and served as the control group (CG), as proposed in other previous studies [24]. Of them, 22 (males, 10; females, 12) were under 65 years old (U65) and 36 (females, 11; males, 25) were over 65 years old (O65). Part of them has already been considered in another study published by our group [25]. Before their inclusion in our study, all of them had previously been evaluated for the absence of clinical signs of AD by an experienced neurologist (A.M.), and the MRI, performed 7 ± 2 days before PET/CT examination, was negative for brain injury in all of them.

PET/CT Scanning

The PET/CT system Discovery VCT (GE Medical Systems, Knoxville, Tenn., USA) was used to assess ¹⁸F-FDG brain distribution in all patients by means of a 3-dimensional mode standard technique in a 256 × 256 matrix. Reconstruction was performed using the 3-dimensional reconstruction method of ordered subset expectation maximization with 20 subsets and with 4 iterations. The system combines a high-speed ultra 16-detector row (912 detectors per row) CT unit and a PET scanner with 13,440 bismuth germanate crystals in 24 rings (axial full width at half maximum 1-cm radius, 5.2 mm in the 3-dimensional mode, axial field of view 157 mm). A low-ampere CT scan of the head for attenuation correction (40 mA; 120 Kv) was performed before PET image acquisition.

All the subjects had fasted for at least 6 h before intravenous injection of ¹⁸F-FDG; the dose range administered was 185–210 MBq. After the injection, all the patients lay down in a noiseless and semi-darkened room with their eyes open and without any artificial stimulation. PET/CT acquisition started 30 min after ¹⁸F-FDG injection.

Patients and controls with diabetes, psychiatric disorders, a history of oncologic disease, HIV, epilepsy and surgery, radiation or trauma to the brain were excluded from the study. Patients were not taking any medications. Moreover, we excluded from our study all the patients treated with drugs that could interfere with ¹⁸F-FDG uptake and distribution in the brain [26].

Statistical Analysis

We calculated the mean and SD for age, p-Tau, t-Tau, A β_{1-42} amyloid peptide and MMSE. In order to make sure that the values of the main clinical and CSF parameter examined had a Gaussian distribution, D'Agostino's K squared normality test was applied (where the null hypothesis means that the data are normally distributed). Differences in clinical and CSF parameters between EOAD and LOAD and CG subjects were evaluated by means of the Mann-Whitney U test. Differences in brain ¹⁸F-FDG uptake were analyzed using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB 2012b (Mathworks, Natick, Mass., USA). PET data were subjected to affine and nonlinear spatial normalization into the Montreal Neurological Institute space. The spatially normalized set of images was then smoothed with an 8-mm isotropic Gaussian filter to blur individual variations in gyral anatomy and to increase the signal-to-noise ratio. Images were globally normalized using proportional scaling to remove confounding effects to global cerebral glucose metabolism changes, with a threshold masking of 0.8. The resulting statistical parametric maps (SPM{t}) were transformed into a normal distribution (SPM{z}) unit. Correction of SPM coordinates to match the Talairach coordinates was achieved by the subroutine implemented by Matthew Brett (<http://www.mrc-cbu.cam.ac.uk/Imaging>). Brodmann areas (BAs) were then identified at a range of 0–3 mm from the corrected Talairach coordinates of the SPM output isocenters, after having imported them from the Talairach client (<http://www.talairach.org/index.html>). Thresholds ≤ 0.001 corrected at cluster level were accepted as significant. Only those clusters containing more than 125 ($5 \times 5 \times 5$ voxels, i.e. $11 \times 11 \times 11$ mm) contiguous voxels were accepted as significant, based on the calculation of the partial volume effect resulting from the spatial resolution of the PET camera (about double the full width at half maximum). The following voxel-based comparisons were assessed for AD patients: LOAD versus EOAD and vice versa. As far as the CG is concerned, the following voxel-based comparisons were assessed: O65 versus U65 and vice versa. In the comparison between AD and CG subjects, the following voxel-based comparisons were assessed: LOAD versus O65 and vice versa, and EOAD versus U65 and vice versa. All the comparisons were performed using a 'two-sample t test' design model.

