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Data-driven subtypes of mixed semantic-logopenic primary progressive aphasia: Linguistic features, biomarker profiles and brain metabolic patterns

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ABSTRACT

Mixed primary progressive aphasia (mPPA) accounts for a substantial proportion of primary progressive aphasia (PPA) cases. However, the lack of a standardised definition of this condition has resulted in misclassification of PPA cases. In this study, we enrolled 55 patients diagnosed with PPA, comprising 12 semantic variant (svPPA), 23 logopenic variant (lvPPA), and 20 mPPA cases with linguistic characteristics consistent with both svPPA and lvPPA (s/lvPPA). All patients underwent language assessments, evaluation of Alzheimer's disease biomarkers (via cerebrospinal fluid analysis or Amyloid-PET), and ^{18}F-FDG-PET brain scans. An agglomerative hierarchical clustering (AHC) analysis based on linguistic characteristics revealed two distinct clusters within the s/lvPPA group: cluster k1 ($n = 10$) displayed an AD-like biomarker profile, with lower levels of $A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$ ratio, along with higher levels of t-tau and p-tau compared to cluster k2 (n = 10). Interestingly, k1 exhibited linguistic features that were similar to those of svPPA. Both clusters exhibited extensive temporoparietal hypometabolism. These findings support the hypothesis that a subgroup of s/lvPPA may represent a clinical manifestation of AD-related PPA.

Abbreviations: PPA, Primary Progressive Aphasias; svPPA, Semantic Variant of Primary Progressive Aphasia; nfvPPA, Nonfluent Variant of Primary Progressive Aphasia; lvPPA, Logopenic Variant of Primary Progressive Aphasia; AD, Alzheimer's Disease; SPM, Statistical Parametric Mapping; 18F-FDG-PET, Positron Emission Tomography with 18F-Fluorodeoxyglucose; CSF, Cerebrospinal Fluid; APOE, Apolipoprotein E; APP, Amyloid Precursor Protein; PSEN1, Presenilin 1; PSEN2, Presenilin 2; GRN, Progranulin; MAPT, Microtubule-Associated Protein Tau; C9orf72, Chromosome 9 Open Reading Frame 72; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; RAVLT, Rey Auditory Verbal Learning Test; ROCF, Rey-Osterrieth Complex Figure; TMT-A, Trail-Making Test part A; TMT-B, Trail-Making Test part B; SAND, Screening for Aphasia in NeuroDegeneration battery; HRMA, High-Resolution Melting Analysis; PCR, Polymerase Chain Reaction; CLEIA, Chemiluminescent Enzyme Immunoassay; t-tau, Total Tau; p-tau, Phosphorylated Tau; NIA-AA, National Institute on Aging and Alzheimer's Association; EANM, European Association of Nuclear Medicine; FWHM, Full Width at Half Maximum; MNI, Montreal Neurological Institute; HC, Healthy Controls; PCA, Principal Component Analysis; AHC, Agglomerative Hierarchical Clustering.

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1. Introduction

Primary progressive aphasia (PPA) represents a heterogeneous group of neurodegenerative syndromes characterised by a prominent and gradual progressive decline in speech and language function [1]. The current consensus classification identifies three prototypical variants [2]: the semantic variant (svPPA), nonfluent variant (nfvPPA), and logopenic variant (lvPPA). However, a significant number of PPA patients (6%–41%) [3,4] do not meet the criteria for a prototypical variant and are classified as mixed PPA subtypes (mPPA).

The lack of a common definition of this non-prototypical PPA subtype as well as clinical and etiological characterisation leads to misclassification of PPA cases [5,6] and indicates the need for better characterisation of this patient group [7]. Traditionally, mPPA patients have been considered to be affected by more advanced stages of a single PPA variant [8]. Nevertheless, subsequent studies demonstrated that within the group of patients who do not strictly meet the criteria for a specific PPA variant, it is possible to identify repetitive linguistic and pathological patterns [9] that cannot solely be explained as a more severe and prolonged disease course [10,11].

Previous studies found that the majority of mPPA cases showed the pathological hallmarks of the lvPPA variant [12,13], leading the authors to include these cases in the spectrum of AD-related PPA. Similarly, in a previous study by our group, we showed that a subgroup of mPPA patients who presented deficits in both naming and repetition, as well as agrammatism (features consistent with either nfvPPA or lvPPA), consistently displayed positive AD biomarkers [14]. Other reports showed that mPPA patients can exhibit single-word comprehension deficits along with apraxia of speech or agrammatism, which are overlapping features of nfvPPA and svPPA [10].

To untangle the complexity of linguistic patterns of this neurodegenerative disorder that did not emerge by applying clinical criteria, other studies applied data-driven approaches. For instance, a study that used K-means clustering based on semantic and non-linguistic cognitive scores showed segregation between semantic and non-semantic variants, identifying a cluster of patients mainly populated by those with mPPA and characterised by more severe deficits in speech, repetition, syntax, and semantic and other cognitive deficits [15]. Another study used hierarchical cluster analysis and identified two clusters of mPPA, one resembling logopenic PPA with phonological errors, and a second cluster including patients with naming difficulties and impaired object knowledge, hence being more characteristic of svPPA [13].

In the current study, our primary focus was on patients diagnosed with mPPA who displayed linguistic characteristics consistent with both svPPA and lvPPA, which we categorised as semantic-logopenic variant of PPA (s/lvPPA). We hypothesised that distinct subgroups would be identified in the s/lvPPA group. To test this hypothesis, we employed a data-driven approach using an unsupervised learning algorithm to discern clusters based on linguistic features. Subsequently, we conducted an in-depth analysis of the neuropsychological performance, brain metabolic patterns, and AD biomarker profiles within the identified clusters.

2. Methods

2.1. Participants and assessments

Between January 2015 to March 2022, 110 patients referred to our centre for language disturbance fulfilled the current consensus criteria for PPA [16]. Patients were classified into PPA variants by two neurologists (SM and VB) and two neuropsychologists (CP and SP) with expertise in cognitive disorders, according to the current diagnostic criteria of PPA [2]. For the purpose of this study, we considered patients with lvPPA, svPPA, and mPPA who showed linguistic features shared between logopenic and semantic variants (s/lvPPA). Supplementary Table 1 details all the linguistic features for each s/lvPPA patient. We defined as s/lvPPA those patients that exhibited linguistic features of both svPPA and lvPPA, suggestive of disruption of two different circuit (the semantic system in the first case and the phonologic loop in the latter). For example: P.6 showed both core and subsidiary features for svPPA (impaired picture naming and single-word comprehension; impaired object knowledge, spared motor speech, and absence of frank agrammatism) and both core and subsidiary features for lvPPA (impaired picture naming and repetition of sentences; spared motor speech, absence of frank agrammatism); P. 8 showed core (impaired picture naming and single-word comprehension) and subsidiary (impaired object knowledge, spared repetition, spared motor speech, absence of frank agrammatism) criteria for svPPA, but also a core (impaired picture naming) and a subsidiary criterion (phonologic errors) for lvPPA as well as impaired non-word repetition (with spared word repetition), that are features suggestive of involvement of the phonologic loop; P.13 showed core (impaired picture naming and repetition of sentences) and subsidiary criteria (spared single-word comprehension, spared speech production and absence of frank agrammatism), but also a core (impaired picture naming) and a subsidiary criterion (surface dyslexia) for svPPA and suggestive of involvement of the semantic system; P.15 showed only one core criterion for svPPA (impaired single-word comprehension) and only one criterion for lvPPA (impaired repetition of sentences).

