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ORIGINAL ARTICLE

Clinical and metabolic imaging features of late-onset and early-onset posterior cortical atrophy

Valeria Isella[1,2] | Daniele Licciardo[2,3] | Giulia Nastasi[4] | Valentina Impagnatiello[2,3] | Francesca Ferri[2,3] | Cristina Mapelli[3] | Cinzia Crivellaro[5] | Monica Musarra[5] | Sabrina Morzenti[6] | Ildebrando Appollonio[1,2,3] | Carlo Ferrarese[1,2,3]

[1]Neurology, School of Medicine, University of Milano—Bicocca, Monza, Italy

[2]Milan Center for Neurosciences, NeuroMI, Milan, Italy

[3]Neurology Department, San Gerardo Hospital, Monza, Lombardia, Italy

[4]Neurology Department, ASST of Vimercate, Vimercate, Lombardia, Italy

[5]Nuclear Medicine Unit, San Gerardo Hospital, Monza, Lombardia, Italy

[6]Medical Physics, San Gerardo Hospital, Monza, Lombardia, Italy

Correspondence
Valeria Isella, School of Medicine, University of Milano—Bicocca, Via Cadore 48, 20900 Monza (MB), Italy.
Email: valeria.isella@unimib.it

Abstract

Background and purpose: Late-onset (LO) and early-onset (EO) dementia show neurobiological and clinical differences. Clinical and ^{18}fluoro-deoxy-glucose positron emission tomography (FDG-PET) features of LO and EO posterior cortical atrophy (LO_PCA, EO_PCA), the visual variant of Alzheimer's disease (AD), were compared. LO_PCA patients were also compared with a group of patients with LO typical AD (tAD).

Methods: Thirty-seven LO_PCA patients (onset age ≥ 65 years), 29 EO_PCA patients and 40 tAD patients who all underwent a standard neuropsychological battery were recruited; PCA patients were also assessed for the presence of posterior signs and symptoms. Brain FDG-PET was available in 32 LO_PCA cases, 23 EO_PCA cases and all tAD cases, and their scans were compared with scans from 30 healthy elderly controls. Within the entire PCA sample FDG uptake was also correlated with age at onset as a continuous variable.

Results: The main difference between the two PCA groups was a higher prevalence of Bálint–Holmes symptoms in EO cases, which was associated with the presence of severe bilateral occipito-temporo-parietal hypometabolism, whilst LO_PCA patients showed reduction of FDG uptake mainly in the right posterior regions. The latter group also showed mesial temporal hypometabolism, similarly to the tAD group, although with a right rather than left lateralization. Correlation analysis confirmed the association between older age and decreased limbic metabolism and between younger age and decreased left parietal metabolism.

Conclusions: The major involvement of the temporal cortex in LO cases and of the parietal cortex in EO cases reported previously within the AD spectrum holds true also for the visual variant of AD.

KEYWORDS
Alzheimer's disease, dementia, early-onset Alzheimer's disease, FDG-PET, posterior cortical atrophy

INTRODUCTION

Age at onset (AaO) may have an impact on neural and clinical features of degenerative dementia. Several studies comparing the characteristics of patients with late-onset (LO) or early-onset (EO) Alzheimer's disease (AD) highlighted that LO cases usually show the classical, predominantly amnestic, phenotype, underpinned by prevalent mesial temporal neurodegeneration, whilst EO cases often present atypical, non-amnestic, profiles, associated with prominent parietal or frontal damage and relative sparing of temporo-limbic structures [1-7].

Since a high proportion of patients with PCA show AD pathology, this disorder has been labelled 'the visual variant of AD' [8,9]. In PCA neurodegeneration targets primarily the occipito-temporo-parietal (OTP) regions, leading to early and prominent deficits of visual perception of objects, space and words, and to elements of Bálint–Holmes and Gerstmann syndromes, whilst episodic memory and executive functions, as well as disease insight, are relatively preserved [10-13].

Posterior cortical atrophy more frequently presents in the mid-50s or early 60s, but later onset cases are not rare. A recent study by Suárez-González et al. [14] explored the differential clinical and structural neuroimaging (cortical thickness) features of a large cohort of patients with PCA dichotomized according to the sample median age of onset (58 years) and found a significant influence of AaO on cognitive and atrophy patterns in this form of dementia. EO cases showed a major involvement of the left parietal lobe and of the right OTP intersection associated with worse performance on dominant parietal functions like digit span, calculation and spelling, whilst LO cases showed major atrophy in the anterior cingulate, inferior frontal lobe, and anterior and mesial temporal cortex.

The current study was aimed at investigating further the influence of AaO in PCA by contrasting the clinical and metabolic imaging features of a group of patients with LO_PCA and a group of patients with EO_PCA as well as with a group of patients with typical LO AD (tAD). The following metabolic imaging patterns were therefore expected in our three study groups: extensive OTP hypometabolism in EO_PCA patients with a prevalent parietal focus, classical AD-like temporo-parietal and mesial temporal hypometabolism in tAD patients, and a somewhat in-between pattern in LO_PCA patients characterized by hypometabolism of posterior (perhaps occipital more than parietal) regions but also of temporo-limbic areas. Consistently with this topography of neurodegeneration, more severe impairment of parietal functions in EO_PCA and of memory and occipital functions in LO_PCA were also expected.

METHODS

Subjects

Patients' enrolment was based both on retrospective clinical records review, dating back to September 2010, and on prospective recruitment, conducted from January 2018 to December 2021. Participants met Tang-Wai et al.'s criteria for PCA [11] or met McKhann et al.'s criteria for tAD [9] *and* had an AaO ≥65 years. Briefly, criteria for PCA included early, insidious and progressive disturbances of posterior cognitive functions, and proportionally minor impairment of memory, language, executive functions and behaviour.

