J Neurol (2015) 262:1463–1472
DOI 10.1007/s00415-015-7738-z

ORIGINAL COMMUNICATION

# Amyloid and FDG-PET study of logopenic primary progressive aphasia: evidence for the existence of two subtypes

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Received: 22 February 2015 / Revised: 29 March 2015 / Accepted: 2 April 2015 / Published online: 11 April 2015
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**Abstract** The logopenic variant of primary progressive aphasia (lvPPA) has been associated with Alzheimer disease, although this relationship is still subject to debate. The purpose of this study is to determine the frequency of amyloid biomarkers in patients with lvPPA, and record any potential clinical or topographic differences between patients with and without amyloid deposits. We conducted cognitive examination and positron-emission tomography studies with fluorodeoxyglucose ($^{18}$F) and florbetapir ($^{18}$F) in a cohort of 16 patients diagnosed with lvPPA. We evaluated the prevalence of amyloid deposits as well as any clinical and metabolic differences between the groups with and without significant presence of amyloid deposits. Eleven patients (69 %) were considered amyloid-positive. The amyloid-positive group displayed less metabolic activity in the left temporoparietal region than the control group, while the amyloid-negative group showed lower metabolism in the left temporoparietal region extending to the anterior temporal and basal frontal regions. The percentage of change in patients with clinical and FDG-PET follow-up did not differ between the amyloid-positive and amyloid-negative subgroups. The frequency of amyloid-positive cases confirms that lvPPA is frequently associated with Alzheimer disease. Amyloid-negative patients show a different cerebral metabolic pattern. These findings show the relevance of using amyloid PET to study lvPPA, and also suggest that the logopenic variant may not be specific to Alzheimer disease in certain cases.

**Keywords** Primary progressive aphasia · Amyloid · PET · Alzheimer disease · Frontotemporal dementia

## Introduction

Primary progressive aphasia (PPA) is a disease of neurodegenerative origin which is characterized by progressive language impairment [1, 2]. Three variants have been described to date: nonfluent, semantic, and logopenic. The logopenic variant (lvPPA) has been linked to Alzheimer-type pathology (AD) and is in fact considered an atypical form of Alzheimer disease (AD) [3].

Logopenic variant PPA is characterized by difficulty in retrieving names and other words in spontaneous speech. While it is also associated with sentence repetition deficits, semantic and grammatical knowledge are relatively spared [4]. Voxel-based morphometry studies have shown a pattern of atrophy and hypometabolism affecting the left temporoparietal region; the pattern seen in AD is similar, but bilateral [4, 5].

Few studies have examined biomarkers in cerebrospinal fluid (CSF) and imaging results from positron-emission tomography (PET) using amyloid tracers in PPA [6–11]. Furthermore, recently published autopsy studies suggest that the association between lvPPA and AD may be weaker than was previously expected [12, 13].

**Electronic supplementary material** The online version of this article (doi:10.1007/s00415-015-7738-z) contains supplementary material, which is available to authorized users.

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Thanks to the development of amyloid radiotracers, we are currently able to study fibrillar amyloid deposition in vivo. The presence of fibrillar amyloid deposits is associated with AD [14]. Validity of these radiotracer methods is supported by the correlation between PET imaging results and autopsy results showing amyloid deposits [15]. Previous studies have demonstrated equivalent results for different radiotracers, including florbetapir ($^{18}$F) and Pittsburgh Compound B (PiB), in the detection of fibrillar amyloid [16, 17]. The above suggests that the new $^{18}$F-labelled tracers, such as florbetapir ($^{18}$F), may make it easier to apply these techniques in clinical practice due to the longer half-life of F18 tracers.

The purpose of our study is twofold: firstly, to assess the prevalence of amyloid deposits in patients with lvPPA; and secondly, to evaluate the potential clinical or topographic differences between patients with and without amyloid deposits. To this end, a cohort of 16 patients underwent cognitive testing and PET studies with fluorodeoxyglucose (FDG-PET) and amyloid-ligand florbetapir (florbetapir-PET).

## Methods

### Patients and clinical assessment

We included 16 patients diagnosed with lvPPA. All patients met the diagnostic criteria by Gorno-Tempini et al. [4] and showed left temporoparietal hypometabolism in FDG-PET images. All patients were being treated in the cognitive and behavioral neurology unit at our hospital; 18 consecutive patients with lvPPA were at follow-up, of which 16 agreed to participate in the study. The study protocol was approved by the Clinical Research Ethics Committee at our hospital. Patients signed an informed consent form prior to inclusion in the study. Addenbrooke's Cognitive Examination (ACE) [18] was used to measure general cognitive function. Speech assessment included word production and comprehension, object naming, repetition, and semantic knowledge, according to the recommended diagnostic criteria [4]. Tests administered to this end included a verbal fluency test in which participants list as many animal names and words beginning with 'p' as possible in one minute, the Boston Naming Test, the Cookie Theft picture description from the Boston Diagnostic Aphasia Examination [19], and language subtests from the Barcelona Test [20, 21]. These language subtests include repetition of syllables, syllable pairs, words, word pairs, pseudowords, and increasingly long phrases and sentences. Word comprehension was assessed by asking patients to point to images (objects, actions, numbers, and geometric shapes) and parts of the body. This test included comprehension of instructions since patients were asked to perform tasks of varying complexity. Non-verbal oral praxis was also evaluated. We assessed functional activity using the Functional Activity Questionnaire (FAQ) and the Interview for Deterioration in Daily Living Activities in Dementia (IDDD). Language deficits were staged on the Progressive Aphasia Severity Scale (PASS) [22].