We excluded i) non-native Italian speakers; ii) patients with a history of head injury, current neurological and/or systemic disease, or substance use disorder; and iii) patients with severe language impairment that did not allow neuropsychological evaluation. For Statistical Parametric Mapping (SPM) analysis of ^{18}F-Fluorodeoxyglucose-PET brain scan (^{18}F-FDG-PET), we excluded 12 patients with predominant right-hemisphere hypometabolism. Ultimately, 55 patients were included in this study.

All the patients underwent speech and language testing, brain magnetic resonance imaging (MRI), computed tomography (CT), and ^{18}F-FDG-PET. Forty-eight patients (11 svPPA, 21 lvPPA and 16 s/lvPPA) underwent lumbar puncture for CSF collection. Seven patients who refused lumbar puncture underwent amyloid-PET.

Forty-four patients (12 svPPA, 20 lvPPA and 12 s/lvPPA) gave further informed consent for genetic analysis of Apolipoprotein E (*APOE*), amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), progranulin (*GRN*), microtubule-associated protein tau (*MAPT*), and chromosome 9 open reading frame 72 (*C9orf72*).

We defined "age" as the age at the time of neuropsychological assessment, and disease duration as the timeframe from the onset of symptoms and baseline evaluation.

2.2. Standard protocol approvals, registrations, and patient consents

The study procedures and data analysis were performed in accordance with the Declaration of Helsinki and the ethical standards of the Committee on Human Experimentation of our Institute. The study was approved by the local Institutional Review Board (reference 15691oss). All participants provided informed consent to participate in the study and to obtain details and results of their research about them published.

2.3. Neuropsychological and language evaluation

All patients were evaluated using a neuropsychological battery, including the Mini-Mental State Examination (MMSE) [17], Frontal Assessment Battery (FAB) [18], Digit-Span and Spatial-Span forward and backward [19], Rey Auditory Verbal Learning Test [20] (RAVLT), Short Story recall [21], Rey-Osterrieth Complex Figure (ROCF) copy and delayed recall[22], Trail-making Test part A (TMT-A) and part B (TMT—B) [23], attentional matrices[24], and Stroop test (time and errors) [25]. Language was assessed using the Category Fluency Task [26], the Phonemic Fluency Task [27], and the Screening for Aphasia in NeuroDegeneration (SAND) battery [28].

2.4. Blood collection, DNA extraction and gene analysis

Blood was collected by venipuncture into standard polypropylene EDTA test tubes (Sarstedt, Nümbrecht, Germany) and centrifuged within two hours at 1300 rcf at room temperature for 10 min. Plasma was isolated and stored at −80 °C until testing. A standard automated method (QIAcube, QIAGEN) was used to isolate DNA from the peripheral blood samples. *APOE* genotypes were investigated using HRMA. Two sets of PCR primers were designed to amplify the regions encompassing rs7412 [NC_000019.9: g.45412079C > T] and rs429358 (NC_000019.9:g.45411941 T > C). Samples with known *APOE* genotypes that were validated by DNA sequencing were used as standard references. Patients who were carriers of the ε4 allele (one or two *APOE* ε4 alleles) were classified as *APOE* $\varepsilon4^+$, whereas those who were not carriers of the ε4 allele (no *APOE* ε4 alleles) were classified as *APOE* $\varepsilon4^-$.

All coding exons and intron/exon boundaries of familial AD genes (*APP, PSEN1*, and *PSEN2*) and frontotemporal dementia genes (*GRN* and *MAPT*) were amplified by polymerase chain reaction (PCR) using primers designed with Primer3 software (http://bioinfo.ut.ee/primer3-0.4.0/primer3/). The analysis was performed using high-resolution melting analysis (HRMA), followed by direct sequencing of amplicons showing heteroduplexes (310 ABI PRISM Genetic Analyser; Applied Biosystems). *C9orf72* repeat expansion was searched using the repeat-primed PCR and automatic sequencing (3700 ABI PRISM Genetic Analyser; Applied Biosystem), the characteristic stutter amplification pattern was considered as indication of pathogenic repeat expansion (>22 repeats).

2.5. CSF biomarker collection and analysis

CSF samples were collected at 8:00 a.m. by lumbar puncture at the Neurology Unit of Careggi University Hospital. The samples were immediately centrifuged and stored at −80 °C until analysis at the Laboratory of Neurogenetics of Careggi University Hospital. $A\beta_{42}$, $A\beta_{40}$, t-tau, and p-tau were measured using a chemiluminescent enzyme immunoassay (CLEIA) analyser LUMIPULSE G600 (Fujirebio, Tokyo, Japan). Cut-off values for CSF biomarkers were determined following Fujirebio guidelines (diagnostic sensitivity and specificity using clinical diagnosis and the follow-up gold standard as of November 19th, 2018). The normal values for CSF biomarkers were $A\beta_{42}$ > 670 pg/ml, $A\beta_{42}/A\beta_{40}$ ratio > 0.062, t-tau <400 pg/ml, and p-tau <60 pg/ml [29].

2.6. Amyloid Pet acquisition and rating

Amyloid PET imaging was performed according to standard national and international guidelines [30] with any of the available fluorine18-labeled tracers (^{18}F-Florbetaben [FBB]-Bayer-Pyramal, ^{18}F-Flutemetamol [FMM]-General Electric). Images were rated as positive or negative, according to the criteria defined by the manufacturer.

2.7. Classification of patients according to the ATN classification

Based on biomarker results, patients were classified according to the NIA-AA Research Framework [31]: A+ if at least one of the amyloid biomarkers (CSF or amyloid PET) revealed the presence of Aβ pathology; A- if none of the biomarkers revealed the presence of Aβ pathology; T+ or T- if CSF p-tau concentrations were higher or lower than the cut-off value, respectively; and N+ or N- if CSF t-tau concentrations were higher or lower than the cut-off value, respectively.

2.8. ^{18}F-FDG-PET scan acquisition and SPM analysis

^{18}F-FDG-PET scans were acquired following the EANM procedure guidelines[32] using an advanced hybrid PET-CT scanner in 3D list mode. PET data were reconstructed using a 3D iterative algorithm and corrected for attenuation, randomness, and scattering using the manufacturer's software.

^{18}F-FDG-PET images were normalised to MNI space using a validated procedure [30]. The images were smoothed with an isotropic 3D Gaussian kernel with an FWHM of 8 mm in each direction and then used for a single-subject SPM-based routine [33] for diagnostic purposes. Age was included as a covariate in the two-sample *t*-test analysis.

The SPM t-map of hypometabolism resulting from statistical comparison with the normal ^{18}F-FDG-PET image database (i.e. one patient versus 77 healthy controls [HC]) allowed the definition of disease-specific metabolic patterns. The threshold was set at $p = 0.05$, and FWE-corrected for multiple comparisons at the voxel level. Only clusters containing >100 voxels were considered to be statistically significant. HC were selected from among subjects included in the ^{18}F-FDG-PET HC database of the "*Associazione Italiana di Medicina Nucleare*." HC were included in the SPM analysis only if data on age, sex, education, cognitive status, and follow-up assessment for at least one year were available ($n = 77$; age 62.32 ± 13.89; MMSE 29.23 ± 0.94; education 11.16 ± 4.29). The SPM two-sample *t*-test was performed to compare lvPPA, svPPA, k1, and k2 patients with HC. The threshold was set at $p < 0.05$, and FWE-corrected for multiple comparisons at the cluster level. Only clusters containing >100 voxels were considered to be statistically significant.

Post-hoc ROI analyses were conducted on normalised ^{18}F-FDG-PET scans. ROIs were extracted using the MarsBar tool by constructing a spherical ROI of 10 mm radius, centred on the local maxima coordinates of the significant clusters resulting from the comparison between k1 and k2 with HC. The ^{18}F-FDG uptake of the ROIs was normalised to the Gray Matter global mean.