In the SPM maps, we searched the brain areas with a significant correlation using a statistical threshold of $p = 0.001$, familywise error corrected for the problem of multiple comparisons, with an extent threshold of 100 voxels.

With the exception of the comparisons in which a CG was used (in which CSF was not tested), age, sex, MMSE, t-Tau, p-Tau and A β_{1-42} were used as covariates in the SPM analyses.

Results

The values for MMSE, age, p-Tau, t-Tau and A β_{1-42} amyloid peptide were not normally distributed ($p < 0.001$). We did not find statistically significant differences when comparing age, p-Tau, t-Tau, A β_{1-42} amyloid peptide and MMSE in EOAD versus LOAD patients. In particular, the results of the comparisons were: $p > 0.9$ for MMSE; $p = 0.226$ for t-Tau; $p = 0.284$ for p-Tau, and $p = 0.429$ for A β_{1-42} amyloid peptide (fig. 1).

AD Patients (O65 vs. U65 and vice versa)

As compared to LOAD patients, EOAD patients showed a significant decrease in glucose consumption in a wide portion of the left parietal lobe (BA7, BA31 and BA40). No significant differences were obtained when subtracting the EOAD group from the LOAD group (no increased glucose consumption in the LOAD as compared to the EOAD group). Detailed results are provided in table 3 and figure 2.

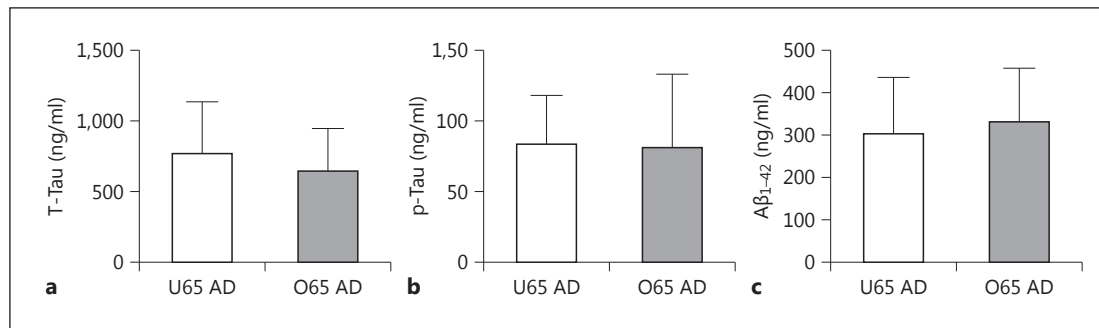


Fig. 1. Box plots of the data in table 1 showing no significant differences in t-Tau (a), p-Tau (b) and Aβ₁₋₄₂ amyloid peptide (c) levels in CSF in LOAD versus EOAD patients.

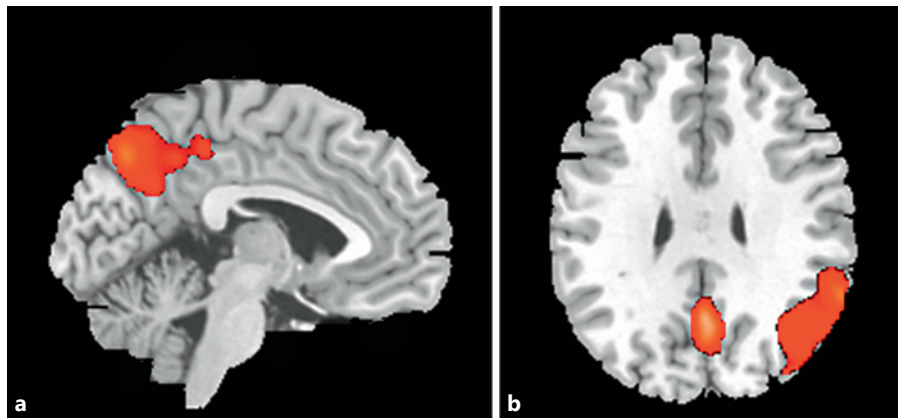


Fig. 2. T1-weighted magnetic resonance superimposition of the data presented in table 2. Comparisons between ¹⁸F-FDG uptake in LOAD patients (n = 61) and that in EOAD patients (n = 23) showing a reduction in cortical glucose consumption in the left precuneus (a, sagittal view) and in the left supramarginal gyrus (b, axial view) in the latter group.