### Imaging studies

All patients underwent PET-CT studies with both FDG and florbetapir ($^{18}$F). Florbetapir-PET imaging studies were conducted between May and June 2014. All patients completed at least one FDG-PET study at some point during the disease. Ten patients each underwent two FDG-PET studies separated by a mean (SD) interval of 21 (4.5) months (Fig. 1). In 15 patients, the time elapsed between one of the FDG-PET studies and the florbetapir-PET study was less than 3 months. Florbetapir-PET was performed at the time of the second FDG-PET, except in five cases in which it was performed at the time of diagnosis.

### PET image acquisition

PET images were generated by a PET-CT Siemens Biograph True Point platform integrating a 6-slice detector with a latest-generation PET scanner featuring a lutetium oxyorthosilicate crystal array.

Florbetapir ($^{18}$F) was delivered intravenously to each patient (mean dose, 370 MBq) 30–40 min prior to image acquisition using the unit described above [23, 24]. Total

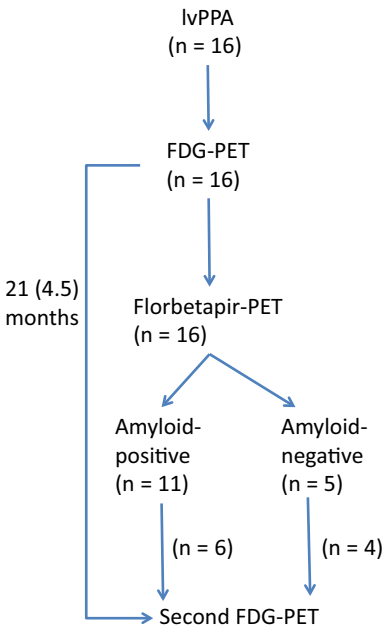


**Fig. 1** Flowchart of patients included in the study and follow-up

scan duration was 15 min with a single bed position. Images were reconstructed in three-dimensional planes using an iterative method, with 4 iterations, 14 subsets, a field-of-view of 30 cm and a Gaussian filter of 3 mm full width half-maximum.

Patients fasted a minimum of 6 h before the FDG-PET scan. FDG (185 MBq) was administered intravenously 30 min before images were taken. During this time, patients rested in a dark room with their eyes closed. Glucose levels had previously been checked and found to be lower than 150 mg/dL. PET images were acquired for 10 min at a single bed position. CT parameters were 130 kVp, 40 effective mAs, and 1 rotation. Slice thickness was 3 mm, the reconstruction interval was 1.5 mm, and pitch was 0.75 mm. Reconstruction was performed using an iterative method in three-dimensional planes, with 2 iterations and 21 subsets. A field of view of 30 cm and a Gaussian filter of 4 mm full width half-maximum were used. FDG-PET and florbetapir-PET studies were performed on different days.

### Florbetapir-PET image preprocessing and analysis

Images were visually analyzed by two nuclear medicine specialists. We used the previously validated binary visual reading method that distinguishes between significant and non-significant cortical amyloid uptake [25]. Patients were considered amyloid-positive when amyloid uptake was significant, that is, when borders between white and gray matter were poorly defined. The rest of the cases were considered amyloid-negative.

All florbetapir-PET images were preprocessed using Statistical Parametric Mapping software version 8 (SPM8) (The Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College of London) software [26], and spatial normalization to Montreal Neurological Institute (MNI) templates was performed for all patients. We later analyzed the images using automatically detected regions of interest (ROI) from the Automated Anatomical Labeling (AAL) atlas with MarsBaR software [27]. We calculated uptake in each of the regions included in the AAL atlas, comparing them to the whole cerebellum. Regions examined in the analysis were similar to those described by other authors [28]: posterior cingulate, anterior cingulate, medial orbital frontal gyrus, precuneus, inferior temporal gyrus, and superior temporal gyrus. These regions are shown in Figure 1 of the Supplementary Material.