2.9. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics Software Version 25 (SPSS Inc., Chicago, USA), R 4.2.3 (R Foundation for Statistical Computing, Vienna, 2013) and Python 3.11.4 (Python Software Foundation, www.python.org). All *p*-values were two-tailed and the significance level for all analyses was set at $p = 0.05$. Distributions of all variables were assessed using the Shapiro-Wilk test. Descriptive statistics were calculated using means and standard deviations (SD) for continuous variables, and frequencies or percentages and 95% confidence intervals (95%C.I.) for categorical variables. We used the t-test for comparisons between the two groups and analysis of covariance (ANCOVA) to adjust for age as a possible confounding factor. Associations between categorical variables were tested using the chi-square (χ^2) test. Correlations between variables were tested using Pearson's coefficient. Dimensionality of language scores (phonemic fluency, category fluency, picture naming, single-word comprehension, auditory sentence comprehension, sentence repetition, word repetition, non-word repetition, word reading, non-word reading, semantic association) was reduced using a principal component analysis (PCA). To ensure that all variables were on the same scale, the data were standardised as z-scores based on the mean and SD of the whole cohort. The eigenvalues and eigenvectors were computed from the covariance matrix of the standardised dataset. The explained variance and component matrix were extracted to assess the contribution of each principal component. We set the cut-off for selecting the number of principal components (PC) at 80% of the explained variance. Agglomerative hierarchical clustering (AHC) was performed based on the extracted PCs, using Ward's method, and a dendrogram was visualised to explore the hierarchical relationships among data points. To determine the optimal number of clusters and assess their quality, the silhouette method was applied. The average silhouette coefficient across all clusters was used to evaluate the overall quality of clustering.

3. Results

3.1. Description of samples and between-group comparisons

Twelve patients were classified as having svPPA (21.82%) and 23 as having lvPPA (41.82%). Twenty patients (36.36%) showed overlapping features of svPPA and lvPPA and were classified as having mixed s/lvPP (a detailed description of the PPA criteria met by each s/lvPPA patient is reported in Supplementary Table 1). The descriptions and comparisons between the groups are shown in (Table 1). In particular, patients with s/lvPPA were older than those with svPPA ($p = 0.002$, $d = 1.324$) and lvPPA ($p = 0.003$, $d = 1.052$). There were no statistically significant differences between the groups regarding disease duration, family history of dementia, gender and *APOE* ε4 prevalence. There were no differences in language and neuropsychological scores between s/lvPPA and svPPA, or between s/lvPPA and lvPPA (s/lvPPA language and neuropsychological data are reported in Supplementary Table 2). Correlations between language scores are reported in Supplementary Figure. We found significant correlations between phonemic and category fluency ($\chi^2 = 0.052$, $p = 0.014$), category fluency and picture naming ($\chi^2 = 0.493$, $p = 0.032$), sentence comprehension and non-word repetition ($\chi^2 = 0.499$, $p = 0.025$), single-word comprehension and semantic association ($\chi^2 = 0.645$, $p = 0.005$), word reading and non-word reading ($\chi^2 = 0.615$, $p = 0.004$). We did not observe any variation in the analysed genes.

3.2. Cluster analysis and between-group comparisons

PCA of the language scores identified five principal components (PC) that explained 80% of the variance. Fig. 1 shows the weights of the variables for each PC. We did not address multicollinearity considering the low level of correlation among the variables. Based on these five components, we performed AHC analysis of the s/lvPPA group. Our analysis identified two distinct clusters (k1 and k2) that yielded the highest average silhouette score (0.25). This score suggested a moderate level of separation between clusters. Either k1 and k2 included 10 patients (Fig. 2). Patients in k1 group were older than svPPA (74.01 [4.13] vs. 64.42 [8.57], $p = 0.006$, $d = 1.451$) and lvPPA (74.01 [4.13] vs. 66.22 [7.02], $p = 0.013$, $d = 1.180$). The mean age of the k2 cluster was 72.12 (4.79), with no differences with svPPA and lvPPA. There were no statistically significant differences between svPPA, lvPPA, k1, and k2 regarding disease duration, family history of dementia, sex, or *APOE* ε4 prevalence.

Table 1
Demographic variables and *APOE* ε4$^+$ proportion of svPPA, lvPPA, and s/lvPPA.

	svPPA	lvPPA	s/lvPPA
N (%)	12 (21.82%)	23 (41.82%)	20 (36.36%)
Age	64.42 (8.58)[a]	66.22 (7.02)[b]	73.13 (4.44)[a, b]
Disease duration	3.34 (2.35)	2.20 (1.37)	2.66 (1.73)
Women	5/12 (41.67%)	10/23 (43.48%)	12/20 (60.00%)
Family history of dementia	6/12 (50.00%)	13/23 (56.52%)	6/20 (30.00%)
Year of education	11.17 (4.15)	14.87 (5.24)	11.48 (5.02)
APOE ε4$^+$	2/12 (16.67%)	5/20 (25.00%)	3/12 (25.00%)

Values quoted in the table are mean (SD) for continuous variables and frequencies (%) for dichotomous variables. Age, disease duration, and education are reported in years. Between-group comparisons: *t*-test (for normally distributed variables); categorical data comparisons: χ^2 test. Size effect: Cohen's *d* for continuous measures, Cramer's V for categorical data. Statistical significance was set at $p < 0.05$.

[a] $p = 0.002$, $d = 1.324$.

[b] $p = 0.003$, $d = 1.052$.

3.3. AD biomarker profiles

We performed an ANCOVA adjusted for age to compare CSF biomarker concentrations between PPA subgroups (Table 2). We found that k1 had lower $A\beta_{42}$ ($p = 0.048$, $\eta^2 = 0.256$), lower $A\beta_{42}/A\beta_{40}$ ratio ($p = 0.033$, $\eta^2 = 0.313$), and higher p-tau ($p = 0.031$, $\eta^2 = 0.294$) than k2. k1 also had lower $A\beta_{42}$ ($p = 0.036$, $\eta^2 = 0.243$), lower $A\beta_{42}/A\beta_{40}$ ratio ($p < 0.001$, $\eta^2 = 0.742$), higher p-tau ($p < 0.001$, $\eta^2 = 0.539$) and t-tau ($p = 0.040$, $\eta^2 = 0.232$) than svPPA. k2 had higher $A\beta_{42}/A\beta_{40}$ ratio ($p = 0.006$, $\eta^2 = 0.262$) than lvPPA. No differences were observed between k1 and lvPPA expression. lvPPA had lower $A\beta_{42}$ ($p = 0.001$, $\eta^2 = 0.307$), lower $A\beta_{42}/A\beta_{40}$ ratio ($p < 0.001$, $\eta^2 = 0.707$), higher p-tau ($p = 0.002$, $\eta^2 = 0.284$) and higher t-tau ($p = 0.023$, $\eta^2 = 0.164$) than svPPA (Fig. 3).

Regarding the proportion of A, T, and N positivity, we found that among the k1 patients, 90% were A+, 75.00% were T+, and 87.5% were N+. Among k2 patients, 50% were A+, 50.00% were T+, and 62.5% were N+. The proportions of A+ and T+ were significantly higher in k1 than in svPPA ($\chi2 = 7.25$, $p = 0.007$, $V = 0.574$; $\chi2 = 4.23$, $p = 0.040$, $V = 0.472$, respectively) and lvPPA than in k2 ($\chi2 = 9.76$, $p = 0.002$, $V = 0.544$; $\chi2 = 4.03$, $p = 0.045$, $V = 0.373$, respectively). There were no differences between k1 and k2, k1 and lvPPA, or k2 and svPPA (Table 2).