Table 3. Numerical results of SPM comparisons between ¹⁸F-FDG uptake in O65 AD patients (n = 61) and U65 AD patients (n = 23)

Analysis	Cluster level					Voxel level		
	cluster p (FWE-corr)	cluster p (FDR-corr)	cluster extent	cortical region	Z score of maximum	Talairach coordinates	cortical region	BA
O65 – U65	0.000	0.000	14932	L parietal L parietal L parietal	4.83 4.50 4.38	-2, -72, 46 -2, -52, 30 -60, -48, 34	Precuneus Precuneus Supramarginal gyrus	7 31 40
U65 – O65	-	-	-	-	-	-	-	-

In the 'cluster level' section on the left, the number of voxels, the corrected p value of significance and the cortical region where the voxel is found are all reported for each significant cluster. In the 'voxel level' section, all of the coordinates of the correlation sites (with the Z score of the maximum correlation point), the corresponding cortical region and the BA are reported for each significant cluster. In case the maximum correlation is achieved outside the gray matter, the nearest gray matter (within a range of 5 mm) is indicated with the corresponding BA. FWE = Familywise error; FDR = false discovery rate.

Table 4. Numerical results of SPM comparisons between ¹⁸F-FDG uptake in O65 CG subjects (n = 36) and U65 CG subjects (n = 22)

Analysis	Cluster level					Voxel level		
	cluster p (FWE-corr)	cluster p (FDR-corr)	cluster extent	cortical region	Z score of maximum	Talairach coordinates	cortical region	BA
U65 – O65	0.000	0.000	2683	R limbic R limbic	5.84 4.50	2, 30, 22 -2, -52, 30	Anterior cingulate Cingulate gyrus	24 32
O65 – U65	-	-	-	-	-	-	-	-

In the 'cluster level' section on the left, the number of voxels, the corrected p value of significance and the cortical region where the voxel is found are all reported for each significant cluster. In the 'voxel level' section, all of the coordinates of the correlation sites (with the Z score of the maximum correlation point), the corresponding cortical region and the BA are reported for each significant cluster. In the case that the maximum correlation is achieved outside the gray matter, the nearest gray matter (within a range of 5 mm) is indicated with the corresponding BA. FWE = Familywise error; FDR = false discovery rate.

Fig. 3. T1-weighted magnetic resonance superimposition of the CG data presented in table 2. Comparisons between ¹⁸F-FDG uptake in O65 CG subjects (n = 36) and that in U65 CG subjects (n = 22) showing a reduction in cortical glucose consumption in the left anterior cingulate cortex in O65 as compared to U65 subjects.



CG Subjects (O65 vs. U65 and vice versa)

As compared to O65 subjects, U65 subjects did not show any area of decreased glucose consumption. As compared to U65 subjects, O65 subjects showed a reduced glucose consumption in the right cingulate cortex (BA24 and BA32). Detailed results are provided in table 4 and figure 3.

AD versus CG Subjects

As compared to CG subjects with a similar age, LOAD patients showed a significant reduction in glucose consumption in a wide portion of the right parietal lobe (BA7) and the left temporal lobe (BA20 and BA37). No significant differences were obtained when subtracting the O65 LOAD subjects from the LOAD group. As compared to CG subjects with a similar age, the EOAD group showed a significant reduction in glucose consumption in a wide portion of the right parietal lobe (BA7). No significant differences were obtained when subtracting the U65 from the EOAD subjects. Detailed results are provided in tables 5 and 6.

Discussion

In the early phases, AD is mainly characterized by memory dysfunction, except for cases with early onset that present with an atypical neuropsychological profile. Most of the available literature focused on these cases with a typical presentation, describing their neuropsychological

Table 5. Numerical results of SPM comparisons between ¹⁸F-FDG uptake in O65 AD patients (n = 61) and O65 CG subjects (n = 36)