### FDG-PET image preprocessing and analysis

Images were preprocessed and analyzed using SPM8 [26]. Images obtained using FDG-PET were normalized to MNI space and later smoothed using a 12-mm full width at half maximum (FWHM) Gaussian kernel. Using the cerebellum as the reference region, we performed cerebellum metabolism scaling for each patient in order to remove the variability in FDG uptake between subjects. The control group consisted of 16 age-matched patients with no cognitive disabilities; their characteristics have previously been described elsewhere [29]. A *t* test for two independent samples was completed in order to compare the different groups, using age and sex as covariates. Comparisons were as follows: (1) lvPPA group vs healthy controls; (2) amyloid-positive lvPPA patients vs healthy controls; (3) amyloid-negative lvPPA patients vs healthy controls; and (4) amyloid-positive lvPPA patients vs amyloid-negative lvPPA patients. We regarded uncorrected $p$ values $<0.001$ as statistically significant and set an extent threshold of 50 voxels to correct for multiple comparisons.

### Longitudinal follow-up

Although evaluating patients' follow-up data was not listed among the purposes of this study, these data have been included in our analysis. Ten patients underwent two assessments and two FDG-PET studies. To provide a clinical perspective, we calculated the percentage of variation on three tests: the ACE test for global cognitive function, PASS for staging linguistic deficits, and FAQ for functional performance of daily life activities.

To evaluate changes in brain metabolism, we used ROI analysis and also calculated the percentage of change between the first and second FDG-PET studies. Mean normalized FDG uptake was extracted from each ROI for each subject at each time point. We considered three following regions: (1) hypometabolic regions obtained by SPM analysis in each subgroup (lvPPA-positive and lvPPA-negative), compared to controls. (2) One ROI including the topography affected in all three PPA variants (language network ROI) [29]; these ROI were calculated as the sum of the regions with lower metabolism of each variant of PPA, in comparison to controls, in the same way as it had been calculated previously [30]. And (3) uptake in whole brain including cortical regions and basal ganglia.

Percentage of change for these variables was calculated as follows:

$$\text{Percentage of change} = (\text{parameter } 2 - \text{parameter } 1)/\text{parameter } 1 \times 100,$$

where 'parameter 1' is the value registered in the first assessment (for example, ACE or ROI uptake in FDG-PET) and 'parameter 2' in the second assessment.

### Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 20 for Mac. Results are shown as frequencies with percentages, and as means (SD). We used

the Mann–Whitney $U$ test to compare means between two groups. Qualitative variables were compared using the Fisher exact test. A $p$ value $<0.05$ was considered statistically significant.

## Results

### Clinical and demographical data

Mean age at symptom onset was 72 years (range 64–87). Women accounted for 56.3 % of the total ($n = 9$). Mean years of education were 10.7 (range 0–18). Mean age at first FDG-PET study was 75 years (range 68–89), and 76 years (range 69–90) at time of the florbetapir-PET study. Progression time from symptom onset to the initial FDG-PET study was 2.8 (2.0) years, and 4.1 (2.4) years from symptom onset to the florbetapir-PET study.

### Florbetapir-PET imaging

The binary visual reading method revealed significant binding to amyloid deposits in 11 patients (69 %), whereas five (31 %) were found to be amyloid-negative (Fig. 1). The agreement rate for the two raters was 100 %. Table 1 of Supplementary Material shows cortico-cerebellar uptake values.

Patients whose PET results were amyloid-negative were older than amyloid-positive patients at the time the imaging study was conducted. No statistically significant differences were found regarding age at onset, sex, years of education, global cognitive function scores, or functional impairment scores (Table 1). We found greater impairment in phonemic verbal fluency in amyloid-negative patients, but no differences in other assessed language domains (Table 2).

**Table 1** Characteristics of amyloid-positive and amyloid-negative groups

| | lvPPA-pos | lvPPA-neg | $p$ value |
|---|---|---|---|
| Age at onset | 71.1 (5.1) | 75.6 (9.4) | 0.335 |
| Age at first FDG-PET | 72.8 (4.8) | 80 (7.6) | 0.053 |
| Age at amyloid-PET study | 74.1 (5.1) | 81.8 (7.3) | **0.040** |
| Female sex, $n$ (%) | 7 (63.6 %) | 2 (40 %) | 0.596 |
| Years of education | 11.0 (5.1) | 9.8 (7.2) | 0.827 |
| MMSE score | 19.3 (6.8) | 12.8 (6.9) | 0.100 |
| ACE score | 49.0 (22.6) | 29.8 (13) | 0.126 |
| FAQ score | 8.5 (10.5) | 10.6 (11.6) | 0.954 |
| PASS score | 5.3 (3.8) | 8.4 (3.8) | 0.145 |

Table lists numbers with percentages in brackets or mean values (SD)

Statistically significant results are shown in bold

### FDG-PET imaging

FDG-PET studies in all lvPPA patients, compared to controls, showed lower metabolism in the superior, medial, inferior, and fusiform temporal gyri, as well as in the left superior and inferior parietal lobules, supramarginal gyrus, and precuneus (Fig. 2a). We also observed a small cluster in the left inferior frontal gyrus. Compared to controls, amyloid-positive lvPPA patients (lvPPA-pos) exhibited less metabolic activity in the left superior and medial temporal gyri, inferior parietal lobule, precuneus, and angular and supramarginal gyri (Fig. 2b). Several smaller clusters were seen in the right precuneus and left inferior frontal gyrus. On the other hand, amyloid-negative lvPPA patients (lvPPA-neg) displayed lower metabolism in the left superior, medial, and inferior temporal gyri, left fusiform gyrus, and uncus, left parietal lobule, and supramarginal gyrus (Fig. 2c). MNI coordinates and statistical data are shown in Table 2 of Supplementary Material.