3.4. Neuropsychological scores and linguistic profiles

We performed an ANCOVA adjusted for age to compare neuropsychological and linguistic scores between PPA subgroups. Regarding neuropsychological scores (Supplementary Table 3), k1 had lower score than k2 in MMSE ($p = 0.007$, $\eta^2 = 0.320$), FAB ($p = 0.037$, $\eta^2 = 0.251$), ROCF copy ($p = 0.018$, $\eta^2 = 0.296$) and attentional matrices ($p = 0.014$, $\eta^2 = 0.328$). k2 had higher scores than lvPPA in the MMSE ($p = 0.025$, $\eta^2 = 0.132$) and attentional matrices ($p = 0.043$, $\eta^2 = 0.151$). There were no differences between k1 and svPPA, or between svPPA and lvPPA.

Regarding linguistic profiles (Table 2, Fig. 4), k1 had lower score than k2 in semantic fluency ($p = 0.017$, $\eta^2 = 0.291$), naming ($p < 0.001$, $\eta^2 = 0.574$), single-word comprehension ($p = 0.003$, $\eta^2 = 0.397$), and semantic association ($p = 0.012$, $\eta^2 = 0.330$). k1 also had lower score than lvPPA in naming ($p = 0.036$, $\eta^2 = 0.152$) and semantic association ($p = 0.031$, $\eta^2 = 0.574$), whereas k2 had higher scores than svPPA in category fluency ($p = 0.048$, $\eta^2 = 0.201$), naming ($p = 0.009$, $\eta^2 = 0.307$), and single-word comprehension ($p = 0.016$, $\eta^2 = 0.267$). There were no differences between k1 and svPPA or between k2 and lvPPA.

To exclude the possibility that the differences between k1 and k2 might be driven by the pathological substrate, we compared s/lvPPA with A- ($n = 6$ [30.00%]) and s/lvPPA with A+ ($n = 14$ [70%]) and found no differences in the linguistic profiles between these two groups (Supplementary Table 4).

3.5. Brain metabolic patterns

The ^{18}F-FDG-PET SPM group analysis (Fig. 5, Supplementary Table 5) revealed that compared to HC:

1. svPPA and lvPPA exhibited typical patterns of hypometabolism (respectively, involvement of the anterior temporal region and parietotemporal hypometabolism);
2. k1 showed extensive temporoparietal hypometabolism, ranging from the left inferior temporal gyrus (ITG), including the left temporal pole (TP), to the left middle temporal gyrus (MTG), including the fusiform gyrus, reaching the left angular gyrus;
3. k2 showed extensive temporoparietal hypometabolism, ranging from the left ITG, including the left TP, to the left MTG, including the fusiform gyrus, reaching the superior temporal gyrus (STG) and left angular gyrus. An additional area of hypometabolism was found in the left gyrus rectus.

We extracted the mean ^{18}F-FDG uptakes in the ROIs centred on the

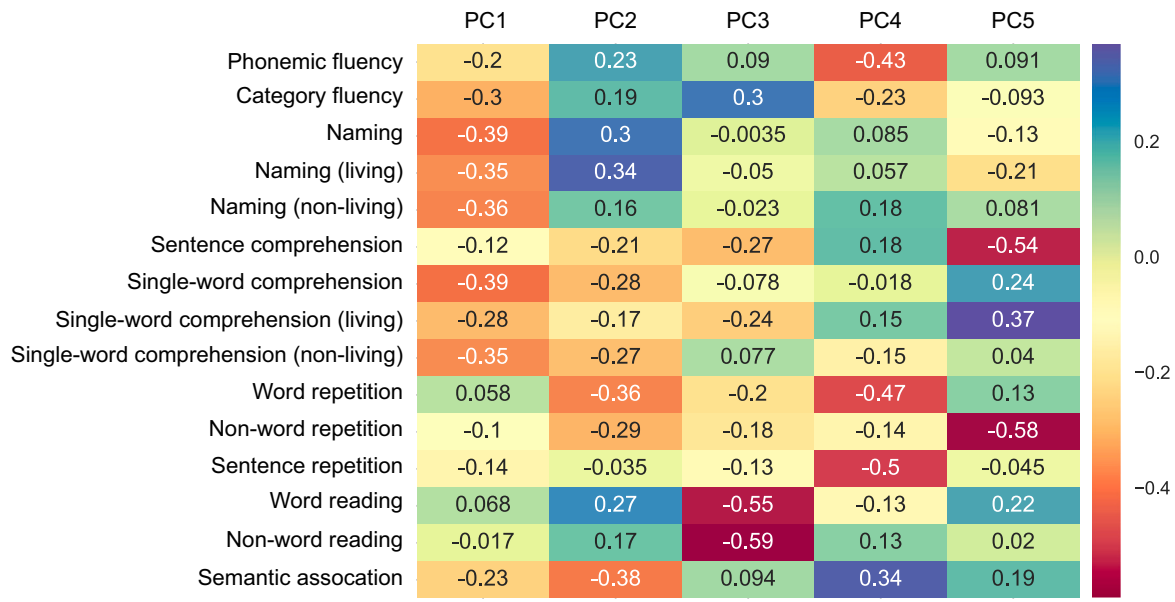

Fig. 1. Correlation matrix showing the weight of language tests in each principal component (PC1, PC2, PC3, PC4, PC5).
Each cell represents the contribution of a language test to its corresponding principal component.

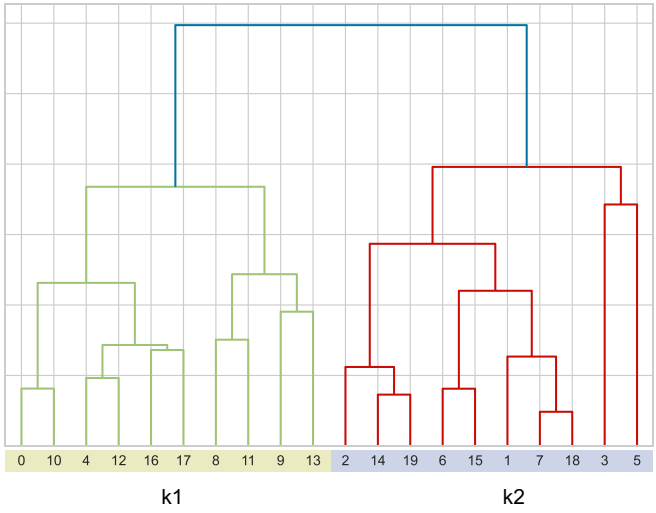

Fig. 2. Dendrogram showing the classification of s/lvPPA cases into two clusters (k1 and k2) performed with AHC analysis.
Each number represents an individual with s/lvPPA. The lines and divisions illustrate the pairwise similarities and distances between these cases, and the vertical lines depict the clustering process, where cases are grouped into distinct clusters, denoted as k1 and k2.

peak coordinates of the significant clusters resulting from the comparison between k1 and HC, and between k2 and HC.

We performed ANCOVA adjusted for age to compare the 18F-FDG uptake values in each ROI between the PPA subgroups (Table 2).