Consensus classification criteria for PCA distinguish between PCA-pure and PCA-plus [13]. As our interest was in assessing the effect of AaO in pure PCA, patients with PCA-plus were excluded. Other exclusion criteria were history of stroke, brain injury or other neurological disorders, severe medical conditions, psychiatric disturbances (including major depression), substance abuse, mental insufficiency, or presence of large and/or numerous vascular lesions on brain computed tomography/magnetic resonance imaging scan. Rapidly progressive dementia and a history of ophthalmological disease were additional exclusion criteria. Whilst the only other published report about AaO in PCA [14] used the sample median age (58 years) for separating EO and LO cases, we chose the conventional age cut-point of 65 years for ensuring comparability across studies.

The study was conducted in accordance with the guidelines of the World Medical Association Declaration of Helsinki and approved by our institution's ethics committee, Comitato Etico Brianza.

General neuropsychological assessment

All study participants underwent a battery of standardized neuropsychological tests including the Mini-Mental State Examination (MMSE) [15], Attentional Matrices [16] as a test of selective attention, the Digit Span [17] and Rey Auditory Verbal Learning Test [18] for the assessment of verbal short- and long-term memory, a copy of the Rey–Osterrieth Complex Figure (ROCF) [19] as a task of visuospatial and constructional abilities, Category and Letter Fluency [20] for the evaluation of verbal semantics and lexical retrieval, and the Frontal Assessment Battery [21] and Raven Coloured Progressive Matrices (RCPM) [22] as measures of executive functions. Mood and behaviour were assessed with the Neuropsychiatric Inventory (NPI) [23].

Assessment of posterior functions

In patients with PCA, cognitive complaints indicative of impairment of posterior functions were recorded as present or absent. Complaints classified as 'posterior' were difficulties in 'seeing' objects, recognizing faces, carrying out tasks requiring visuospatial or praxic abilities (e.g., telling the time on an analogue watch, parking, getting dressed), writing, performing calculations, reading and orienting in space.

Level of insight was rated as preserved or impaired based on the medical interview with the patient. Limb apraxia was assessed with the De Renzi Ideomotor Apraxia test [24].

The following posterior deficits were identified through neurological examination and, in some cases, through formal testing, and rated as absent/mild or moderate/severe.

(i) Bálint–Holmes syndrome: simultanagnosia was examined with a complex figure description [25] and with Poppelreuter–Ghent

Overlapping Figures [26], whilst ocular apraxia and optic ataxia were assessed during neurological examination.

(ii) Gerstmann syndrome: acalculia and agraphia were examined with MMSE 7s serial subtraction and writing of a sentence, respectively; left–right disorientation and finger agnosia were assessed during neurological examination.

(iii) Visual agnosia: agnosia for objects was established based on the presence of misrecognitions on complex figure description [25] and confrontation naming [27].

(iv) Visual neglect: neglect was identified with calculation of position preference on RCPM [28], with line bisection [29] or the Bells cancellation test [30], and through inspection of figure copies (ROCF and MMSE pentagons). As a word of caution, PCA may sometimes cause visual field defects [10,12,13], but the visual field was not tested systematically; therefore some cases of lateralized deficit of visual exploration may have been interpreted incorrectly as due to visual neglect.

Statistical analysis

Statistical analysis was performed using SPSS 27.0 (SPSS Statistics for Windows: IBM Corp.).

Comparison of socio-demographic, clinical and neuropsychological features between study groups (LO_PCA vs. EO_PCA and LO_PCA vs. tAD) was performed with Fisher's exact test for categorical variables, whereas for continuous variables Student's *t* test or the one-way analysis of variance with years of schooling as covariate (ANCOVA) was employed. Years of schooling were included as covariate also in partial correlation analysis carried out between AaO and continuous neuropsychological scores within the whole PCA sample. Threshold for significance was set at $p<0.05$, corrected using the Holm–Bonferroni method to control for type I error [31].

Analysis of metabolic images

All brain ^{18}fluoro-deoxy-glucose positron emission tomography (FDG-PET) scans were performed on a General Electric Discovery LS PET/CT scanner, within 6 months from cognitive testing (details about acquisition, preprocessing and analysis are provided in Appendix S1) [32].

Two analyses were performed on PET scans, using Statistical Parametric Mapping (SPM) (https://www.fil.ion.ucl.ac.uk/spm): (i) assessment of the distribution of hypometabolism in the three clinical groups, through comparison of each group's scans with scans from 30 healthy controls using a two-sample *t* test and including age and sex as covariates; (ii) correlation between AaO as continuous variable and FDG uptake within the entire sample of PCA patients using linear regression, with glucose uptake as the dependent variable and including sex as a covariate of no interest.

The significance threshold was set at $p<0.05$ familywise error (FWE) corrected or $p<0.001$ uncorrected, and only clusters with a minimum size of 100 voxels were taken into account.

RESULTS

Study sample

Seventy-two patients with PCA and 46 patients with tAD were identified. Six PCA cases and six tAD cases were excluded due to incomplete neuropsychological data. Thus, the final study sample was composed of 66 PCA patients, 37 LO_PCA and 29 EO_PCA, and 40 tAD patients.

The PCA group had the following socio-demographic and general clinical features: 49 women (74.2%); mean age 67.3 years ± 9.4 (range 41–82); mean AaO 64.9 years ± 9.5 (range 39–80); mean education 8.3 years ± 3.6 (range 5–18); mean disease duration 2.4 years ± 0.9 (range 1.0–4.9); mean MMSE score 20.8 ± 4.4 (range 8–28). As per the selection criteria, LO_PCA patients were significantly older than EO_PCA patients at disease onset and at participation in the study (Table 1). Sex distribution, disease duration and disease severity as measured by MMSE were overlapping, whilst education was significantly higher for EO_PCA patients; thus years of schooling were entered as a covariate when comparisons of the continuous neuropsychological scores were run.

There was no difference between LO_PCA and tAD patients in demographics or disease duration and severity (Table 1).