We also compared brain metabolism between amyloid-positive and amyloid-negative patients. The first subgroup showed lower metabolism in the superior and inferior parietal lobules and right posterior cingulate; amyloid-negative patients, however, displayed less metabolic activity in the left anterior temporal and left frontal regions, mainly affecting the left inferior and middle frontal gyri, bilateral orbital gyri, left uncus, and left superior and medial temporal gyri (Fig. 3).

### Longitudinal follow-up

Mean (SD) time elapsed between the first and second cognitive assessments and the FDG-PET study was 21 (3.7) months in the amyloid-positive group, and 20.2 (6.8) months in the amyloid-negative group ($p = 0.915$). Mean percentages of change on ACE tests were $-42.2$ % (22.9) in amyloid-positive and $-56.7$ % (20.6) in amyloid-negative patients ($p = 0.476$). Mean percentages of change were 123.9 % (130.1) and 50.1 % (60.2) on the PASS scale ($p = 0.352$), and 146.4 % (155.0) and 129.5 % (190.4) on the FAQ scale ($p = 0.886$). Brain metabolism decreased a mean of 7.8 % (5.9) in the affected areas in amyloid-positive patients, and 9.3 % (3.1) in amyloid-negative patients ($p = 1.0$). The mean decrease in brain metabolism in the ROI for areas affected in PPA was 7.3 % (6.4) in amyloid-positive patients and 8.9 % (3.4) in amyloid-negative patients ($p = 0.831$). Whole brain metabolism decreased a mean of 3.3 % (3.7) and 4.8 % (4.1) in the amyloid-positive and amyloid-negative subgroups, respectively ($p = 1.0$). Absolute values of scale scores and brain metabolism for each patient are shown in Figs. 4 and 5.

**Table 2** Language domains in amyloid-positive and amyloid-negative groups

| | lvPPA-pos | lvPPA-neg | *p* value |
|---|---|---|---|
| Object naming, ACE (/12) | 6.2 (3.7) | 3.0 (2.4) | 0.115 |
| Semantic fluency test (animals) | 5 (3.4) | 4.0 (2.4) | 0.603 |
| Phonemic fluency (words beginning with 'p') | 5.9 (2.4) | 3.1 (1.6) | **0.040** |
| Repetition of syllables (/8) | 7.2 (1.4) | 7.8 (0.4) | 0.583 |
| Repetition of syllable pairs (/8) | 6.0 (2.7) | 6.2 (2.9) | 1.00 |
| Repetition of words (/10) | 9.6 (1.2) | 8.0 (3.4) | 0.377 |
| Repetition of pseudowords (/8) | 5.7 (2.8) | 4.2 (3.5) | 0.441 |
| Repetition of sentences (/60) | 31.2 (18.1) | 20.2 (19.4) | 0.320 |
| Word comprehension (matching) (/36) | 33.0 (7.9) | 29.2 (10.0) | 0.148 |
| Word comprehension (body parts) (/18) | 18 (0) | 18 (0) | 0.304 |
| Orofacial praxis (/20) | 17.8 (3.6) | 14.8 (3.7) | 0.145 |

Table shows mean values (SD). Maximum score on each test is given in parentheses (/X)
Statistically significant results are shown in bold