Analysis	Cluster level					Voxel level		
	cluster p (FWE-corr)	cluster p (FDR-corr)	cluster extent	cortical region	Z score of maximum	Talairach coordinates	cortical region	BA
O65 CG – O65 AD	0.000	0.000	12182	R parietal	7.22	12, –58, 36	Precuneus	7
				R parietal	6.95	10, –52, 36	Precuneus	7
				R parietal	6.68	4, –72, 36	Precuneus	7
	0.012	0.009	14460	L temporal	5.58	–60, –36, –20	Inferior temporal gyrus	20
				L temporal	3.24	–44, –56, –12	Fusiform gyrus	37
O65 AD – O65 CG	–	–	–	–	–	–	–	–

In the 'cluster level' section on the left, the number of voxels, the corrected p value of significance and the cortical region where the voxel is found are all reported for each significant cluster. In the 'voxel level' section, all of the coordinates of the correlation sites (with the Z score of the maximum correlation point), the corresponding cortical region and the BA are reported for each significant cluster. In case the maximum correlation is achieved outside the gray matter, the nearest gray matter (within a range of 5 mm) is indicated with the corresponding BA. FWE = Familywise error; FDR = false discovery rate.

Table 6. Numerical results of SPM comparisons between ¹⁸F-FDG uptake in U65 AD patients (n = 23) and U65 CG subjects (n = 22)

Analysis	Cluster level					Voxel level		
	cluster p (FWE-corr)	cluster p (FDR-corr)	cluster extent	cortical region	Z score of maximum	Talairach coordinates	cortical region	BA
U65 CG – U65 AD	0.000	0.000	22089	R parietal	7.93	42, –62, 50	Precuneus	7
				R parietal	7.75	42, –76, 42	Precuneus	19
U65 AD – U65 CG	–	–	–	–	–	–	–	–

In the 'cluster level' section on the left, the number of voxels, the corrected p value of significance and the cortical region where the voxel is found are all reported for each significant cluster. In the 'voxel level' section, all of the coordinates of the correlation sites (with the Z score of the maximum correlation point), the corresponding cortical region and the BA are reported for each significant cluster. In case the maximum correlation is achieved outside the gray matter, the nearest gray matter (within a range of 5 mm) is indicated with the corresponding BA. FWE = Familywise error; FDR = false discovery rate.

logical, biomarker (CSF/PET) and MRI profiles. Here, we studied CSF and ¹⁸F-FDG PET differences between the EOAD and LOAD groups with a typical amnesic presentation. Our results show that EOAD patients with an amnesic presentation show features comparable to those observed in the EOAD group with an atypical presentation, and, moreover, confirm the finding that EOAD CSF and ¹⁸F-FDG PET features differ from LOAD. CSF biomarker analysis showed comparable levels of Aβ_{1–42} and Tau (both total and phosphorylated) between EOAD and LOAD, although t-Tau levels showed higher levels in the EOAD group. These findings are in line with the previous literature [27–29] and indicate that in younger individuals the neurodegenerative process remains dependent on Aβ pathology, shows a stronger intensity of neurodegeneration and likely progresses more rapidly than what is observed in LOAD individuals. Although the t-Tau levels in our group of EOAD patients remained higher than those

found in the LOAD group, the differences did not reach significance, and, unfortunately, we are unable to help solving controversies on CSF differences between EOAD and LOAD [27, 28, 30]. ¹⁸F-FDG PET showed unexpectedly that typical EOAD presents an asymmetric pattern with hypometabolism in the left precuneus (BA7 and BA31) and supramarginal gyrus (BA40), as observed in the description of atypical cases, and with a localization that differs from LOAD. Such findings led us to suppose that the asymmetric localization observed in ¹⁸F-FDG PET is not dependent on the clinical presentation of the cases (typical/atypical), but rather on a regional vulnerability of associative areas of the brain, whose involvement might determine the slower/faster evolution observed in AD cases [30, 31].