TABLE 1 General features of the three study groups

	LO_PCA, *n* = 37	EO_PCA, *n* = 29	LO_PCA vs. EO_PCA	tAD, *n* = 40	LO_PCA vs. tAD
Age	74.3 ± 3.7	58.2 ± 6.2	$p<0.0001$	75.6 ± 5.0	n.s.
Age at onset	72.2 ± 3.8	55.5 ± 5.6	$p<0.0001$	72.8 ± 5.2	n.s.
Sex (female)	30, 81.0%	19, 65.5%	n.s.	23, 57.5%	n.s.
Education (years)	6.6 ± 2.8	10.3 ± 3.4	$p<0.0001$	7.5 ± 3.4	n.s.
Disease duration (years)	2.2 ± 0.7	2.6 ± 1.2	n.s.	2.7 ± 1.8	n.s.
MMSE	21.1 ± 4.4	20.4 ± 4.5	n.s.	21.5 ± 2.6	n.s.

Note: Data are presented as mean ± standard deviation except for sex (*n*, %). Comparison of MMSE scores between LO_PCA and EO_PCA groups was covaried for education.

Abbreviations: EO_PCA, early-onset posterior cortical atrophy; LO_PCA, late-onset posterior cortical atrophy; MMSE, Mini-Mental State Examination; n.s., not significant; tAD, typical Alzheimer's disease.

Comparisons of the prevalence of posterior complaints and of average scores on the general neuropsychological battery confirmed that the LO_PCA group more often reported visual complaints (seeing objects) and performed more poorly on the copy of ROCF and on a visually mediated logical reasoning task, that is, RCPM, whilst tAD patients had poorer scores on the Rey Auditory Verbal Learning Test immediate and delayed recalls (Figure 1, Table 2). There were no significant intergroup differences on the Digit Span, Category and Letter Fluency, Frontal Assessment Battery and NPI.

A pathophysiological biomarker, that is, beta-amyloid, total tau and phospho-tau in cerebrospinal fluid or PET with an amyloid tracer, was available in six LO_PCA cases, 19 EO_PCA cases and eight tAD cases, and indicated an amyloidopathy in all cases.

Clinical profiles

On history taking there was a significantly lower proportion of LO_PCA than EO_PCA patients reporting at least one posterior cognitive complaint and, in particular, reporting difficulties with object perception supposedly related to simultanagnosia, whilst all other posterior complaints were equally frequent in the two groups (Figure 1). Conversely, insight was impaired in a higher percentage of LO_PCA (91.9%, 34) than EO_PCA (55.2%, 16) patients ($p < 0.001$).

On the general neuropsychological battery (Table 2) no score was significantly different between the LO_PCA and EO_PCA groups. The NPI total score and subscores were also overlapping.

On neurological examination or formal testing, Bálint–Holmes symptoms were less frequent in the LO_PCA group, whilst Gerstmann syndrome, visual agnosia and visual neglect had the same prevalence in the two groups (Figure 2). (Poppelreuter–Ghent Overlapping Figures was available in 28/37 (75.7%) LO_PCA patients and 12/29 (41.4%) EO_PCA patients (six more EO_PCA patients were unable to complete the test due to severe impairment), confrontation naming was available in 26/37 (70.3%) LO_PCA patients and 23/29 (79.3%) EO_PCA patients, and line bisection or the Bells cancellation test in 27/37 (73.0%) LO_PCA patients and 18/29 (62.1%) EO_PCA patients.)

Correlation analysis performed within the entire PCA sample did not show any significant relationship between AaO and test scores (data not shown).

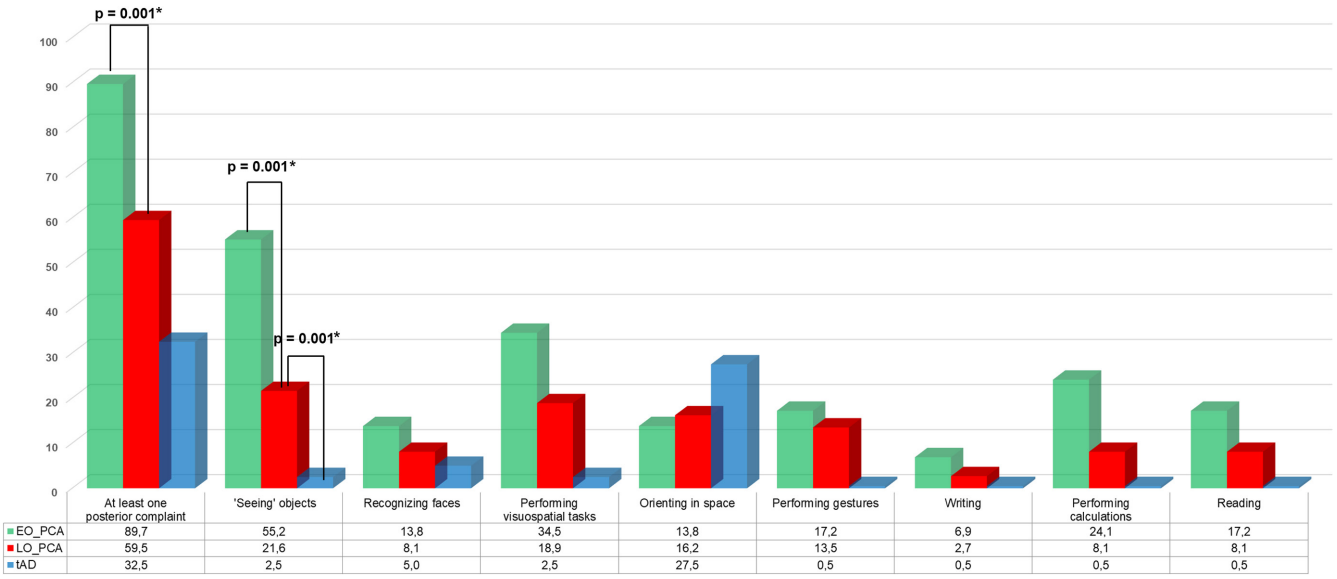
Metabolic imaging patterns

Brain FDG-PET was available for 32/37 LO_PCA patients, 23/29 EO_PCA patients and all tAD patients.