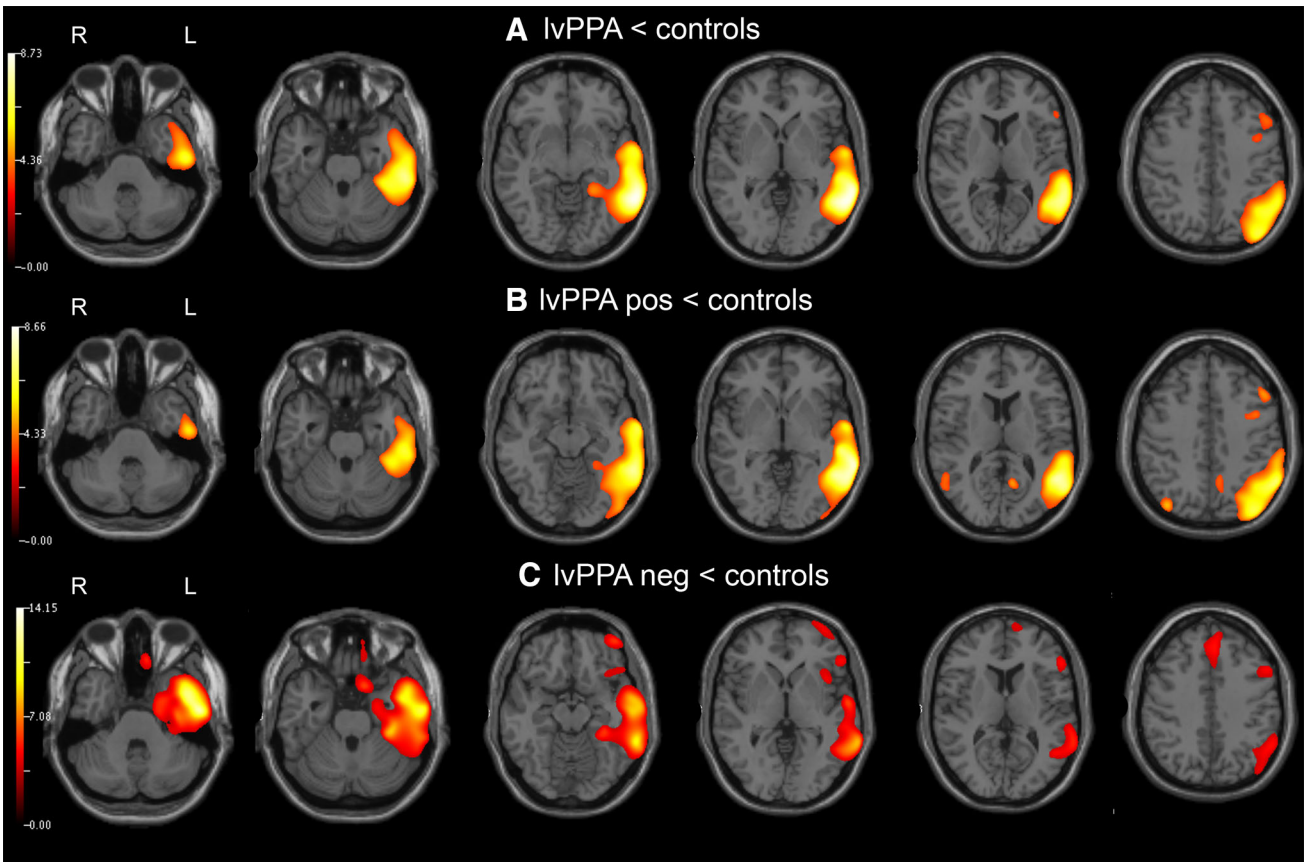


**Fig. 2** SPM map (radiological orientation) **a** regions with lower metabolism in the lvPPA group (all patients) compared to healthy controls. **b** Regions with lower metabolism in the amyloid-positive lvPPA patients compared to healthy controls. **c** Regions with lower metabolism in amyloid-negative lvPPA patients compared to healthy controls. *L* left, *R* right

## Discussion

A growing body of evidence shows that amyloid-PET imaging may contribute to the diagnostic process for AD [31]. Furthermore, amyloid-PET findings have been proposed as a biomarker for selecting appropriate participants for clinical trials aimed at testing new AD treatments. The main question about its use relates to its specificity, since false positives are frequent in the population aged over 60. A recent study found that 20 % of

