# SPECT analysis and language profile in Greek speaking patients with subtypes of frontotemporal dementia

**Dimitra Mamouli**[1], **Stavroula Stavrakaki**[2] **PhD**, **Ioannis Iakovou**[3] **MD, PhD**, **Dimitrios Parisis**[4] **PhD**, **Dimitrios Karacostas**[4] **PhD**, **Emmanouil Papanastasiou**[3] **PhD**, **Panagiotis Ioannidis**[4] **PhD**

*1. 424 General Military Training Hospital, Thessaloniki, Greece.*
*2. Aristotle University of Thessaloniki, School of Philosophy, Department of Italian Language and Literature, Thessaloniki, Greece.*
*3. AHEPA University Hospital, Department of Nuclear Medicine, Thessaloniki, Greece.*
*4. AHEPA University Hospital, B' Department of Neurology, Thessaloniki, Greece.*

*Keywords:* Single photon emission computed tomography (SPECT) - Linguistics - Non-fluent primary progressive aphasia
- Semantic primary progressive aphasia
- Frontotemporal dementia

***Corresponding authors:***
Panagiotis Ioannidis PhD,
AHEPA University Hospital, B' Department of Neurology, Thessaloniki, Greece.
Tel: +302310994697
ispanagi@auth.gr

*Received:*
24 March 2022
*Accepted revised:*
1 April 2022

**Abstract**

**Objective:** We aimed to examine if single photon emission computed tomography (SPECT) can discriminate between variants of frontotemporal dementia (FTD). As a secondary investigation we identify and establish the linguistic differences between those variants. **Materials and Methods:** Nine patients with semantic variant primary progressive aphasia (svPPA), 8 with non-fluent variant primary progressive aphasia (nfvPPA) and 17 with behavioral variant of frontotemporal dementia (bvFTD) were compared on Addenbrooke's cognitive examination-revised (ACE-R), auditory comprehension, oral expression and verbal fluency. All patients were also compared with healthy controls. Patients were evaluated using technetium-99m-hexamethylproylene-amine oxime ($^{99m}$Tc-HMPAO) brain SPECT as a measure of regional cerebral flow. **Results:** Significant group differences between all patients and controls were found for ACE-R, auditory comprehension and oral expression. Semantic variant primary progressive aphasia patients performed higher in letter compared to category fluency with significant deficits in auditory comprehension and oral expression. Non-fluent variant primary progressive aphasia patients showed significant deficits in auditory comprehension but not oral expression while performed lightly worse in letter fluency compared to category. Behavioral variant of frontotemporal dementia patients showed deficits in auditory comprehension and oral expression and performed similar in category and letter fluency. Single photon emission computed tomography analysis revealed left frontotemporal hypoperfusion extending to the right frontotemporal region in svPPA patients. Non-fluent variant primary progressive aphasia patients presented left frontotemporal hypoperfusion with participation of the left parietal and right frontotemporal regions. Behavioral variant of frontotemporal dementia patients showed bilateral frontotemporal hypoperfusion compared to parietal and visual cortices. **Conclusion:** Our findings suggest that SPECT may assist in the discrimination of the FTD variants. We also confirmed that bvFTD patients share similar language deficits with svPPA patients.

*Hell J Nucl Med 2022; 25(1): 43-56* *Epub ahead of print: 8 April 2022* *Published online: 29 April 2022*

## Introduction

The behavioral variant of frontotemporal dementia (bvFTD) is the clinical subtype of frontotemporal dementia (FTD) characterized by progressive deterioration of beha vior and cognition often including some of the following manifestations: disinhibition, apathy or inertia, loss of sympathy, perseverative behavior, hyperorality, dietary changes and predominant executive deficits in neuropsychological assessments (possible bvFTD) [1]. Hypoperfusion of the frontal and temporal lobes is typically seen in neuroimaging studies (probable bvFTD) [1]. Of note, the above-listed clinical criteria do not encompass language deficits. However, some studies on bvFTD have reported language deficits similar to those characterizing the semantic variant primary progressive aphasia (svPPA) [2-4]. Specifically previous studies on bvFTD have reported impairments in confrontation naming, word and sentence comprehension [2, 5-8]. Some studies have additionally revealed difficulties in action naming [9-11] while others have suggested that noun and verb naming as well as abstract word comprehension may also be impaired in bvFTD [2, 12]. However, patients with bvFTD rarely meet any of the core criteria of the nonfluent variant primary progressive aphasia (nfvPPA) such as apraxia of speech and agrammatism [5].

Semantic variant primary progressive aphasia is a clinical syndrome principally manifestating with severe anomia and impaired single word comprehension. Patients with svPPA present with impaired object knowledge initially restricted to the low-familiarity items. Dyslexia and dysgraphia with spared repetition and motor speech constitute common supportive features. Anterior temporal lobe atrophy and hypoperfusion in neuroimaging investigations support the clinical diagnosis of svPPA [13]. On the other hand, nfvPPA is a clinical syndrome characterized by agrammatism or effortful-halting speech with articulation deficits (apraxia of speech). The comprehension of syntactically

complex sentences is also impaired with relatively spared object knowledge and single word comprehension. Left posterior fronto-insular atrophy or hypoperfusion in neuroimaging studies support the clinical diagnosis of nfvPPA [13].