The precuneus is a medial parietal lobe region with associative functions. It is highly connected to other cortical regions and also receives innervations from subcortical nuclei like the cholinergic basal forebrain [32]. It has also been shown that the precuneus together with other cortical regions (i.e. medial prefrontal and posterior cingulate cortices, hippocampus) act as a hub region of the rest-active default mode network (DMN). This consists of a specific set of brain areas that decrease activity during the performance of a wide range of tasks, and that are active during the period of rest [33]. The different DMN structures are highly interconnected cortical processing networks involved in tasks like memory, vision, hearing and emotions. Early changes of the DMN were recently described and implicated in the pathogenesis of AD symptoms, where reduced activation of the prefrontal and cingulate cortices and the precuneus appear as reliable markers from the early phases of the disease [34]. Interestingly, reduced activity of the precuneus has been associated with AD variants, with nonamnesic presentation, while in this work we show that also in the amnesic presentation of EOAD patients, the precuneus presents with reduced metabolic activity. Such a finding, on the one hand, strengthens the concept of heterogeneity of presentations in AD, but on the other hand, it indicates that the onset and evolution of the neurodegeneration of AD could be dependent specifically on the site or regional cortical vulnerability or on the specific involvement of DMN nodes. Indeed, both the LOAD and EOAD groups in our study showed focal hypometabolism, although in different cortical regions (left precuneus for the EOAD group and right cingulate cortex for the LOAD group, both considered nodes of the DMN). Apparently, each node has its specific vulnerability and, therefore, shows a different age at onset as well as evolution. Of note, such differences in cortical vulnerability could also be independent of the normal aging process. Aging induces changes in the DMN and may have further deleterious effects on cortical connectivity deconstruction. Thus, precocious cortical deafferentation, due to abnormal A β metabolism or Tau hyperphosphorylation [35], would induce rapid cortical disorganization in regions less involved in memory functions, like the precuneus, and determine the intensity of degeneration as well as the evolution rate (slow/fast) of cognitive deficits, besides a neuropsychological presentation [34, 36, 37]. Such a notion would also help to solve the controversies about CSF biomarkers, showing that differences between the two groups reside in the intensity of neurodegeneration of cortical hubs. Of course this is a suggestive hypothesis, and studies of larger cohorts of patients are needed to deepen our knowledge.

In conclusion, we found that EOAD patients with a typical amnesic presentation show CSF abnormalities with low A β _{1–42} and very high t-Tau levels, though not significantly different from LOAD patients, as well as precuneus hypometabolism. These features are similar to those described in the literature for cases with an atypical presentation, which confirms that EOAD represents a unique clinicopathologic entity. Finally, we suggest that EOAD should be considered as an expression of precocious cortical network hub disorganization. In addition, using CSF biomarkers as a covariate in the SPM analyses, we are also able to evaluate the age factor independently of CSF biomarkers and main cognitive parameters (see the Materials and Methods section). This type of analysis allows demonstrating that 'age at onset of AD' is

a factor related to a peculiar metabolic phenotype of the disease and suggests that in EOAD patients the cortical metabolism in the left precuneus and supramarginal gyrus should be considered carefully in the evaluation of PET images independently of the expected results based on other factors such as CSF biomarkers. In a recently published study performed on a large cohort of AD subjects, it has been shown that an increased amyloid burden in the brain is related to nonselective cortical dysfunction in AD (with a great reduction of brain glucose metabolism being detectable in those patients with low Aβ_{1–42} levels in CSF) [38]. A more selective pattern that mainly involves the cingulate cortex was related to high t-Tau and p-Tau values in CSF. All these areas were not detectable in the comparison between EOAD and LOAD, as shown in table 2. As a last aspect, our study shows an age-related reduction in glucose consumption in the right anterior cingulate cortex in the CG's BA24 and BA32 (table 3). Cerebral glucose metabolism is mainly related to glucose consumption in neural cells due to synaptic activity; hence, the reduced glucose consumption observed is consistent with an age-related, reduced function of BA24 and BA32. Our findings are in agreement with several investigations reporting an age-related reduction in synaptic density or in synaptic count in the human cerebral cortex [39, 40], and such reductions have most consistently been reported in the frontal neocortex [41]. A reduced cortical activity in BA24 and BA32 in O65 as compared to U65 subjects could be explained with an age-related impairment in the working memory process, with this structure being actively involved during memory tasks [42].

A significant limitation of our study is the lack of a dedicated neuropsychological evaluation of this domain in the CG; it will be necessary for future studies to include longitudinal assessments of neuropsychological performance in order to investigate an impairment of those areas where a hypometabolism has been found in elderly as compared to young healthy subjects.

Disclosure Statement

The authors have no conflicts of interest to declare.

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