In LO_PCA patients (Figure 3, two top rows) severe hypometabolism was evident bilaterally but was nevertheless strongly asymmetric, with a right hemisphere predominance. The right hypometabolic cluster was centred around the OTP region, extending to the posterior parietal and inferior temporal cortex, on the lateral brain surface, and involved the precuneus, the posterior cingulate and the parahippocampal and hippocampal gyri along the mesial surface. The left hemisphere clusters were more focal and encompassed the precuneus, the angular gyrus and the posterior inferior temporal cortex.

Patients with EO_PCA (Figure 3, middle two rows) showed extensive hypometabolism in the posterior parietal, posterior temporal and occipital lobes bilaterally, with a symmetrical distribution along the lateral surface and with a left hemisphere predominance along the mesial surface.

In patients with tAD (Figure 3, bottom two rows) hypometabolism encompassed the inferior parietal and posterior inferior temporal cortex, with a left hemisphere predominance, and an array of



	At least one posterior complaint	'Seeing' objects	Recognizing faces	Performing visuospatial tasks	Orienting in space	Performing gestures	Writing	Performing calculations	Reading
EO_PCA	89,7	55,2	13,8	34,5	13,8	17,2	6,9	24,1	17,2
LO_PCA	59,5	21,6	8,1	18,9	16,2	13,5	2,7	8,1	8,1
tAD	32,5	2,5	5,0	2,5	27,5	0,5	0,5	0,5	0,5

FIGURE 1 Prevalence of posterior cognitive complaints across the three study groups. *Significant after Holm–Bonferroni correction. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Scores obtained by the three study groups on the general neuropsychological battery (education was included as covariate as appropriate)

		LO_PCA ($n = 37$)		EO_PCA ($n = 29$)		LO_PCA vs. EO_PCA	tAD ($n = 40$)		LO_PCA vs. tAD
	Maximum score	*n*	Score	*n*	Score		*n*	Score	
Attentional Matrices	60	33	29.2 ± 10.2	24	19.9 ± 9.0	n.s.	38	35.3 ± 9.5	n.s.
Digit Span	9	37	4.8 ± 1.0	29	4.1 ± 1.1	n.s.	39	4.5 ± 0.9	n.s.
RAVLT immediate recall	75	35	26.6 ± 8.4	27	22.5 ± 9.8	n.s.	39	18.1 ± 5.5	$p = 0.001^*$
RAVLT delayed recall	15	35	3.5 ± 3.2	27	3.1 ± 3.2	n.s.	39	0.8 ± 1.9	$p = 0.001^*$
Copy of ROCF	36	35	8.4 ± 4.8	28	6.9 ± 7.4	n.s.	38	23.1 ± 6.1	$p = 0.001^*$
Category Fluency	–	36	22.4 ± 7.6	28	22.6 ± 8.9	n.s.	38	22.4 ± 6.0	n.s.
Letter Fluency	–	36	20.2 ± 9.0	28	20.9 ± 12.0	n.s.	38	18.4 ± 7.3	n.s.
Frontal Assessment Battery	18	36	10.6 ± 2.4	29	10.5 ± 4.1	n.s.	38	11.9 ± 2.3	n.s.
RCPM	36	37	13.7 ± 5.5	27	12.0 ± 6.8	n.s.	39	19.3 ± 6.1	$p = 0.001^*$
IMA test (left + right arm)	144	32	108.6 ± 22.7	24	97.7 ± 29.1	n.s.	–	–	–
Neuropsychiatric inventory									
Total score	144	37	11.5 ± 11.9	24	12.8 ± 20.4	n.s.	39	12.5 ± 12.0	n.s.
Delusions	12	37	0.3 ± 0.7	24	0.6 ± 1.9	n.s.	39	0.6 ± 2.1	n.s.
Hallucinations	12	37	0.2 ± 1.1	24	0.0 ± 0.0	n.s.	39	0.1 ± 0.2	n.s.
Agitation/aggression	12	37	0.5 ± 1.2	24	0.8 ± 2.6	n.s.	39	1.2 ± 2.3	n.s.
Depression/dysphoria	12	37	2.4 ± 3.0	24	1.6 ± 2.1	n.s.	39	2.3 ± 3.4	n.s.
Anxiety	12	37	2.7 ± 3.1	24	2.3 ± 3.1	n.s.	39	1.8 ± 3.0	n.s.
Euphoria	12	37	0.1 ± 0.4	24	0.1 ± 0.3	n.s.	39	0.2 ± 0.5	n.s.
Apathy	12	37	1.3 ± 2.2	24	2.5 ± 2.3	n.s.	39	2.9 ± 3.1	n.s.
Disinhibition	12	37	0.2 ± 0.5	24	0.2 ± 0.8	n.s.	39	0.4 ± 1.1	n.s.
Irritability/lability	12	37	0.9 ± 1.5	24	1.4 ± 3.4	n.s.	39	1.6 ± 2.5	n.s.
Aberrant motor behaviour	12	37	0.9 ± 1.9	24	1.0 ± 3.0	n.s.	39	0.9 ± 2.0	n.s.
Sleep	12	37	0.2 ± 0.6	24	0.9 ± 2.8	n.s.	39	0.3 ± 0.8	n.s.
Appetite	12	37	1.9 ± 3.7	24	1.5 ± 3.3	n.s.	39	1.1 ± 2.3	n.s.

Note: Data are presented as mean ± standard deviation. Comparisons between LO_PCA and EO_PCA groups were covaried for education.

Abbreviations: EO_PCA, early-onset posterior cortical atrophy; IMA, ideomotor apraxia; LO_PCA, late-onset posterior cortical atrophy; n.s., not significant; RAVLT, Rey Auditory Verbal Learning Test; RCPM, Raven Coloured Progressive Matrices; ROCF, Rey–Osterrieth Complex Figure; tAD, typical Alzheimer's disease.