The aim of the study is to examine if single photon emission computed tomography (SPECT) can discriminate efficiently among and between the above-listed variants of FTD. Single photon emission computed tomography was selectively investigated owing to the fact that cerebral hypoperfusion may appear prior to brain atrophy [14-16] and could be an auxiliary tool in the clinical diagnosis of FTD [17]. Since bvFTD is a clinically and anatomically heterogeneous neurodegenerative disease [18-20], different hypoperfusion patterns could differentiate between the different FTD entities. As a secondary investigation, participants with behavioral and language variants of FTD were subjected to neuropsychological investigations with a specific focus on language in order to clearly establish the linguistic differences between the different variants of FTD.

## Materials and Methods

Nine patients with svPPA, 8 with nfvPPA and 17 with bvFTD were recruited between January 2014 and January 2018 from the 2nd Neurological Department of the AHEPA University Hospital, which is affiliated with the Aristotle University of Thessaloniki. Participants were diagnosed according to the criteria proposed by Gorno-Tempini et al. (2011) and Rascovsky et al. (2011). Three age-, sex- and education- matched control groups consisting of healthy individuals were assembled, as well. Each control group was evenly numbered to the respective group of cases. The natural handedness (right-handed) and native language (Greek) of all participants (cases and controls) were uniform. Study procedures were approved by the Institutional Ethics Review Board of the Aristotle University of Thessaloniki. Participants provided informed consent prior to participation the demographic and neurophysiological characteristics of the participants are summarized in Tables 1, 2 and 3.

### Neuropsychological assessments

The Addenbrooke's cognitive examination-revised (ACE-R) battery standardized for the Greek population [21] was used as a measure of global cognitive impairment: lower ACE-R scores were indicative of more advanced cognitive deficits. Composite cognitive impairment was determined according to the cut-off of 88, with satisfactory sensitivity and specificity qualities. The ACE-R incorporates the mini mental state examination (MMSE) and provides an evaluation of six crucial cognitive domains, i.e., orientation, attention, memory, verbal fluency, language and visuospatial ability [22]. Addenbrooke's cognitive examination-revised has been found to differentiate quite well between Alzheimer's disease (AD) and FTD [23] including the svPPA and nfvPPA [24]. Of note, ACE-R has been found to outperform MMSE in terms of sensitivity and specificity, especially regarding its semantic qualities [25-26]. Measures of verbal fluency (category and letter) were further capitalized on, in the context of the secondary-linguistic investigations (Table 4).

### Aphasia assessment

The sections of auditory comprehension and oral expression of the Boston diagnostic aphasia examination standardized for the Greek population [27] were used as measures of aphasia and as tools in the diagnostic classification of the participants. Auditory comprehension is divided into three subtests: assessment of basic word comprehension, following commands and understanding complex ideational material. Oral expression evaluates automatized sequences (days and counting), verbal repetition (words and sentences) and naming. Free conversation and description of the cookie theft picture were also performed. From the above-listed examinations, articulation agility and prosody were assessed and used as indices of apraxia of speech, whereas grammatical facility was evaluated as an index of agrammatism. From the writing part of the examination, conclusions were extracted with respect to the presence of dysgraphia.

### Imaging

All patients underwent magnetic resonance imaging (MRI) using a 1.5 Tesla scanner. The results were evaluated by an experienced senior radiologist to assess for potential brain atrophy (Tables 1, 2 and 3). All patients underwent technetium-99m-hexamethylproyleneamine oxime ($^{99m}$Tc-HMPAO) brain SPECT at the Department of Nuclear Medicine of the Aristotle University of Thessaloniki in order to evaluate regional cerebral perfusion. Images were acquired 30 minutes after the intravenous injection of 740MBq $^{99m}$Tc-HMPAO while patients were lying down with their eyes open in a quiet room. We acquired 120 images, with an image acquisition time of 20 seconds, using a single-head gamma camera (Philips). Reconstruction was performed using a Butterworth filter with a frequency cut-off 0.35 and an order of 5. Individual cortical areas (region of interest, ROI) were created (4X4 pixels) for each hemisphere. For each ROI, regional cerebral blood flow (r-CBF) was estimated using a perfusion index calculated as the cortex to cerebellum ratio. Results are presented per patient group in Table 5.

### Statistical analysis

Continuous variables were expressed as means or medians and standard deviations. Shapiro-Wilk test was applied to evaluate the normality of distributions. Categorical data were expressed as absolute numbers and percentages. Continuous variables were analysed using analysis of variance (ANOVA). Categorical parameters were compared using chi-squared test without continuity correction. Correlations were investigated through Pearson's R or Spearman's rho, depending on normality considerations. Two-sided probability values of $<0.05$ were considered to be statistically significant. Statistical analysis was performed with SPSS version 25 (SPSS Inc, Chicago, IL).

## Results

The baseline characteristics of each case-control pair are provided in Table 6. Groups were similar in terms of age and educational attainment (P=0.943, P=0.718 for svPPA, P=0.951, P= 0.826 for nfvPPA and P=0.809, P=0.667 for bvFTD). As ex-