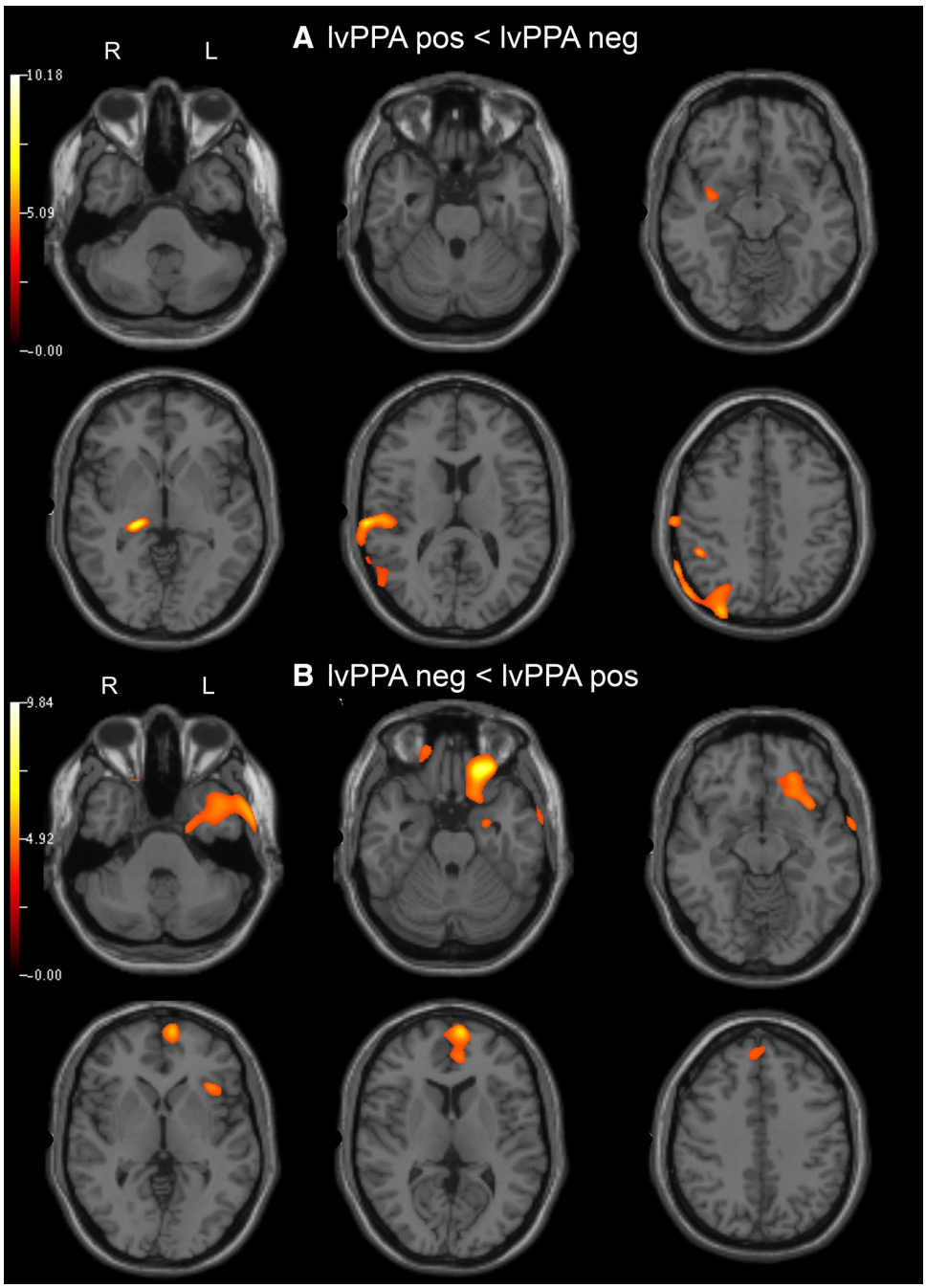


**Fig. 3** SPM map (radiological orientation) **a** regions with lower metabolism in the amyloid-positive lvPPA group compared to the amyloid-negative lvPPA group. **b** Regions with lower metabolism in the amyloid-negative lvPPA group compared to the amyloid-positive lvPPA group. *L* left, *R* right

subjects aged over 60 were amyloid-positive although no neurodegeneration could be seen in MRI and FDG-PET studies [32].

The percentage of patients with amyloid deposits in our study is similar to the rate found in autopsy series that report non-Alzheimer pathology in about 40 % of all patients [12]. Our findings are consistent with those described by Teichmann et al. According to these authors, cerebrospinal fluid biomarker results were indicative of AD in 8 cases and not indicative of AD in 5 cases (61 %) [10]. These findings contrast with those reported in the first studies using PET with amyloid tracers; 4 out of 4 patients tested positive using PiB-PET in one study [7] and 13 out of 14 patients (92 %) tested positive in another study employing the same tracer [8]. Our results may be supported by the fact that all patients included in our study were examined after publication of the latest diagnostic criteria [4] and FDG-PET findings in all cases were compatible with the logopenic variant of PPA. Furthermore, in a recent study Whitwell et al. found that 44 out of 50 patients