*Significant after Holm–Bonferroni correction.

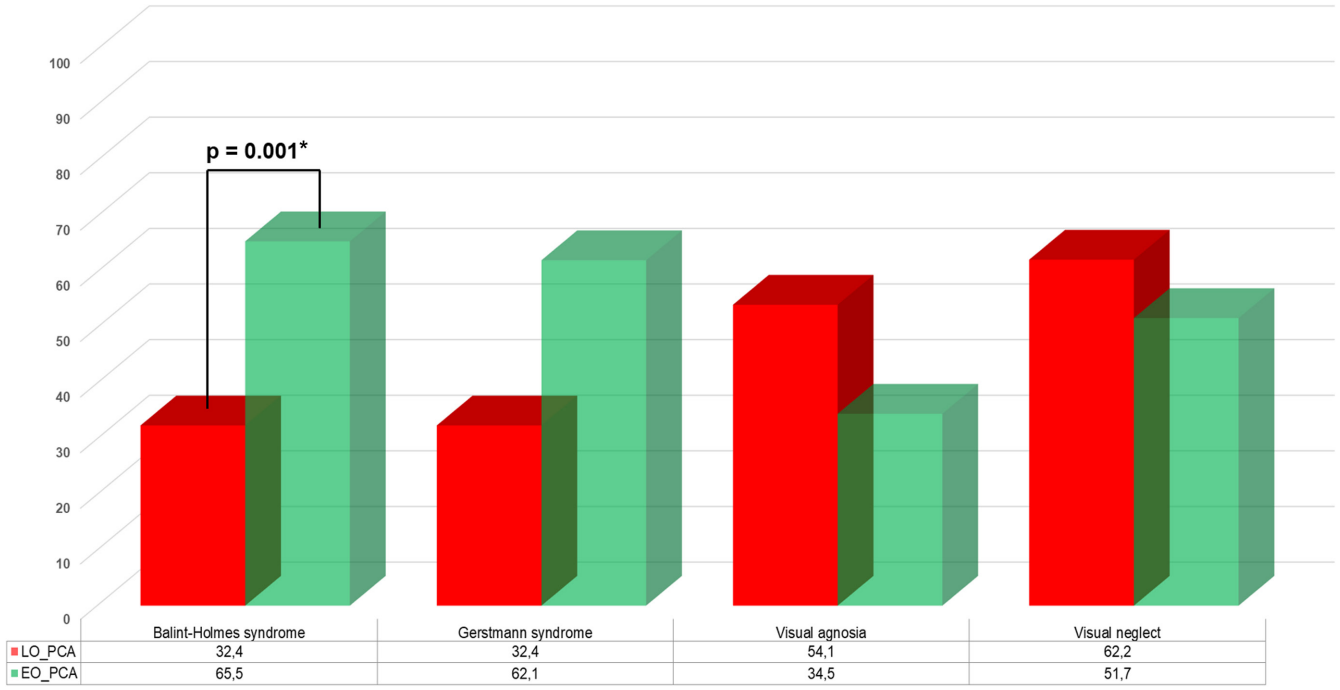


FIGURE 2 Prevalence of posterior deficits in late-onset and early-onset PCA. *Significant after Holm–Bonferroni correction. [Colour figure can be viewed at wileyonlinelibrary.com]

mesial areas comprising the retrosplenial cortex and the parahippocampal gyrus, and the thalamus.

The contrast of metabolic patterns across groups showed that, in comparison with LO_PCA patients, EO_PCA patients showed a much more severe involvement of the left posterior (parietal, occipital and temporal) regions, both on the lateral and mesial brain surfaces (Figure 4a). Conversely, the LO-PCA group showed more severe hypometabolism in the posterior cingulate and parahippocampal and hippocampal gyri of the right hemisphere. On the other hand, the main difference in the hypometabolic pattern between this group and LO-PCA patients was a greater involvement of the right occipital, occipito-temporal, occipito-parietal and superior parietal cortex in the latter group (Figure 4b). The lateral parietal and temporal clusters in the left hemisphere were similar in the two groups, whilst hypometabolism along the left mesial region was more severe in tAD than in LO_PCA patients.

Metabolic correlates of age at onset

Linear regression in the PCA sample using AaO as a continuous variable (Figure 5) showed that older age was associated with more severe hypometabolism at the level of three large clusters within the right hemisphere: one encompassing the anterior cingulate, the second encompassing the insular region and the temporal pole, and the third encompassing the retrosplenial cortex, the parahippocampal gyrus and the thalamus. Younger age at disease onset, on the other hand, was associated with more severe hypometabolism at the level of the left posterior parietal lobe and bilateral precuneus, and in a small area of the left pre-central cortex.

DISCUSSION

In the present study the neurological, neuropsychological and brain FDG-PET features of 37 patients with LO_PCA (≥65 years of age at symptom onset) and 29 patients with EO_PCA were evaluated, matched for disease duration and global severity of cognitive impairment, and FDG uptake was correlated with AaO within the PCA sample. Our aim was to establish whether AaO has an impact on the clinical presentation and the distribution of metabolic abnormalities in this AD variant.

Our LO_PCA and EO_PCA patients were equally impaired on tests of episodic memory, language and executive functions, and also showed visuospatial deficits, visual agnosia, neglect, Gerstmann symptoms and limb apraxia of comparable severity, consistent with the similar degree and topography of hypometabolism at the level of the right OTP cortex and left angular gyrus evident in their PET scans. However, the EO_PCA group showed more preserved disease insight and a higher prevalence of Bálint–Holmes symptoms (simultanagnosia in particular), which was also reflected in more frequent complaints about not finding and recognizing objects in everyday life, consistent with an involvement of the left OTP cortex much more severe than in the LO_PCA group. SPM regression analysis also indicated a positive correlation between left parietal damage and earlier AaO [33]. These findings overall confirmed our prediction of greater vulnerability to neurodegeneration of the parietal cortex in younger individuals, and are also in line with the results of Suárez-González et al.'s study on the cognitive profiles and atrophy patterns of EO_PCA versus LO_PCA [14]. Furthermore, our results also confirmed the prediction of greater vulnerability to neurodegeneration of the mesial temporal cortex in LO_PCA than EO_PCA.