**Table 1.** *Demographic variables and language scores in svPPA patients and controls.*

| | Age (years) | Years of education | Disease duration (years) | ACE-R | Auditory comprehension (%) | Oral expression (%) | Sequences (%) | Repetition (%) | Naming (%) | Dysgraphy | AOS | Agrammatism | Brain atrophy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P1 | 72 | 16 | 2.5 | 76 | 100 | 93.75 | 100 | 100 | 86.48 | No | No | No | No |
| P2 | 56 | 16 | 3 | 47 | 68.75 | 87.5 | 75 | 100 | 86.48 | Yes | No | No | No |
| P3 | 67 | 9 | 3 | 43 | 64.06 | 66.66 | 75 | 100 | 59.45 | Yes | No | No | Yes |
| P4 | 66 | 6 | 3.5 | 32 | 81.25 | 89.58 | 100 | 100 | 86.48 | Yes | No | No | Yes |
| P5 | 73 | 12 | 3 | 45 | 89.06 | 81.25 | 100 | 100 | 75.67 | Yes | No | No | Yes |
| P6 | 66 | 12 | 2 | 81 | 96.87 | 93.75 | 100 | 100 | 89.18 | No | No | No | No |
| P7 | 74 | 9 | 4 | 63 | 93.75 | 79.16 | 100 | 100 | 72.97 | Yes | No | No | Yes |
| P8 | 73 | 16 | 3 | 64 | 76.56 | 83.33 | 100 | 100 | 78.37 | No | No | No | Yes |
| P9 | 76 | 6 | 2 | 52 | 87.5 | 85.41 | 100 | 100 | 81.08 | Yes | No | No | Yes |
| C1 | 73 | 16 | - | 97 | 100 | 100 | - | | | | - | | |
| C2 | 72 | 12 | - | 99 | 96.87 | 95.83 | - | | | | - | | |
| C3 | 63 | 12 | - | 98 | 100 | 97.91 | - | | | | - | | |
| C4 | 71 | 16 | - | 95 | 100 | 93.75 | - | | | | - | | |
| C5 | 69 | 6 | - | 90 | 100 | 100 | - | | | | - | | |
| C6 | 71 | 9 | - | 91 | 93.75 | 91.66 | - | | | | - | | |
| C7 | 70 | 9 | - | 95 | 100 | 91.66 | - | | | | - | | |
| C8 | 54 | 16 | - | 100 | 100 | 93.75 | - | | | | - | | |
| C9 | 78 | 12 | - | 90 | 96.87 | 95.83 | - | | | | - | | |

*P = patient, C = control, ACE-R = Addenbrooke's Cognitive Examination-Revised, AOS = apraxia of speech, % = percentage correct*

***Table 2.*** *Demographic variables and language scores in nvPPA patients and controls.*

| | Age (years) | Years of education | Disease duration (years) | ACE-R | Auditory comprehension (%) | Oral expression (%) | Sequences (%) | Repetition (%) | Naming (%) | Dysgraphy | AOS | Agrammatism | Brain atrophy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P1 | 72 | 12 | 2 | 20 | 76.56 | 87.50 | 100 | 57.14 | 91.89 | No | Yes | Yes | Yes |
| P2 | 55 | 17 | 2 | 84 | 96.87 | 93.75 | 100 | 57.14 | 100 | No | Yes | Yes | No |
| P3 | 74 | 6 | 2 | 56 | 81.25 | 97.91 | 100 | 85.71 | 100 | No | No | Yes | Yes |
| P4 | 79 | 16 | 3 | 83 | 85.93 | 100 | 100 | 100 | 100 | No | No | Yes | Yes |
| P5 | 70 | 16 | 2 | 79 | 96.87 | 95.55 | 100 | 28.57 | 100 | No | No | Yes | No |
| P6 | 62 | 12 | 4 | 30 | 50.00 | 29.16 | 100 | 14.28 | 24.32 | No | Yes | Yes | Yes |
| P7 | 66 | 12 | 3 | 91 | 56.25 | 50.00 | 100 | 42.85 | 45.94 | No | Yes | Yes | Yes |
| P8 | 61 | 12 | 3 | 75 | 62.50 | 79.16 | 100 | 42.85 | 81.08 | No | No | Yes | Yes |
| C1 | 70 | 14 | - | 98 | 100 | 100 | - | | | - | | | |
| C2 | 62 | 12 | - | 90 | 100 | 100 | - | | | - | | | |
| C3 | 72 | 12 | - | 99 | 96.87 | 95.83 | - | | | - | | | |
| C4 | 63 | 12 | - | 98 | 100 | 97.91 | - | | | - | | | |
| C5 | 54 | 16 | - | 100 | 100 | 93.75 | - | | | - | | | |
| C6 | 67 | 12 | - | 98 | 100 | 91.66 | - | | | - | | | |
| C7 | 73 | 6 | - | 90 | 100 | 100 | - | | | - | | | |
| C8 | 80 | 16 | - | 89 | 96.87 | 95.83 | - | | | - | | | |

*P = patient, C = control, ACE-R = Addenbrooke's Cognitive Examination-Revised, AOS = apraxia of speech, % = percentage correct*