K1 had a lower uptake than lvPPA in the left ITG ($p = 0.016$, $\eta^2 = 0.170$) and left MTG ($p = 0.018$, $\eta^2 = 0.166$).

k2 had lower uptake than lvPPA in left superior TP ($p = 0.009$, $\eta^2 = 0.191$), left ITG ($p = 0.014$, $\eta^2 = 0.187$), left MTG ($p = 0.010$, $\eta^2 = 0.206$), and left gyrus rectus ($p = 0.014$, $\eta^2 = 0.207$). lvPPA had a greater uptake than svPPA in left superior TP ($p < 0.001$, $\eta^2 = 0.566$), left ITG ($p < 0.001$, $\eta^2 = 0.563$), left MTG ($p < 0.001$, $\eta^2 = 0.574$), and left gyrus rectus ($p = 0.008$, $\eta^2 = 0.213$).

There were no differences between k1 and k2, between k1 and svPPA, and between k2 and svPPA.

There were no differences in ^{18}F-FDG uptake between s/lvPPA with A- and s/lvPPA with A+. (Supplementary Table 4).

4. Discussion

The main result of our study was that patients classified as having s/lvPPA could be clustered into two subgroups based on language features. K1 individuals exhibited greater impairment than k2 patients in both global cognition (as assessed by MMSE) and frontal function (evaluated through FAB and attentional matrices), and their linguistic profile more closely resembled that of svPPA. In contrast, k2 individuals exhibited a linguistic profile more akin to lvPPA, albeit with relatively preserved global cognitive functions, than lvPPA. A similar classification was shown in a previous study [13] using the same clustering methods (hierarchical cluster analysis) on a group of 26 unclassifiable PPA cases, in which the authors identified a first cluster resembling logopenic PPA and a second cluster including naming difficulties and impaired object knowledge, which are more characteristic of svPPA.

We further showed that these two clusters also correspond to different AD biomarker profiles, with k1 presenting a biomarker profile consistent with AD in most cases, whereas k2 was more heterogeneous, with only half of the patients being positive for AD. Interestingly, there was no correspondence between the pathologic substrate and the expected linguistic features, and the linguistic profile of k1 was more similar to the linguistic profile of svPPA, whereas k2 had a linguistic profile partially overlapping with lvPPA.

Analysis of brain ^{18}F-FDG-PET data has provided intriguing insights that can be correlated with biomarkers and linguistic information. Specifically, our findings revealed the following key observations: i) both k1 and k2 clusters exhibited temporoparietal hypometabolism, including the involvement of the temporal pole. This observation validates that the mixed linguistic presentation in our subjects corresponds to a neuronal correlate shared between the typical hypometabolic patterns seen in svPPA and lvPPA; ii) no significant differences were observed between the s/lvPPA clusters and svPPA alone. This aligns with previous evidence suggesting that patients exhibiting overlapping clinical features of svPPA and lvPPA also display a gray matter loss profile similar to that of pure svPPA patients [13]; iii) the k2 cluster exhibited a more extensive hypometabolism pattern in the temporal lobe than lvPPA, and additionally involved the frontal lobe, specifically

Table 2
Comparison of AD biomarker profiles, linguistic scores, and ^{18}F-FDG uptake between PPA groups.

	svPPA	lvPPA	k1	k2
N (%)	12 (21.43%)	23 (41.07%)	10 (17.86%)	10 (19.64%)
	AD biomarker profiles			
$A\beta_{42}$	977.64 (412.99) [a, b]	564.76 (231.43) [a]	470.88 (275.66) [b, c]	894.13 (503.68) [c]
$A\beta_{42}/A\beta_{40}$	0.12 (0.19) [d, e]	0.05 (0.02) [d, f]	0.05 (0.11) [e, g]	0.08 (0.03) [f, g]
p-tau	38.33 (15.44) [h, i]	131.96 (88.12) [h]	134.13 (53.08) [i, j]	70.20 (45.07) [j]
t-tau	413.82 (243.36) [k, l]	770.95 (448.61) [k]	772.63 (262.28) [l]	484.50 (248.69)
A+	4/12 (33.33%) [m, n]	22/23 (95.65%) [m, o]	9/10 (90.00%) [n]	5/10 (50.00%) [o]
T+	3/11 (27.27%) [p, q]	18/21 (85.71%) [p, r]	6/8 (75.00%) [q]	4/8 (50.00%) [r]
N+	5/11 (45.45%) [s]	18/21 (85.71%) [s]	7/8 (87.5%)	5/8 (62.5%)
Differences between groups: [a] p = 0.001, η^2 = 0.307; [b] p = 0.036, η^2 = 0.243; [c] p = 0.048, η^2 = 0.256; [d] p < 0.001, η^2 = 0.707; [e] p < 0.001, η^2 = 0.742; [f] p = 0.006, η^2 = 0.262; [g] p = 0.033, η^2 = 0.313; [h] p = 0.002, η^2 = 0.284; [i] p < 0.001, η^2 = 0.539; [j] p = 0.031, η^2 = 0.294; [k] p = 0.023, η^2 = 0.164; [l] p = 0.040, η^2 = 0.232; [m] χ2 = 16.03, p < 0.001, V = 0.677; [n] χ^2 = 7.25, p = 0.007, V = 0.574; [o] χ^2 = 9.76, p = 0.002, V = 0.544; [p] χ^2 = 10.93, p < 0.001, V = 0.584; [q] χ^2 = 4.23, p = 0.040, V = 0.472; [r] χ^2 = 4.03, p = 0.045, V = 0.373; [s] χ^2 = 5.79, p = 0.016, V = 0.425				
	Linguistic profiles			
Phonemic fluency	20.77 (9.73)	20.53 (10.17)	16.18 (9.50)	21.33 (10.67)
Category fluency	17.00 (7.07) [a, b]	21.43 (12.11) [a]	15.20 (8.75) [c]	25.80 (8.66) [b, c]
Picture naming	3.64 (4.63) [d, e]	8.73 (4.41) [d, f]	3.70 (2.93) [f, g]	9.73 (2.72) [e, g]
Single-word comprehension	7.42 (3.63) [h, i]	10.70 (1.99) [h]	9.03 (1.67) [j]	11.22 (0.87) [i, j]
Auditory sentence comprehension	6.86 (1.55)	6.04 (1.58)	5.09 (2.94)	6.78 (1.34)
Sentence repetition	3.06 (1.74) [k]	1.66 (1.23) [k]	2.06 (1.57)	2.31 (1.06)
Word repetition	6.00 (0.00)	5.75 (0.52)	5.92 (0.28)	5.71 (0.92)
Non-word repetition	2.15 (1.31)	2.10 (1.51)	1.10 (1.49)	1.68 (1.55)
Word reading	10.02 (2.21)	11.16 (1.77)	11.69 (0.45)	10.90 (1.85)
Non-word reading	3.44 (1.13)	3.65 (0.90)	3.69 (0.45)	3.61 (0.90)
Semantic association	2.16 (1.19)	2.77(1.15) [l]	1.44 (1.18) [l, m]	2.88 (0.85) [m]
Differences between groups: [a] p = 0.017, η^2 = 0.291; [b] 0.048, η^2 = 0.201; [c] p = 0.017, η^2 = 0.291; [d] p = 0.002, η^2 = 0.256; [e] p = 0.009, η^2 = 0.307; [f] p = 0.036, η^2 = 0.152,; [g] p < 0.001, η^2 = 0.574; [h] p = 0.001, η^2 = 0.276; [i] p = 0.016, η^2 = 0.267; [j] p = 0.003, η^2 = 0.397; [k] p = 0.013, η^2 = 0.182; [l] p = 0.031, η^2 = 0.574; [m] p = 0.012, η^2 = 0.330				
	^{18}F-FDG uptakes			
L hippocampus	46.15 (2.29)	45.67 (2.48)	45.10 (3.01)	43.58 (2.67)
L superior temporal pole	26.52 (4.27) [a]	35.81 (4.03) [a, b]	30.97 (5.31)	30.04 (3.13) [b]
L inferior temporal gyrus	33.12 (4.06) [c]	41.70 (3.60) [c, d, e]	36.86 (3.28) [e]	36.55 (4.44) [d]
L middle temporal gyrus	33.18 (4.33) [f]	42.27 (3.67) [f, g, h]	37.32 (3.58) [h]	36.69 (4.74) [g]
L gyrus rectus	47.45 (4.43) [i]	51.27 (3.23) [i, j]	48.15 (5.57)	47.02 (1.53) [j]
Differences between groups: [a] p < 0.001, η^2 = 0.566; [b] p = 0.009, η^2 = 0.191; [c] p < 0.001, η^2 = 0.563; [d] p = 0.014, η^2 = 0.187; [e] p = 0.016, η^2 = 0.170; [f] p < 0.001, η^2 = 0.574; [g] p = 0.010, η^2 = 0.206; [h] p = 0.018, η^2 = 0.166; [i] p = 0.008, η^2 = 0.213; [j] p = 0.014, η^2 = 0.207				