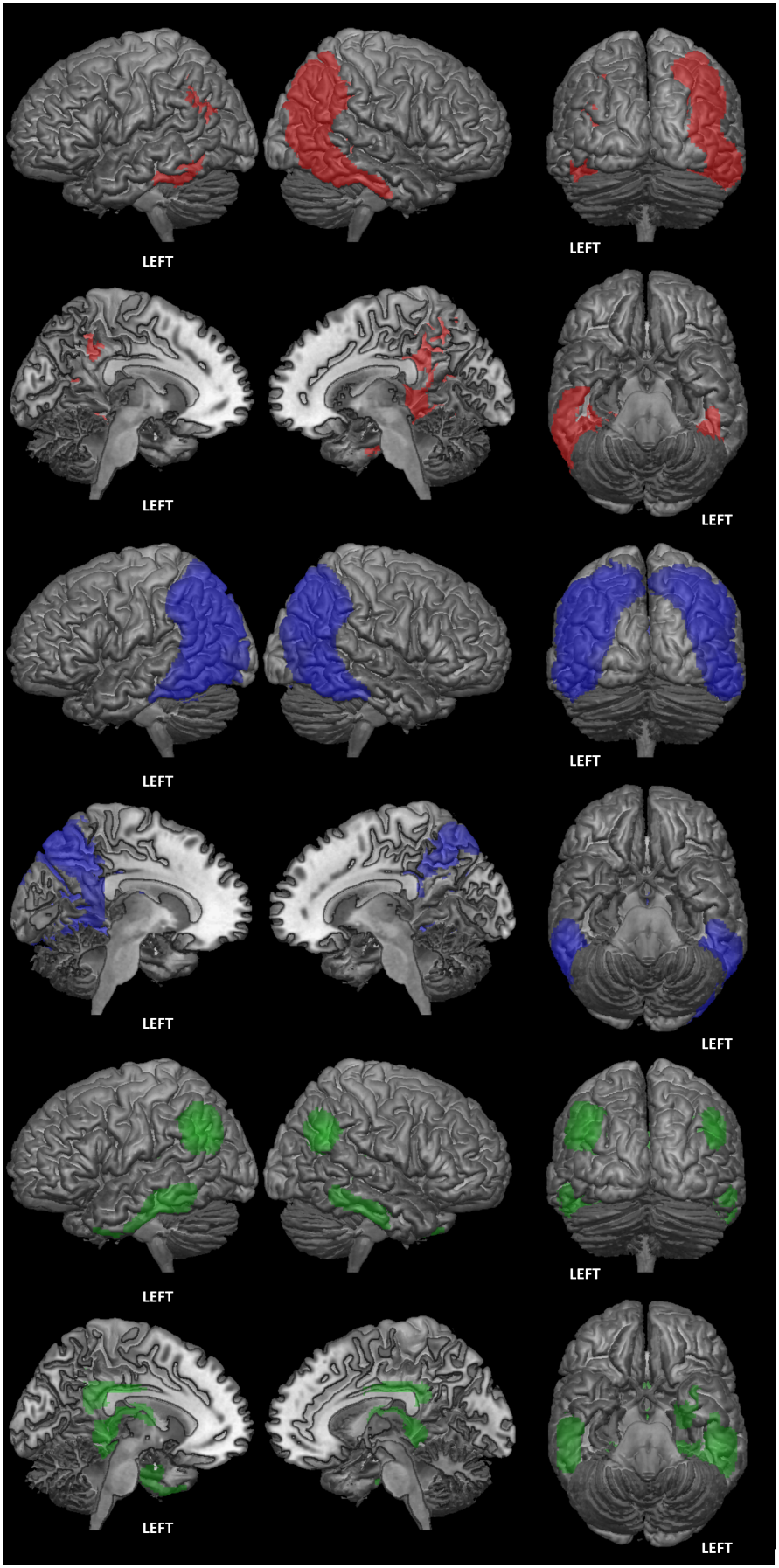


FIGURE 3 Distribution of hypometabolism in the three study groups, each compared with healthy controls. Top rows, in red, late-onset PCA; middle rows, in blue, early-onset PCA; bottom rows, in green, typical Alzheimer's disease. Clusters are shown at $p < 0.05$ FWE corrected and a minimum size of 100 voxels. [Colour figure can be viewed at wileyonlinelibrary.com]