**Table 3.** *Demographic variables and language scores in bvFTD patients and controls.*

| | Age (years) | Years of education | Disease duration (years) | ACE-R | Auditory comprehension (%) | Oral expression (%) | Sequences (%) | Repetition (%) | Naming (%) | Dysgraphy | AOS | Agrammatism | Brain atrophy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P1 | 70 | 9 | 2 | 24 | 71.87 | 85.41 | 100 | 100 | 81.08 | No | No | No | Yes |
| P2 | 60 | 14 | 2 | 75 | 95.31 | 93.75 | 100 | 100 | 91.89 | No | No | No | No |
| P3 | 63 | 6 | 3 | 53 | 84.37 | 91.66 | 100 | 100 | 89.18 | No | No | Yes | Yes |
| P4 | 73 | 12 | 2 | 62 | 90.62 | 97.91 | 100 | 100 | 97.29 | No | No | No | No |
| P5 | 65 | 6 | 3 | 47 | 87.50 | 93.75 | 100 | 100 | 91.89 | No | No | No | Yes |
| P6 | 53 | 12 | 3 | 87 | 93.75 | 79.16 | 100 | 100 | 86.48 | No | No | No | Yes |
| P7 | 77 | 14 | 3 | 48 | 73.43 | 87.50 | 100 | 100 | 83.78 | No | No | No | Yes |
| P8 | 66 | 12 | 2 | 76 | 98.43 | 93.75 | 100 | 100 | 91.89 | No | No | No | No |
| P9 | 70 | 12 | 2 | 32 | 100 | 100 | 100 | 100 | 100 | No | No | No | No |
| P10 | 70 | 6 | 3 | 50 | 81.25 | 87.50 | 100 | 100 | 83.78 | No | Yes | No | Yes |
| P11 | 79 | 12 | 2 | 62 | 100 | 100 | 100 | 100 | 83.78 | No | No | No | No |
| P12 | 67 | 6 | 2 | 57 | 81.25 | 89.58 | 100 | 85.71 | 89.18 | No | No | No | No |

*(Continued)*

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P13 | 73 | 6 | 3 | 70 | 89.06 | 91.66 | 100 | 100 | 89.18 | No | No | No | Yes |
| P14 | 74 | 12 | 2 | 78 | 93.75 | 97.91 | 100 | 85.71 | 100 | No | No | No | Yes |
| P15 | 81 | 16 | 2 | 64 | 90.62 | 100 | 100 | 85.71 | 100 | No | No | No | No |
| P16 | 73 | 14 | 2 | 82 | 93.75 | 100 | 100 | 85.71 | 100 | No | No | No | Yes |
| P17 | 69 | 3 | 3 | 35 | 64.06 | 97.91 | 75.00 | 85.71 | 100 | Yes | No | Yes | Yes |
| C1 | 65 | 6 | - | 90 | 96.87 | 100 | - | | | - | | | |
| C2 | 67 | 8 | - | 92 | 100 | 100 | - | | | - | | | |
| C3 | 70 | 12 | - | 98 | 100 | 100 | - | | | - | | | |
| C4 | 76 | 6 | - | 95 | 100 | 100 | - | | | - | | | |
| C5 | 68 | 12 | - | 98 | 100 | 100 | - | | | - | | | |
| C6 | 54 | 12 | - | 100 | 100 | 100 | - | | | - | | | |
| C7 | 75 | 15 | - | 98 | 96.87 | 95.83 | - | | | - | | | |
| C8 | 68 | 6 | - | 96 | 96.87 | 95.83 | - | | | - | | | |
| C9 | 71 | 12 | - | 90 | 96.87 | 95.83 | - | | | - | | | |
| C10 | 80 | 12 | - | 89 | 100 | 93.75 | - | | | - | | | |

*(Continued)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| C11 | 73 | 16 | - | 97 | 100 | 100 | - | - |
| C12 | 72 | 12 | - | 99 | 96.87 | 95.83 | - | - |
| C13 | 80 | 16 | - | 95 | 100 | 93.75 | - | - |
| C14 | 60 | 14 | - | 92 | 100 | 100 | - | - |
| C15 | 64 | 6 | - | 94 | 100 | 100 | - | - |
| C16 | 80 | 14 | - | 90 | 93.75 | 91.66 | - | - |
| C17 | 70 | 3 | - | 90 | 90.62 | 91.66 | - | - |

*P = patient, C = control, ACE-R = Addenbrooke's Cognitive Examination-Revised, AOS = apraxia of speech, % = percentage correct*

***Table 4.*** *Verbal fluency (letter and category) per patient group.*

| Patients | Fluency Tests | Mean-value & Standard deviation (%) |
|---|---|---|
| svPPA | letter fluency | 41.26 + 25.19 |
| | category fluency | 20.63 + 17.65 |
| nfvPPA | letter fluency | 32.14 + 19.84 |
| | category fluency | 46.42 + 18.31 |
| bvFDD | letter fluency | 36.98 + 22.63 |
| | category fluency | 47.14 + 24.14 |