Values quoted in the table are means (SD) for continuous variables and percentages (95% C.I.) for dichotomous variables. CSF biomarkers ($A\beta_{42}$, p-tau and t-tau) are expressed as pg/mL. Between-group comparisons for continuous variables: ANCOVA adjusted for age. Categorical data comparisons: χ^2 test. Size effect: η^2 for continuous measures. Cramer's *V* for categorical data. Superscript letters refer to the differences between groups reported in the table. Statistical significance was set at $P < 0.05$.

the left inferior frontal gyrus and gyrus rectus.

Therefore, we summarise our findings as follows (Table 3): cluster k1, characterised by linguistic features akin to svPPA, but with a biomarker profile indicative of Alzheimer's disease and a mixed ^{18}F-FDG-PET hypometabolism pattern; cluster k2, displaying linguistic features akin to lvPPA, a heterogeneous biomarker profile, and a mixed ^{18}F-FDG-PET hypometabolism pattern that is not only more extensive than lvPPA but also involves regions typically associated with svPPA. We also want to point out that, at the between-group comparison level, k1 showed no differences with svPPA, and k2 showed no differences with lvPPA regarding language features. This raises questions regarding the classification of these patients as having mPPA. Nevertheless, we showed that the classification of these patients as mPPA is justified at a single-subject level. The classification was indeed made in accordance with both the outcome of the proposed psychometric tests and based on the characteristics of spontaneous speech observed by the clinical neuropsychologist, which shows, as seen in the Supplementary Table 1, the coexistence and overlap of domain-specific difficulties pertaining to multiple prototypical variants. Our classification process (as explained in the methods section) of mPPA is grounded in both a clinical-neuropsychological and cognitive-neuropsychological perspective, in accordance with cognitive models detailing the different anatomical and functional distribution of various language networks in PPA [34,35]. In particular, the impairment of the phonological loop in lvPPA and the semantic degradation in svPPA involve distinct circuits and processes [35,36]. Hence, the simultaneous presence of lvPPA typical difficulties alongside other svPPA characteristics may be the clinical manifestation of the disruption of different functional circuits.

Several hypotheses may have arisen from our analysis. First, the differences in AD biomarker proportions between the two clusters suggest that they might represent the clinical manifestations of the two neuropathological substrates. In more detail k1 can include patients belonging to the spectrum of AD-related PPA, a terminology suggested by Sajjadi et al. [37], which is consistent with several studies showing that the clinical spectrum of PPA due to underlying Aβ pathology is broader than that of pure lvPPA, with language dysfunction extending into the language system, affecting syntactic production, phonological encoding, and semantic representations [38,39,14,40]. As this group presents cognitive and linguistic profiles more similar to svPPA, with brain metabolism involving the temporal pole, we speculate that this group does not represent an extension of lvPPA to a rostral area, but a distinct group with peculiar features.

Against this hypothesis, we should also consider the possibility that AD could represent a co-pathology alongside an underlying fronto-temporal lobar degeneration (FTLD) pathology, which we are currently unable to assess using pathological biomarkers. However, if the combined clinical presentation of these patients was due to a co-pathological condition, we would expect to observe certain linguistic profile distinctions between s/lvPPA cases exhibiting Alzheimer's pathologic changes and those without. However, no significant differences were found between the groups.

Another possibility to be considered is that k1 simply represents a group of patients with more advanced svPPA. Nevertheless, we did not find any difference in disease duration or MMSE scores between k1 and the prototypical svPPA group, which is in line with previous studies on larger samples [12,13]. It should also be considered that the MMSE is predominantly a verbal instrument, and its score is strongly influenced by the involvement of various language domains. Therefore, in PPA cases, poor performance on the MMSE in mPPA patients might not necessarily indicate a more advanced stage of the disease but rather impairment across multiple language domains.

Regarding k2, this cluster represents a more heterogeneous grou:

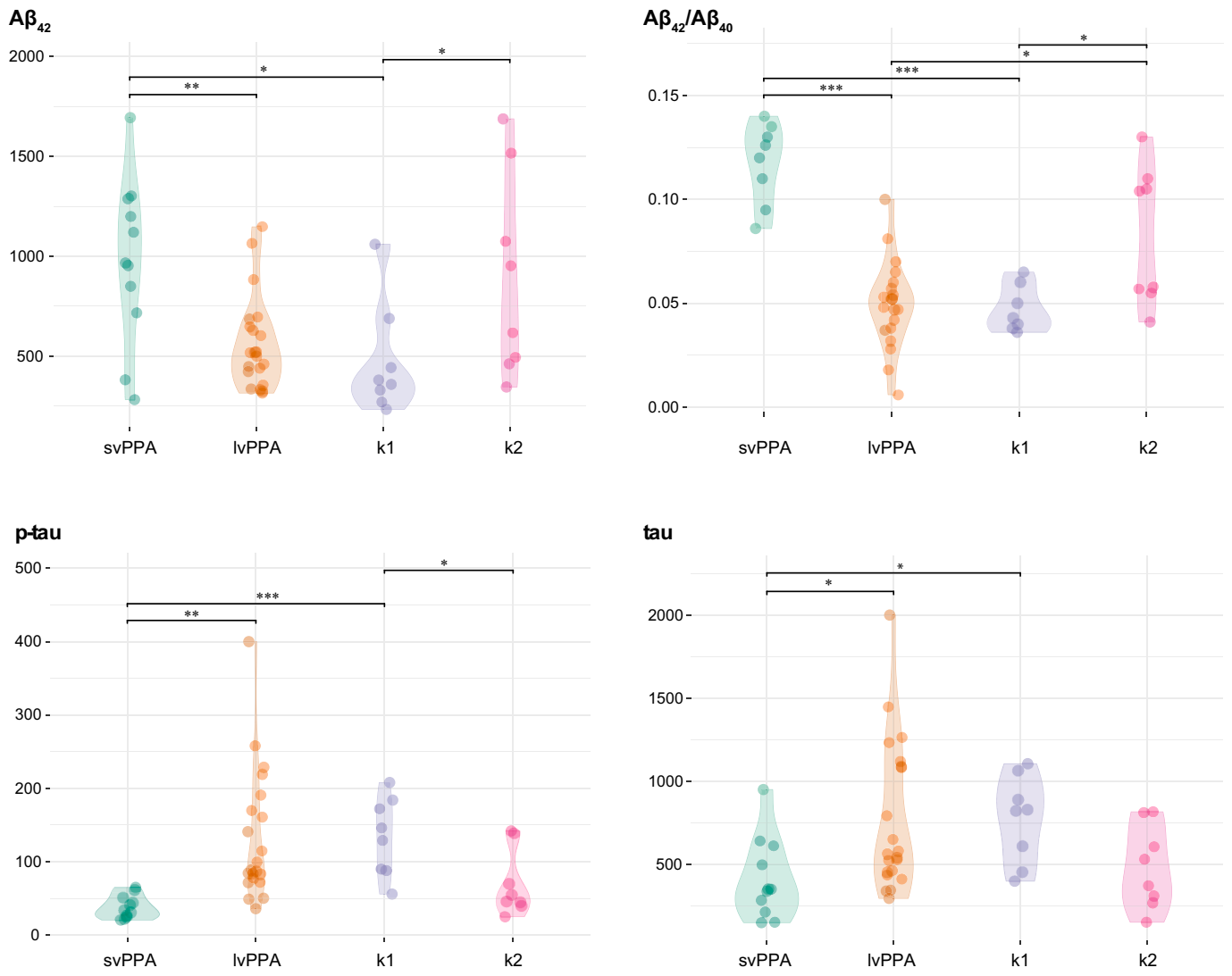

Fig. 3. Comparisons of CSF biomarker concentration between PPA groups.
$A\beta_{42}$ p-tau and t-tau are expresses as pg/mL. Between-group comparisons were adjusted for age.
* = $p < 0.05$; ** = $p < 0.01$; ** = $p < 0.001$.

most of these patients had negative AD biomarkers and presented less impairment in general cognition compared to k1, but a linguistic profile more similar to lvPPA, with differences in the core features of svPPA (single-word comprehension and naming). We did not perform a comparison between k2 cases with Alzheimer's pathological changes and those without, as the sample size would have been too small to draw conclusions. Nevertheless, we believe that focusing on this group might be particularly interesting in future studies to explore the effect of non-AD pathology on language systems. In particular, the observation that half of the patients included in this cluster had mixed PPA despite having negative AD biomarkers supports the hypothesis that AD-FTLD co-pathology cannot be considered the only explanation for mPPA presentation. This is in line with a neuropathology study by Bergeron et al. Bergeron et al. [3] reported Aβ pathology in only a minority of patients with mPPA. Additionally, Spinelli et al. [41] and Bergeron et al. Bergeron et al. [3] also showed a very different neuropathological profile between svPPA and mPPA, as TDP-43 type C pathology, which represents the majority of svPPA cases, was never found in mPPA. In contrast, TDP-43 type A, Pick's disease, and corticobasal degeneration together represent the most common pathological substrates of mPPA, but are very rarely described in svPPA. Based on this evidence, we can speculate that mixed s/lvPPA with negative AD biomarkers (included in cluster k2 according to our analysis) is not a more severe manifestation of svPPA, but might represent the linguistic manifestations of different pathological substrates in the spectrum of FTLD. Further studies including neuropathological correlates are needed to confirm this hypothesis.

Finally, as suggested by previous authors, mPPA might represent a longer and more advanced disease stage of PPA variants [8]. Nevertheless, in our cohort, there was no difference between prototypical and mixed PPA in terms of disease duration, and one of the two clusters (k2) was less impaired than lvPPA in general cognition. Moreover, all analyses were corrected for age, while disease duration was not different between the prototypical and s/lvPPA groups. This might allow us to exclude the possibility that mixed presentations can be attributed to a more advanced disease status. We can also exclude the effect of *APOE* on the prevalence of Aβ pathology, as there were no differences in ε4 between groups, as well as an effect due to a mutation in one of the genes involved in AD or FTLD.

There are some limitations that limit the conclusions of our study: i) the study involved a relatively small sample size and patients were referred to a single centre, which might limit the generalisability of the findings; ii) not all the patients underwent CSF and genetic analysis; iii) we reported that k1 exhibited greater impairment than k2 on the FAB scale, but we were unable to explore the subtests of the FAB scale to

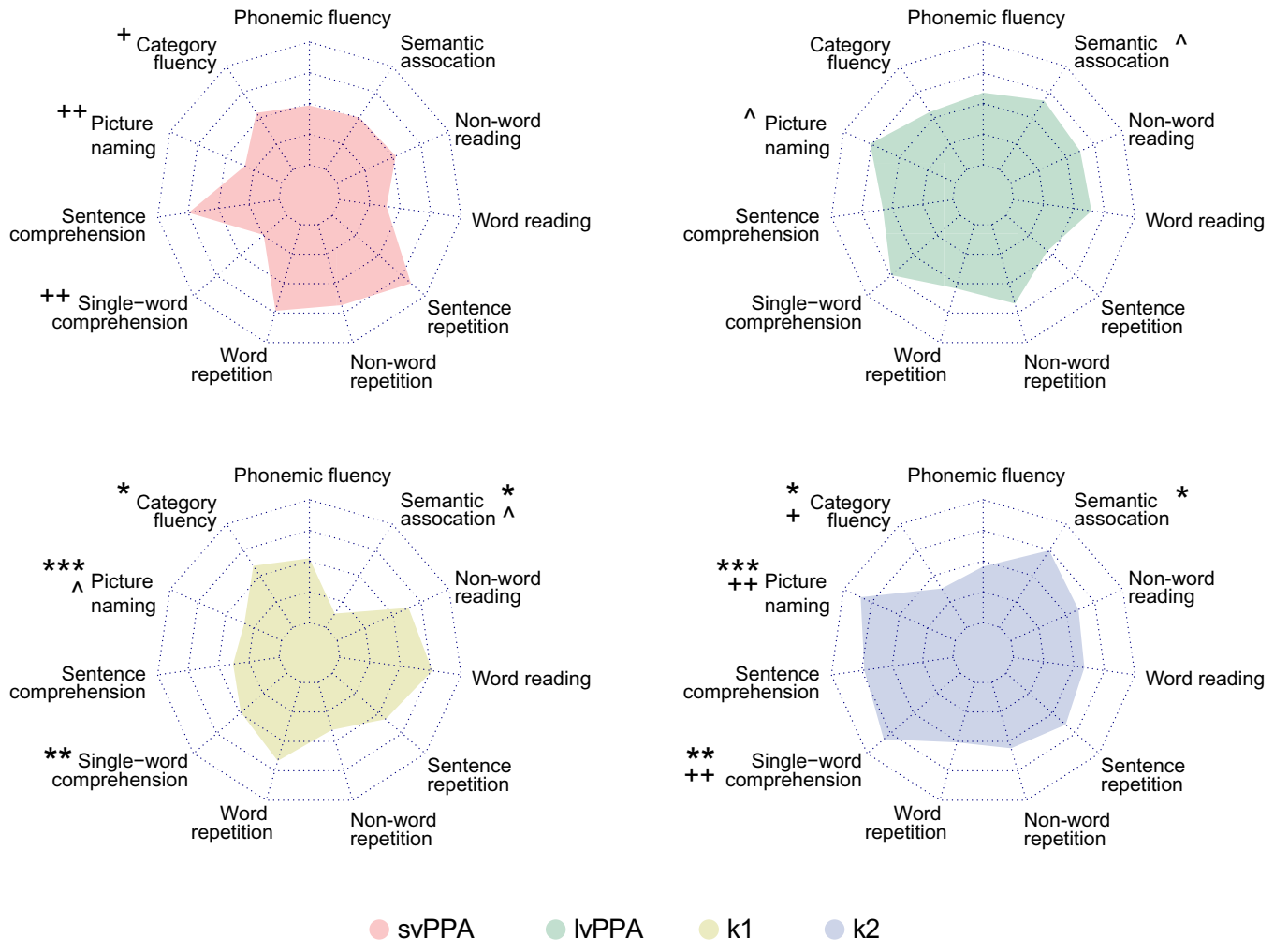

Fig. 4. Comparisons of language scores between PPA groups.
Language scores are reported as standardised values. "*" indicates significant differences between k1 and k2, "^" indicates significant differences between k1 and svPPA, "+" indicates significant differences between k2 and lvPPA. *Between-group comparisons were adjusted for age.*

provide further insight into the specific frontal functions involved; iv) MRI brain scans were evaluated only by visual inspection to exclude non-degenerative causes of aphasia; v) we did not have an independent sample to test our unsupervised hierarchical classification model; vi) neuropathological validation of the identified subgroups was not performed. Further research using post-mortem analysis would provide valuable insights into the underlying pathology.