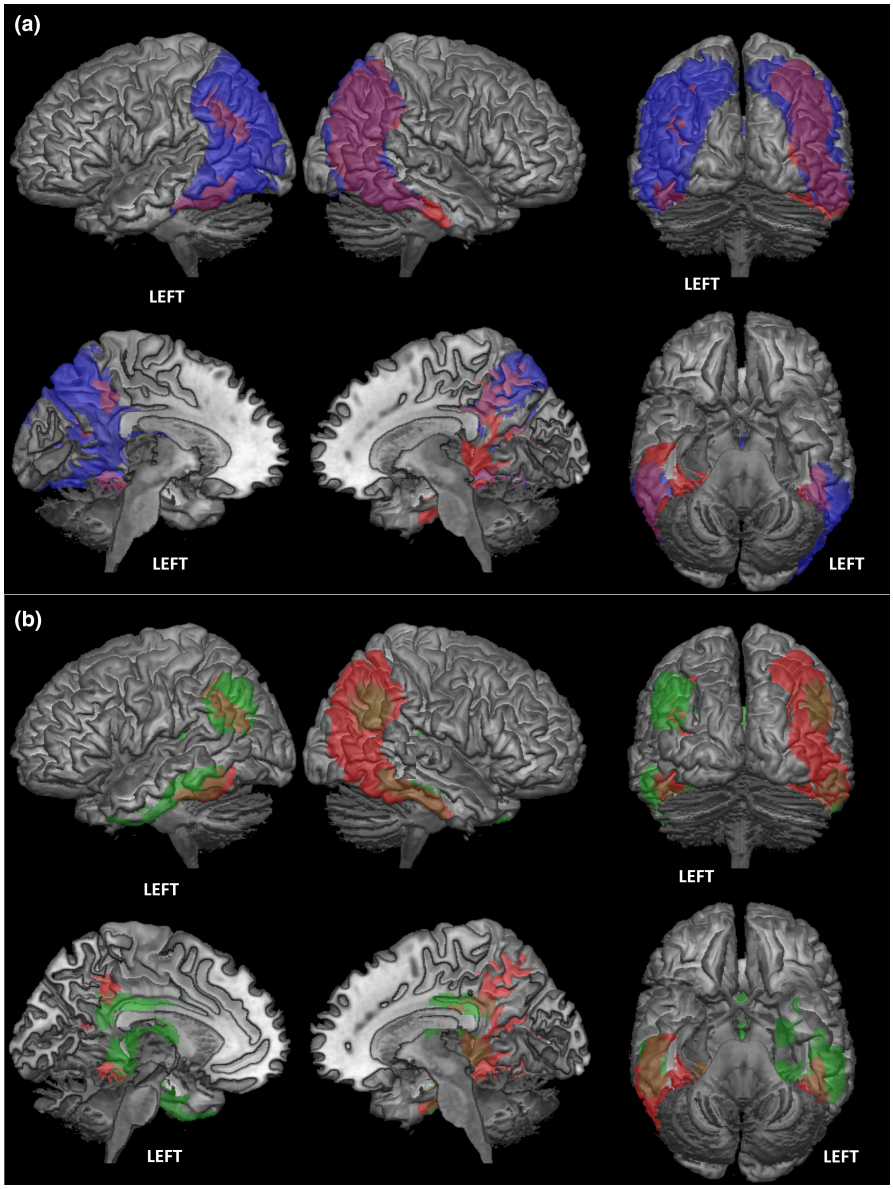


FIGURE 4 Superimposition of hypometabolic maps of late-onset PCA patients (in red) and (a) early-onset PCA patients (in blue); (b) typical Alzheimer's disease patients (in green). Clusters are shown at $p < 0.05$ FWE corrected and a minimum size of 100 voxels. [Colour figure can be viewed at wileyonlinelibrary.com]

The direct comparison of metabolic patterns between the two PCA groups showed a more severe impairment of the posterior cingulate and the parahippocampal and hippocampal gyri in LO cases, and regression analysis clearly highlighted three clusters of worse FDG uptake in older patients that seem to correspond to the nodes of the limbic network described by the 'olfactocentric' and 'hippocampocentric' model of the limbic system [34]. This model defines two divisions that overlap in the anterior cingulate cortex: an orbitofrontal-insular-temporo-polar division engaged in executive and semantic processes, and a hippocampal-parahippocampal-retrosplenial-cingulate division (also including the thalamus in the revised model [34]), subserving episodic memory and spatial orientation. These structures are known to be involved in amnestic AD [34], and, coherently, limbic hypometabolism was found in the tAD group. Our results support the involvement of these structures also in LO_PCA. Previous structural and metabolic imaging studies already highlighted the presence of signs of neurodegeneration at the level of the mesial temporal cortex in PCA [35-37] and also showed a direct relationship between atrophy and older age [36]. Our results are in line with such evidence. Importantly, the finding of limbic hypometabolism in tAD patients compared with age-matched healthy controls also serves as proof of the fact that the correlation between older age and reduced FDG uptake in the mesial temporal cortex in PCA is related specifically to the neurodegenerative process, and not to ageing.

It was also predicted that limbic dysfunction would be associated with more severe impairment of memory functions in LO_PCA than EO_PCA (as found in the tAD group, who showed prominently left mesial temporal hypometabolism and more severe amnesia), but no evidence of greater memory or semantic or executive deficits in our LO_PCA patients was found. A possible explanation is the strong lateralization of the limbic hypometabolism to the right hemisphere in this group, paired with the lack of neuropsychological measures sensitive to right-lateralized limbic functions. Perhaps the inclusion of formal tests of visuospatial memory and topographical orientation would have increased sensitivity for right

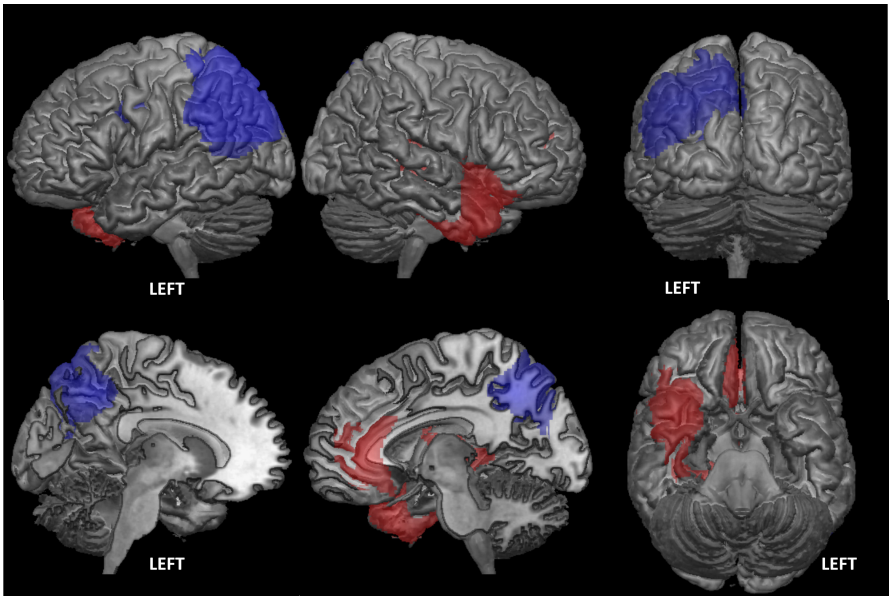


FIGURE 5 Correlation between brain metabolism and age at onset in the PCA sample: negative correlations, i.e., more severe hypometabolism associated with later onset, are depicted in red; positive correlations, i.e., more severe hypometabolism associated with earlier onset, are depicted in blue. Clusters are shown at $p < 0.001$ uncorrected and a minimum size of 100 voxels. [Colour figure can be viewed at wileyonlinelibrary.com]

limbic dysfunction and allowed differences between the two age groups to be detected.