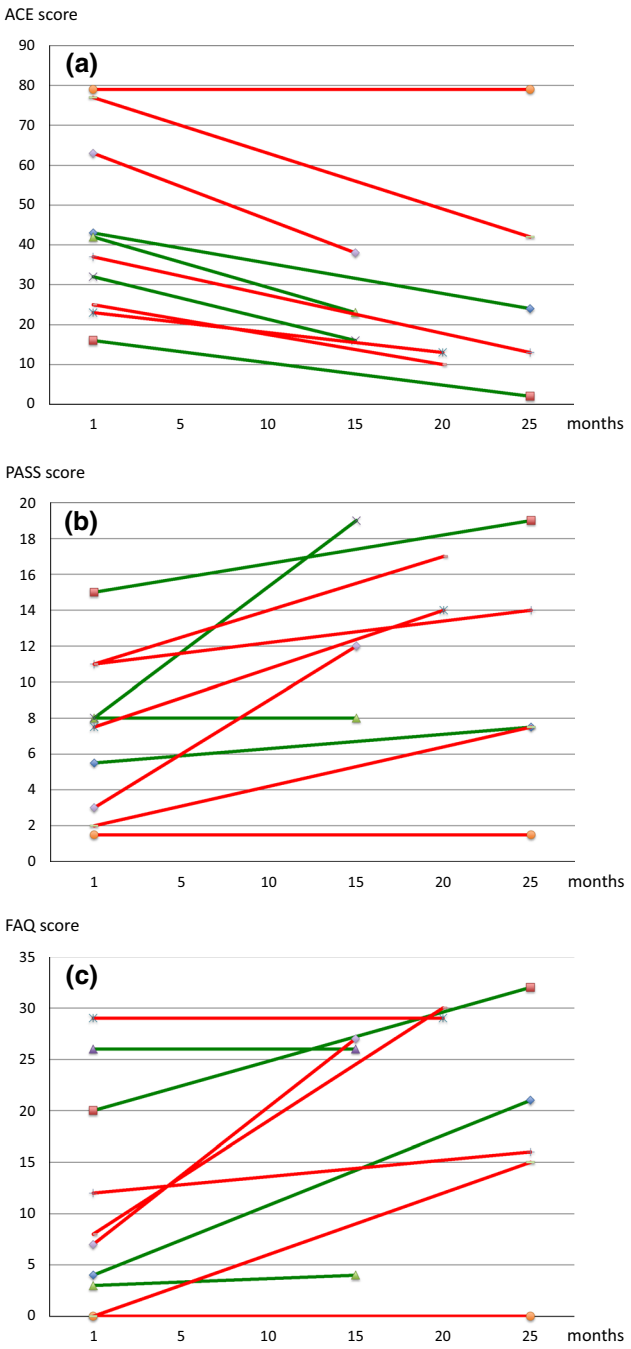


**Fig. 4** Cognitive function scores and performance of functional activities at time of first and second FDG-PET tests **a** Addenbrooke's cognitive examination. **b** Progressive Aphasia Severity Scale. **c** Functional Activity Questionnaire. *Red* amyloid-positive patients, *green* amyloid-negative patients. There were no differences in cognitive and functional impairment between the 2 groups

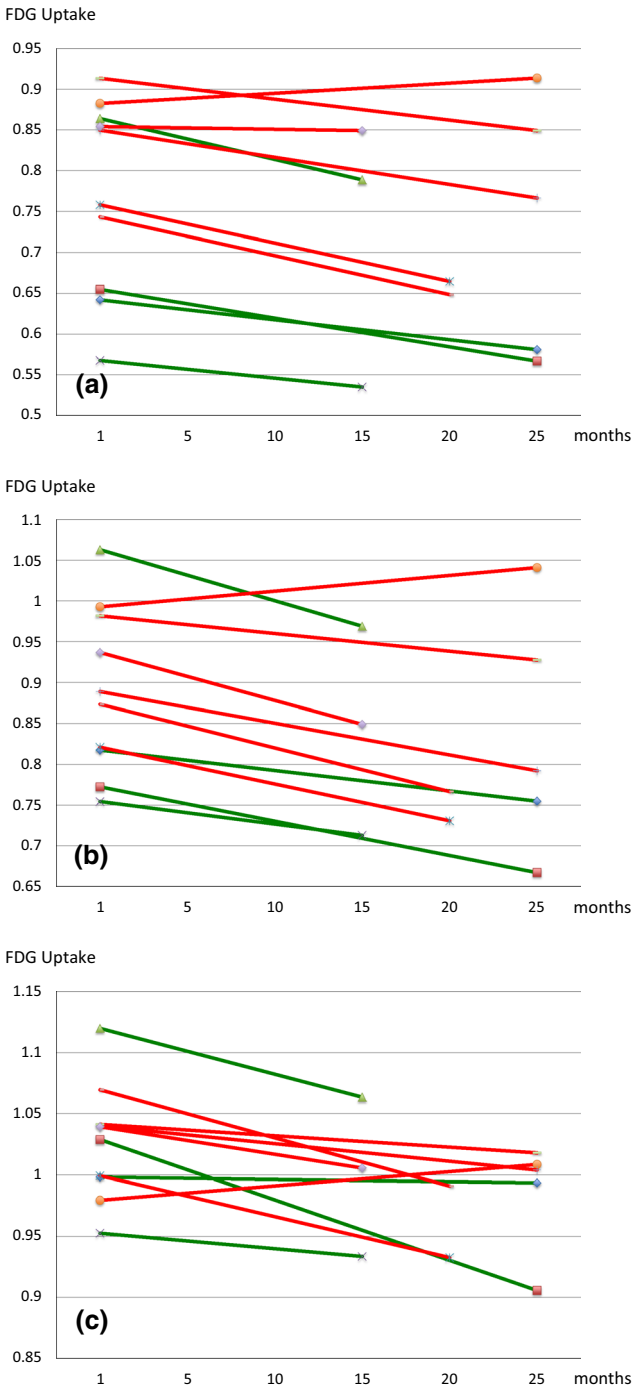


**Fig. 5** Individual ROI uptake at first and second FDG-PET studies. **a** lvPPA ROIs. **b** Language network ROI. **c** Whole brain uptake. *Red* amyloid-positive patients, *green* amyloid-negative patients. There were no differences in metabolism between the two groups

(88 %) were PiB-positive; these findings are similar to our own [11] (Table 3). At the same time, prevalence of amyloid deposits in healthy subjects showing no neurodegeneration ranged from 20 to 28 % (age range 65–89) [32]; this percentage is lower than the one reported in the present study for patients with lvPPA. Overall, this

**Table 3** Studies of lvPPA using amyloid biomarkers

| References | Biomarker of amyloid deposition | Biomarker of neurodegeneration | Number of patients | Amyloid-positive (%) |
|---|---|---|---|---|
| Rabinovici et al. [7] | PiB-PET | FDG-PET | 4 | 100 |
| Leyton et al. [8] | PiB-PET | FDG-PET | 13 | 92 |
| Mendez et al. [9] | Florbetapir-PET | FDG-PET | 3 | 100 |
| Teichmann et al. [10] | CSF | SPECT | 13 | 61 |
| Whitwell et al. [11] | PiB-PET | FDG-PET | 50 | 88 |
| Present study | Florbetapir-PET | FDG-PET | 16 | 68 |

results confirm that lvPPA may be the onset of AD in a high percentage of patients, and that the frequency of amyloid deposition is higher than expected in age-matched healthy controls.