However, there are some strengths that should be highlighted. First, we employed a comprehensive assessment approach that included clinical, neuropsychological, genetic, biomarker, and neuroimaging data. In particular, ^{18}F-FDG-PET scans and AD biomarker data allowed the investigation of the relationship between language profiles and functional and pathological substrates. The inclusion of AD biomarkers enhances the characterisation of patient subgroups and their relationship with underlying pathology. Finally, these patients were extensively characterised using neuropsychological, functional, and biological data. Moreover, although several previous studies have utilised a data-driven approach to investigate patients with PPA with a primary emphasis on neuroimaging data[42,43,44,45], the application of cluster analysis to unravel linguistic patterns in individuals with mPPA remains a relatively underexplored domain [15,46,13]. The adoption of this methodology offers a more objective avenue for exploring discernible patterns within a dataset, surpassing the dependence on conventional methodologies grounded in clinical intuition.

5. Conclusions

Our findings challenge the notion that mixed PPA is a simple extension of the prototypical PPA variants. Instead, they suggest that mPPA encompasses distinct subgroups with unique clinical and pathological characteristics. In particular, we identified two distinct patient clusters (k1 and k2) based on the language features. These two clusters also showed different biomarker profiles and metabolic patterns in the brain. Cluster k1 may represent a clinical manifestation of AD-related PPA, extending beyond the classical lvPPA definition, while cluster k2 appears to represent a more heterogenous group, possibly reflecting different underlying pathological substrates. These results shed light on the complexity of mPPA, and emphasise the importance of considering mixed presentations in research and clinical practice. Future studies with larger cohorts and neuropathological validation are needed to confirm and expand upon these findings, ultimately enhancing our understanding of PPA subtypes and informing the diagnosis and treatment strategies for affected individuals.

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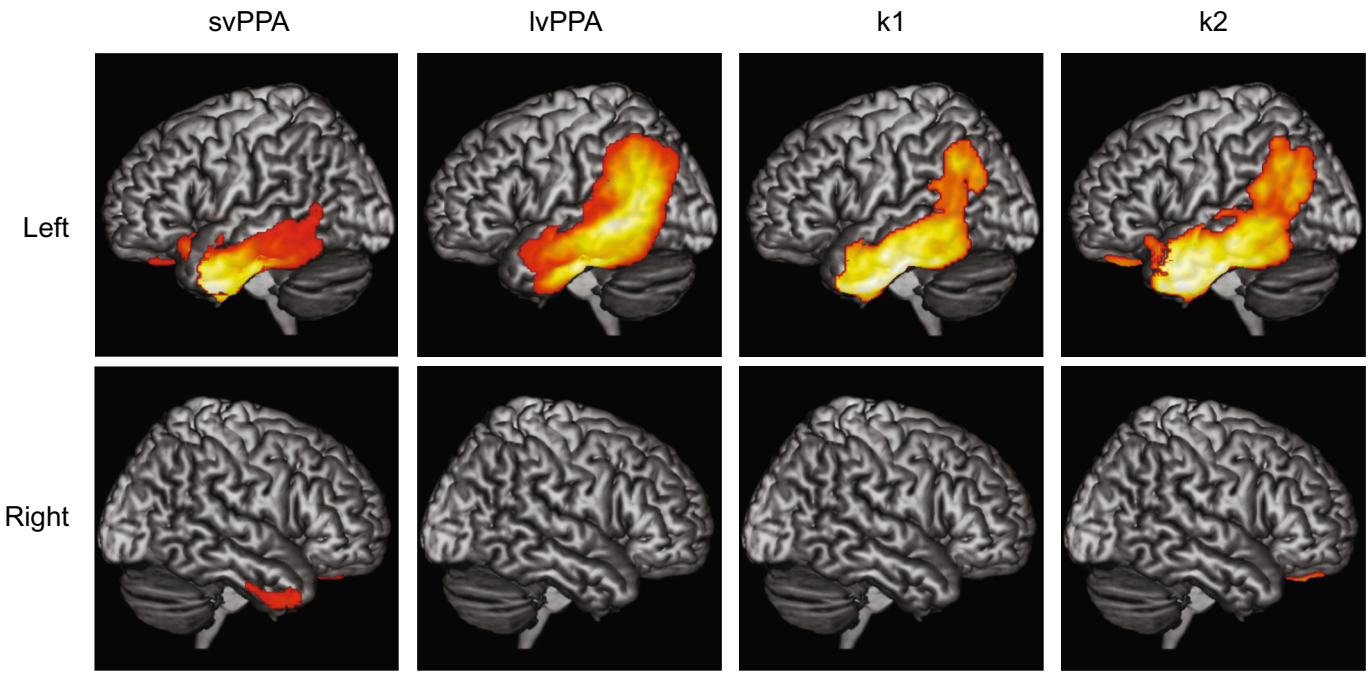

Fig. 5. SPM group analysis of brain metabolic patterns of svPPA, lvPPA, k1, and k2 compared to HC.
Statistical parametric maps showing regional brain metabolism differences between svPPA, lvPPA, k1, and k2 compared to HC. Significance level set at $p < 0.05$, FWE-corrected for multiple comparisons at the cluster-level. Colour maps represent T-scores. lvPPA, patient group with logopenic variant primary progressive aphasia; svPPA, patient group with semantic variant primary progressive aphasia; HC, healthy controls.

Table 3
Summary of features of the s/lvPPA clusters.

Features	k1	k2
Age	Older than lvPPA and svPPA	No differences with lvPPA and svPPA
General cognition	More impaired than k2 in MMSE and FAB	Less impaired than k1 and lvPPA
Language	More impaired than lvPPA in picture naming and semantic association. No differences with svPPA	Less impaired than svPPA in picture naming, single-word comprehension and category fluency. No differences with lvPPA
Biomarkers	AD-like	50% AD-like
Hypometabolism	Left temporoparietal hypometabolism including temporal pole	Left temporoparietal hypometabolism including temporal pole (greater extent than lvPPA)

CRediT authorship contribution statement

Salvatore Mazzeo: Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Carmen Morinelli:** Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Data curation, Conceptualization. **Cristina Polito:** Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Assunta Ingannato:** Visualization, Resources, Methodology. **Juri Balestrini:** Visualization, Resources. **Daniele Frigerio:** Visualization, Resources. **Filippo Emiliani:** Visualization, Resources. **Giulia Galdo:** Visualization, Resources. **Chiara Crucitti:** Visualization, Resources. **Diletta Piazzesi:** Visualization, Resources. **Silvia Bagnoli:** Visualization, Resources, Methodology. **Sonia Padiglioni:** Visualization, Supervision, Resources, Methodology, Data curation. **Sandro Sorbi:** Visualization, Supervision, Resources. **Benedetta Nacmias:** Visualization, Supervision, Resources. **Valentina Bessi:** Visualization, Supervision, Resources, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

Anonymised data supporting the findings of this study will be shared upon request by any qualified investigator.

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Appendix A. Supplementary data

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