**Table 5.** *Results of SPECT imaging per patient group.*

| | Frontal left | Frontal right | Temporal medial left | Temporal medial right | Lateral temporal left | Lateral temporal right | Parietal left | Parietal right | Occipital left | Occipital right |
|---|---|---|---|---|---|---|---|---|---|---|
| svP1 | 0.75 | 0.9 | 0.65 | 0.66 | 0.68 | 0.8 | 0.82 | 0.88 | 0.93 | 0.96 |
| svP2 | 0.69 | 0.76 | 0.55 | 0.7 | 0.70 | 0.73 | 0.88 | 0.86 | 1.00 | 1.00 |
| svP3 | 0.90 | 0.95 | 0.61 | 0.78 | 0.69 | 0.81 | 0.82 | 0.91 | 1.00 | 0.99 |
| SP4 | 0.73 | 0.82 | 0.60 | 0.67 | 0.67 | 0.71 | 0.74 | 0.75 | 1.00 | 1.00 |
| svP5 | 0.82 | 0.77 | 0.52 | 0.7 | 0.45 | 0.79 | 0.57 | 0.83 | 1.00 | 0.92 |
| svP6 | 0.70 | 0.75 | 0.65 | 0.67 | 0.68 | 0.71 | 0.78 | 0.81 | 0.94 | 0.98 |
| svP7 | 0.88 | 0.88 | 0.59 | 0.59 | 0.61 | 0.64 | 0.92 | 0.82 | 0.96 | 0.93 |
| svP8 | 0.75 | 0.83 | 0.54 | 0.56 | 0.59 | 0.69 | 0.88 | 0.90 | 0.90 | 0.95 |
| svP9 | 0.79 | 0.82 | 0.78 | 0.78 | 0.84 | 0.84 | 0.80 | 0.82 | 0.96 | 1.00 |
| nfvP1 | 0.85 | 0.84 | 0.59 | 0.75 | 0.62 | 0.69 | 0.83 | 0.82 | 0.93 | 0.98 |
| nfvP2 | 0.81 | 0.85 | 0.65 | 0.69 | 0.69 | 0.78 | 0.76 | 0.83 | 0.95 | 0.98 |
| nfvP3 | 0.78 | 0.81 | 0.59 | 0.85 | 0.66 | 0.69 | 0.79 | 0.82 | 0.88 | 0.87 |
| nfvP4 | 0.73 | 0.78 | 0.67 | 0.69 | 0.69 | 0.75 | 0.82 | 0.87 | 0.94 | 0.95 |
| nfvP5 | 0.70 | 0.75 | 0.72 | 0.69 | 0.70 | 0.75 | 0.82 | 0.85 | 0.90 | 0.92 |
| nfvP6 | 0.67 | 0.77 | 0.65 | 0.70 | 0.60 | 0.75 | 0.77 | 0.78 | 0.80 | 0.85 |
| nfvP7 | 0.68 | 0.75 | 0.69 | 0.68 | 0.68 | 0.67 | 0.78 | 0.82 | 0.90 | 0.92 |

*(continued)*

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| nfvP8 | 0.70 | 0.73 | 0.84 | 0.88 | 0.86 | 0.85 | 0.78 | 0.83 | 0.92 | 0.98 |
| bvP1 | 0.69 | 0.70 | 0.53 | 0.62 | 0.55 | 0.58 | 0.75 | 0.62 | 0.94 | 0.90 |
| bvP2 | 0.79 | 0.86 | 0.62 | 0.65 | 0.60 | 0.57 | 0.86 | 0.85 | 0.96 | 0.97 |
| bvP3 | 0.62 | 0.75 | 0.61 | 0.80 | 0.68 | 0.66 | 0.83 | 0.93 | 0.96 | 0.97 |
| bvP4 | 0.73 | 0.74 | 0.55 | 0.68 | 0.63 | 0.60 | 0.84 | 0.89 | 0.91 | 0.86 |
| bvP5 | 0.68 | 0.78 | 0.58 | 0.61 | 0.62 | 0.58 | 0.80 | 0.83 | 0.92 | 0.92 |
| bvP6 | 0.64 | 0.70 | 0.69 | 0.69 | 0.65 | 0.53 | 0.77 | 0.75 | 0.87 | 0.92 |
| bvP7 | 0.62 | 0.64 | 0.68 | 0.72 | 0.70 | 0.69 | 0.85 | 0.89 | 0.89 | 0.91 |
| bvP8 | 0.79 | 0.85 | 0.67 | 0.74 | 0.74 | 0.66 | 0.90 | 0.94 | 0.88 | 0.92 |
| bvP9 | 0.60 | 0.71 | 0.62 | 0.58 | 0.69 | 0.75 | 0.88 | 0.86 | 0.93 | 0.97 |
| bvP10 | 0.63 | 0.76 | 0.59 | 0.64 | 0.69 | 0.61 | 0.91 | 0.90 | 0.94 | 0.96 |
| bvP11 | 0.76 | 0.80 | 0.76 | 0.66 | 0.67 | 0.74 | 0.86 | 0.89 | 0.95 | 0.96 |
| bvP12 | 0.86 | 0.87 | 0.70 | 0.80 | 0.74 | 0.69 | 0.81 | 0.91 | 0.98 | 1.04 |
| bvP13 | 0.70 | 0.73 | 0.59 | 0.70 | 0.71 | 0.57 | 0.86 | 0.86 | 0.95 | 0.96 |
| bvP14 | 0.90 | 0.89 | 0.76 | 0.65 | 0.66 | 0.79 | 0.89 | 0.83 | 0.94 | 0.91 |
| bvP15 | 0.64 | 0.66 | 0.44 | 0.54 | 0.48 | 0.49 | 0.79 | 0.80 | 0.94 | 0.94 |
| bvP16 | 0.79 | 0.76 | 0.66 | 0.72 | 0.73 | 0.67 | 0.88 | 0.92 | 0.93 | 0.88 |
| bvP17 | 0.66 | 0.68 | 0.76 | 0.72 | 0.73 | 0.77 | 0.86 | 0.89 | 0.91 | 0.86 |

*svP = semantic variant ppa patient, nfvP = nonfluent variant ppa patient, bvP = behavioral variant FTD patient*

pected, in terms of global cognition (ACE-R), healthy controls outcompeted age-, sex- and education- matched patients (P< 0.001, P=0.001 and P<0.001 for svPPA, nfvPPA and bvFTD, respectively) especially in the context of verbal fluency as well as general language impairment. Semantic variant primary progressive aphasia patients showed significant deficits in auditory comprehension (P=0.004) and oral expression (P=0.002) while performed higher in letter compared to category fluency (P<0.001). On the other hand, nfvPPA patients presented significant deficits in auditory comprehension (P=0.001) but not oral expression (P=0.063) while performed slightly worse in letter compared category fluency but with no significant difference (P=0.157). Behavioral variant of frontotemporal dementia patients showed significant deficits in auditory comprehension and oral expression (P<0.001 and P=0.021, respectively) while performed similar in category and letter fluency (Table 4). Finally, among group comparisons were indicative of similar performances in terms of global cognition (ACE-R) (P=0.655), auditory comprehension (P=0.121) and oral expression (P= 0.052).