One of our most interesting findings was discovering topographic differences in FDG-PET imaging studies between patients classified as amyloid-positive or amyloid-negative according to florbetapir-PET results. Altered function in the posterior superior temporal gyrus and the temporoparietal junction in both groups is consistent with the presence of phonological errors and sentence repetition deficits [33–35]. Furthermore, hypometabolism in amyloid-negative patients extended to more anterior areas. When comparing the amyloid-positive and amyloid-negative subgroups, we found that the positive subgroup displayed less metabolic activity in the right temporoparietal region, whereas the negative one showed lower metabolism in the left frontal and anterior temporal regions. However, no differences between both groups were seen in the left temporoparietal junction and posterior superior temporal gyrus: both areas are considered signature regions for lvPPA [34]. Although critical regions determining the clinical features of lvPPA may overlap, the changes mentioned above suggests that there may be topographical differences between amyloid-positive and amyloid-negative lvPPA. These findings are consistent with a previous observation of reduced brain metabolism more bilateral in PiB-positive lvPPA, and greater impairment in left anteromedial temporal and medial prefrontal cortex in PiB-negative patients [11]. These considerations raise the possibility that a more extensive analysis of speech or other cognitive functions related to the mentioned areas might be useful in differential diagnosis of lvPPA. Amyloid-negative lvPPA patients in our study showed the greatest impairment in phonemic verbal fluency, and Whitwell et al. found impairment on action verbal fluency [11].

The absence of amyloid deposits in a group of lvPPA patients evaluated with PET suggests that amyloid-negative lvPPA may be part of the spectrum of frontotemporal lobar degeneration. This statement may be supported by the article by Josephs et al. [36] which found progranulin gene mutations in three patients of a series of six amyloid-negative lvPPA patients.

On the other hand, the amyloid-positive group in our study did not show increased progression rate. In fact, the percentage of variation on scales assessing cognitive function (ACE), language (PASS), and functional activity (FAQ) was similar in amyloid-positive and amyloid-negative subgroups. Similarly, no differences were determined for the percentage of variation of brain metabolism in the regions involved in language or in whole brain studies. According to these findings, the presence of amyloid deposits does not necessarily point to more aggressive clinical features.

Our study has its strengths and weaknesses. One of its strengths is that the patients were referred to our unit by primary care doctors at our hospital, which reduces the likelihood of selection bias that may arise when patients are referred by doctors at different hospitals [37]. The short follow-up period is one of our study's limitations, since it does not permit us to rule out the presence of differences in clinical progression or brain metabolism. Amyloid-positive lvPPA patients with increased amyloid deposition in occipital regions have been reported to show greater overall cognitive impairment; further research is needed in order to determine how amyloid deposits affect patient prognosis [38]. Another limitation is that MRI was not available at the moment of FDG-PET, and correction for atrophy was not performed. For this reason, we cannot exclude the fact that the observed differences in brain metabolism could be partly due to the presence of concomitant atrophy.

According to our findings, we can draw the following conclusions. Firstly, the frequency of amyloid-positive PET in lvPPA patients is higher than was expected for a population showing no neurodegeneration. This supports the hypothesis that a considerable percentage of patients with lvPPA may be experiencing onset of AD. Secondly, some lvPPA patients are amyloid-negative and show a different brain metabolic pattern on FDG-PET imaging, suggesting that amyloid-negative lvPPA subgroup may be

on the spectrum of frontotemporal lobar degeneration. These findings underline the relevance of describing an amyloid-negative subtype of the lvPPA. Our results with florbetapir-PET confirm those reported by Whitwell et al. using PiB-PET regarding the existence of an amyloid-negative subtype of lvPPA, as well as the possibility of some differences in brain metabolism and language examination between amyloid positive and amyloid negative lvPPA patients [11]. We were unable to demonstrate a connection between progression rate and the presence or absence of amyloid depositions on PET images, although the follow-up period was too short. Overall, our study provides clear evidence that amyloid-PET imaging is a useful technique for studying patients with lvPPA.

**Acknowledgments** The authors would like to thank Spanish Society of Neurology's Research Operations Office staff for their help in preparing this manuscript.

**Conflicts of interest** The authors have no conflicts of interest to declare.

**Ethical standard** The study was approved by the research committee at our hospital and conducted in accordance with the 1964 Helsinki Declaration and its later amendments.

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