In their LO_PCA sample, Suárez-González et al. [14] also found a pattern of cortical thickness similar to our LO_PCA patients' FDG-PET pattern: in addition to posterior atrophy, their LO_PCA cases showed thinning of the mesial temporal, anterior temporal, inferior frontal and anterior cingulate cortex. They reported 'greater involvement of anterior regions' and hypothesized major impairment of 'prefrontal functions' in PCA with a late onset. It is suggested that these findings should be interpreted as a sign of involvement of the limbic system engaged primarily in memory processes.

On the whole, our results suggest that the predominantly simultanagnosic syndrome underpinned by bilateral OTP neurodegeneration, which is considered the most frequent presentation of PCA (sometimes referred to as the biparietal variant of PCA) [8,10,12,13], might actually be representative of EO_PCA, whilst LO_PCA seems to be characterized by asymmetric right > left neurodegeneration involving OTP regions, which leads to impairment of visuospatial abilities and object recognition, but also by neurodegeneration of the limbic network, as seen in LO classical AD. The similarities and differences observed in the LO_PCA and tAD groups actually raise the question of whether LO_PCA might be an extremely asymmetric, right-lateralized subtype of AD. Further studies are needed to establish how far from each other these two variants are, and if they represent two distinct entities or lie along a biological and clinical continuum.

Our study has a number of limitations. First, although this is, to our knowledge, one of the largest group studies on PCA, the sample size was relatively small. Secondly, the assessment of posterior functions was thorough but not comprehensive, and not always based on formal evaluation. For instance, alexia was recorded as a cognitive complaint but not tested, and visual field defects were not examined with visual perimetry. Thirdly, some functions were investigated more extensively than others (e.g., several tasks were reviewed for the identification of visual neglect), possibly introducing a bias in calculating the relative prevalence of the different posterior disturbances. However, this was true for both PCA groups and thus did not affect the comparison of their profiles. Fourthly, the assessment of extra-posterior functions was limited and was in some cases carried out using visually mediated tasks that are inappropriate for visually impaired patients (e.g., Attentional and Raven Matrices). A more extensive investigation of attention, memory, linguistic and executive domains might have revealed more differences, or similarities, between LO_PCA and EO_PCA than those emerging from the current analysis. Fifthly, correlation analysis between AaO and neuropsychological scores did not yield significant results, but they were performed only on the limited subset of cognitive measures expressed by continuous variables. Last but not least, biomarkers were available only for a minority of LO_PCA cases. This did not allow to verify whether differences between our two age groups could be attributed to a different neuropathology (and precisely to non-AD pathology in older cases, since 100% of the 19 EO_PCA patients with a biomarker had an amyloidopathy). This possibility, however, would have not been ruled out completely even if the conventional age cut-point of 65 years was chosen here which ensures comparability across studies the amyloid status had been known in a major number of cases, since disorders that may mimic PCA, like corticobasal syndrome or dementia with Lewy bodies, may also be associated with amyloid pathology. Furthermore, it is hoped that the exclusion of PCA-plus cases reduced the risk of including patients with diagnoses other than PCA, and some of the differences that were observed between our LO_PCA and EO_PCA cases, for example the involvement of the limbic system in the former group, do not suggest a non-amyloid disorder.

PCA is mainly an EO neurodegenerative disease but is not rare in individuals aged 65 or over. Our study showed that LO_PCA differs from EO_PCA in terms of distribution of brain metabolic abnormalities and clinical features. Various factors have been hypothesized to contribute

to the differential topography of neurodegenerative processes in younger and older individuals, for example distinct pathogenetic mechanisms or underlying pathological substrates, or the interaction of neurodegeneration with factors like age-related brain changes or cognitive reserve [1,2,3,4,5,6,7,38,39,40]. Future studies will have to verify our findings, and integrate them with genetic, biological and ideally neuropathological data in the attempt to find an explanation for the mechanisms through which AaO impacts dementia features.

AUTHOR CONTRIBUTIONS

Valeria Isella: Conceptualization (lead); data curation (lead); formal analysis (equal); investigation (supporting); methodology (lead); project administration (lead). **Daniele Licciardo:** Conceptualization (equal); data curation (equal); formal analysis (lead); investigation (equal). **Giulia Nastasi:** Data curation (supporting); formal analysis (supporting); investigation (supporting). **Valentina Impagnatiello:** Data curation (supporting); investigation (supporting); project administration (equal). **Francesca Ferri:** Conceptualization (supporting); data curation (equal); formal analysis (supporting); project administration (supporting). **Cristina Mapelli:** Investigation (supporting); project administration (equal). **Cinzia Crivellaro:** Data curation (supporting); formal analysis (supporting); investigation (equal); methodology (supporting). **Monica Musarra:** Data curation (supporting); methodology (supporting). **Sabrina Morzenti:** Data curation (supporting); methodology (supporting). **Ildebrando Appollonio:** Conceptualization (supporting). **Carlo Ferrarese:** Conceptualization (supporting).

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on reasonable request from the corresponding author.

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study.

ORCID

Valeria Isella https://orcid.org/0000-0003-1850-1236

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