## Classification of hypoperfusion

In the majority of people (especially right-handed), the left hemisphere is considered to shelter areas of pivotal importance for the cerebral language network. Therefore, the rCBF of the different regions of the left hemisphere were compared within and between the three patient groups. In the svPPA, significantly higher hypoperfusion peaks were located in the left medial temporal lobe compared to the left frontal lobe (P=0.010), while the perfusion of the left frontal lobe was not different from the left parietal lobe (P=0.408). Moreover, the parietal lobe showed relative hypoperfusion when compared to the visual cortex (P=0.008). In view of the fact that the pathologic abnormalities of svPPA usually affect the anterior temporal lobes bilaterally, the rCBF of the right and left temporal lobes were also compared. It was concluded that the left temporal region was relatively more impaired than the right temporal region, both in the medial and in the lateral temporal areas (P=0.027 and P=0.031, respectively). The comparison of the rCBF between the left and right hemisphere showed a significant hypoperfusion between the left and right frontal region (P=0.025) as well as between the left and right medial and lateral temporal lobes (P=0.027 and P=0.031, respectively). The right medial temporal lobe showed significant hypoperfusion compared to the right frontal (P=0.009), parietal (P=0.009) and occipital lobes (P<0.001) while the right temporal (lateral and medial), frontal and parietal lobes had significantly lower rCBF compared to the right occipital lobe (P<0.001, P<0.001, P= 0.003, P=0.001, respectively) (Table 7).

In the nfvPPA group, hypoperfusion of the left lateral and medial temporal lobes were observed when compared to the occipital lobe (P<0.001 and P=0.001, respectively) while the left medial temporal lobe differed significantly from the left parietal lobe, as well (P=0.042). Moreover, a relative hypoperfusion of the right frontal, medial temporal, lateral temporal and parietal lobes was revealed compared to right occipital lobe (P=0.01, P<0.01, P=0.04, P=0.02, respectively). Regarding the left-right hemisphere comparisons, differences were found in the frontal (P=0.005), lateral temporal (P=0.024), parietal (P=0.007) and occipital lobes (P=0.011), whereas the medial temporal lobes presented similar rCBF (P=0.09) (Table 8).

***Table 7.*** *The mean values of rCBF between areas of the temporal, frontal, parietal and occipital region (right and left) for svPPA patient group.*

| | Mean | Standard deviation | P-value |
|---|---|---|---|
| Left medial temporal | 0.610 | 0.078 | 0.027 |
| Right medial temporal | 0.679 | 0.074 | |
| Left lateral temporal | 0.658 | 0.104 | 0.031 |
| Right lateral temporal | 0.747 | 0.066 | |
| Left frontal | 0.779 | 0.075 | 0.025 |
| Right frontal | 0.831 | 0.068 | |
| Left parietal | 0.801 | 0.103 | 0.242 |
| Right parietal | 0.842 | 0.051 | |
| Left occipital | 0.966 | 0.037 | 0.756 |
| Right occipital | 0.971 | 0.031 | |

In the bvFTD group, the left medial temporal lobe had significantly lower rCBF in comparison with the left frontal (P= 0.028), parietal (P<0.001) and occipital lobes (P<0.001). Furthermore, the left frontal lobe presented significant hypoperfusion compared to the left parietal (P<0.001) and occipital lobes (P<0.001), whereas significant differences were also found between the left parietal and occipital lobes (P< 0.001). The left lateral temporal lobe had also significantly lower rCBF compared to the left parietal (P<0.001) and occipital lobes (P<0.001). The right lateral and medial temporal lobes presented significant hypoperfusion compared to the right frontal (P=0.01 and P=0.012, correspondingly) parietal (P<0.001) and occipital lobes (P<0.001). Significant differences were also apparent between the left and right frontal lobes (P=0.001) as well as between the left and right medial temporal lobes (P=0.048) (but not between the left and right parietal, occipital and lateral temporal lobes) (Table 9).

In among group comparisons, it was revealed that the bvFTD group presented significantly more important hypoperfusion in the right frontal and lateral temporal lobes than the language variants of FTD (P=0.043). The nfvPPA patients, on the other hand, presented a greater perfusion deficit in the left occipital lobe compared to the svPPA group. No additional among group differences were established.

Finally, the association between perfusion and neuropsychological testing was also investigated. In the nfvPPA, hypoperfusion of the left occipital lobe was positively related to oral expression (P=0.032, r=0.749), whereas in the bvFTD, hypoperfusion of the left frontal lobe was positively assoiated with ACE-R (P=0.041 and r=0.499).

***Table 8.*** *The mean values of rCBF between areas of the temporal, frontal, parietal and occipital region (right and left) for nfvPPA patient group.*

| | Mean | Standard deviation | P-value |
|---|---|---|---|
| Left medial temporal | 0.675 | 0.080 | 0.009 |
| Right medial temporal | 0.741 | 0.079 | |
| Left lateral temporal | 0.687 | 0.078 | 0.024 |
| Right lateral temporal | 0.741 | 0.058 | |
| Left frontal | 0.740 | 0.066 | 0.005 |
| Right frontal | 0.785 | 0.044 | |
| Left parietal | 0.794 | 0.026 | 0.007 |
| Right parietal | 0.827 | 0.026 | |
| Left occipital | 0.902 | 0.047 | 0.011 |
| Right occipital | 0.931 | 0.051 | |

***Table 9.*** *The mean values of rCBF between areas of the temporal, frontal, parietal and occipital region (right and left) for bvFTD patient group.*

| | Mean | Standard deviation | P-value |
|---|---|---|---|
| Left medial temporal | 0.636 | 0.087 | 0.048 |
| Right medial temporal | 0.678 | 0.070 | |
| Left lateral temporal | 0.663 | 0.070 | 0.285 |
| Right lateral temporal | 0.644 | 0.087 | |
| Left frontal | 0.712 | 0.089 | 0.001 |
| Right frontal | 0.758 | 0.075 | |
| Left parietal | 0.843 | 0.046 | 0.348 |
| Right parietal | 0.856 | 0.078 | |
| Left occipital | 0.929 | 0.029 | 0.858 |
| Right occipital | 0.932 | 0.046 | |

## Discussion

In svPPA patients, verbal comprehension was significantly impaired. This part of the BDAE includes word and sentence comprehension tests. Sentence comprehension deficits are a common feature of all PPA variants [28] but impaired single word meaning is a basic characteristic of the svPPA that further contributes to sentence comprehension deficits [29]. As expected, oral expression was also significantly impaired while verbal repetition was intact (Table 3). Dysgraphia was very common, as well (7/9 patients), and constituted a supportive tool in the clinical diagnosis of the svPPA [13]. Both phonemic and category fluency correlate with executive function and semantic reservoir [30] but letter fluency depends more heavily on executive function, whereas category fluency is more heavily based on semantic reservoir [31-34]. Moreover, some studies have shown that each fluency test activates distinct brain regions. Specifically, letter fluency was associated with frontal and temporoparietal regions, whereas category fluency was related to the left temporal cortex [35]. Our svPPA patients performed worse on the category than letter fluency, as anticipated considering their predominant semantic deficiency and prominent left temporal lobe hypoperfusion [36].

In svPPA patients, SPECT analysis revealed significant hypoperfusion of the left frontotemporal region particularly in the left medial temporal lobe, extending to the right frontotemporal region (Table 7) with relative preservation of perfusion of the occipital lobes. This pattern of hypoperfusion is in accordance with previous research which suggested that cerebral atrophy was more marked in the left temporal lobe extending to the inferior frontal gyrus (IFG) and less prominent in the right temporal lobe [37-38]. All svPPA patients, showed decreased perfusion in the left frontotemporal region while 6 of them were additionally found to have focal brain atrophy on MRI (confirming the greater sensitivity of SPECT, especially in the early stages of FTD) [14-16].

NfvPPA patients differed from the control group in ACE-R performance, auditory comprehension but not oral expression (despite the implementation of the gorno tempini diagnostic criteria, potentially due to small number of participants). Moreover, oral expression was estimated as a composite score, extracted from naming, repetition and sequences, therefore, although repetition was impaired owing to agrammatism and articulation deficits, naming was normal, which may have driven our insignificant estimations (Table 2). Furthermore, despite implementing the well-established clinical diagnostic approach, patients with mixed type PPA may have been included [39] introducing important misclassification bias considering the small sample size of the current study. Auditory comprehension was impaired as anticipated, since these patients tend to suffer from difficulties in the comprehension of syntactically complex sentences [13]. In addition, these patients performed in a poorer fashion in letter than category fluency, which is a consequence of the apraxia of speech afflicting nfvPPA patients [31], often leading to substantial variations in verbal fluency testing. Marianna Riello et al. (2022) also confirmed this trend, i.e., the more prominent letter than category fluency impairments, and associated these findings with hypoperfusion of the right dorsolateral prefrontal cortex [40]. Similar findings were reported by Hodges (1996), as well [41]. On the contrary, Libon did not reveal any differences in fluency tasks [32], which were equally affected, on the grounds of frontotemporal cerebral atrophy.

Left fronto-temporal (mostly medial temporal) hypoperfusion was documented in nfvPPA patients, with less prominent participation of the left parietal and right frontotemporal regions (Table 8). According to the gorno tempini criteria, these patients tend to present with left posterior fronto-insular hypoperfusion patterns [13]. However, further studies revealed imaging discrepancies, often related to the clinical manifestations of the participants. A previous article involving fluorine-18-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG) PET investigations found two prevalent hypometabolism patterns, one with dominant left fronto-temporal and less prominent parietal hypometabolism and one with bilateral frontal hypometabolism, which was associated with progressive subnuclear palsy pathology [42]. Using a clinically based approach, nfvPPA patients with prominent agrammatism presented left posterior frontal hypometabolism, including the inferior (Broca's area), middle and superior premotor gyri and extending to the insula, striatum and parietal lobe, whereas patients with apraxia of speech presented superior premotor cortex hypometabolism [43]. Other studies using voxel based morphometry analysis revealed a left sided atrophy in the fronto-insular cortex sparing the premotor cortex [44]. In our study, the frontal region was not further subdivided (e.g., in broca area, motor and premotor cortex) while the temporal lobe was divided in medial and lateral areas. Moreover, nfvPPA was investigated as a whole clinical entity, without any clinical subdivisions. Despite the small sample size, a left fronto-temporal hypoperfusion, including the left posterior fronto-insular region, was found.

Behavioral variant of frontotemporal dementia patients had impaired auditory comprehension, oral expression and verbal fluency measures. Action naming deficits have been found to be associated with executive dysfunction [9-10]. Cousins et al. (2016) showed that bvFTD patients may perform poorer on abstract compared to concrete word processing, due to executive and semantic impairment. In addition, several studies associated executive control processes with word comprehension and lexical acquisition [45-46]. The contribution of the executive and semantic dysfunctions to the individual language profile of bvFTD has been reported previously [2-3]. Naming and word comprehension deficits are prominent characteristics of the bvFTD and a positive correlation between the above features and specific mutations has been reported [3]. There was also a longitudinal progression of naming deficits in bvFTD revealing a potential bio-marker quality for naming in bvFTD [3]. Furthermore, auditory comprehension in bvFTD was mildly impaired due to both word and sentence comprehension deficits. These results are consistent with previous studies suggesting that working memory and executive disorders contribute to sentence comprehension in bvFTD [6-7, 47]. As expected, bvFTD patients presented oral expression difficulties in the Boston Naming Test while verbal repetition was relatively

***Table 10.*** *Hypoperfusion in the right frontal, right lateral temporal and left parietal lobe per patient group.*

| Patients | Right frontal | Right lateral temporal | Left parietal |
|---|---|---|---|
| svPPA | 0.831 | 0.746 | 0.831 |
| nfvPPA | 0.785 | 0.741 | 0.793 |
| bvFTD | 0.757 | 0.644 | 0.843 |

preserved [2, 48]. (Table 3) Overall, the pattern of language differences was similar between the bvFTD and svPPA patients, although bvFTD individuals performed better on most individual tests (Table 1, Table 3, Table 5). The bvFTD patients performed insignificantly better on category compared to letter fluency because of their executive dysfunction. These results could indicate that language impairment in bvFTD is the result of both semantic and executive dysfunction.

Behavioral variant of frontotemporal dementia is characterized by frontotemporal atrophy with relative sparing of the parietal and occipital regions [18, 49]. Some studies suggested that parietal hypoperfusion is rare in FTD and may assist in the differentiation of FTD from AD [17, 50]. In our investigation, we found a significant bilateral hypoperfusion in the frontotemporal regions compared to the parietal and visual cortices confirming the previous studies. Despite the fact that there was greater hypoperfusion in the left than the right frontotemporal region, the mean values of hypoperfusion were very similar with the left medial and right lateral temporal areas being the most affected regions (Table 9). These results could indicate that bvFTD is a radiologically heterogeneous disorder [19, 51]. Whitwell et al. (2009) showed that bvFTD can be divided into four subtypes based on grey matter loss on voxel-based morphometry: the frontal dominant, the temporal dominant, the frontotemporal and the temporofrontoparietal subtype. In addition, the temporal dominant subtype was often related with MAPT mutation while was characterized by bilateral temporal gray matter loss, particularly affecting the right temporal region [19]. Other studies revealed distinct patterns of atrophy which were associated with distinct neuropsychological, genetic and cognitive profiles [52-53]. We did not divide our bvFTD patients into subtypes because of the small number of participants and the main focus of our study, which was to evaluate the radiological profiles of the FTD variants. Our patients were studied as a whole group without subgroup divisions based on imaging considerations. For this reason, they presented statistically significant bilateral frontotemporal hypoperfusion, especially in the left fronto-temporal regions.

Regarding the between group comparisons on hypoperfusion, bvFTD patients manifested with significantly greater right frontal and medial temporal hypoperfusion compared to svPPA and less notably to nfvPPA patients (Table 10). Therefore, imaging findings efficiently discriminated between the bvFTD and the language variants of FTD, owing to the bilateral hypoperfusion pattern of the bvFTD (hypoperfusion was more prominent in the left cerebral regions in the language variants of PPA). In the comparison of the left temporal lobes, o differences were established potentially due to the participation of these areas in all 3 FTD variants. Another important finding might lie on the relative hypoperfusion of the left parietal lobe in nfvPPA (Table 10), which although insignificant (small sample considerations) has been previously reported in larger study samples [43, 54]. Finally, the intact perfusion of the occipital lobe was uniform in all 3 variants, confirming the integrity of the occipital area in FTD [55].

Regarding the between group linguistic comparisons, we did not establish any significant differences. This could be attributed to the analytic approach of our study assessing composite test scores rather than individual test components. Herein, auditory comprehension was affected in all 3 variants (impaired single word meaning in svPPA [7] impaired syntactically complex sentences comprehension in nfvPPA [13] and impaired word and sentence comprehension in bvFTD [3]. Moreover, svPPA, nfvPPA and bvFTD patients presented with oral expression deficits owing to their BNT performance, impaired repetition and impaired naming, respectively. Finally, in view of the small sample size, it is possible that statistical analyses were relatively underpowered to reveal potential linguistic disparities, which are often more prominent during later, follow-up assessments [37, 56-57]. Of note, it is also possible that more specialized linguistic assessments would be more appropriate to indicate clear-cut language differences even in the context of a small sample like ours.

*In conclusion*, we confirmed that SPECT may assist in the discrimination of the FTD variants. Its value principally lies on the distinction of the bvFTD from the language variants of FTD, based on the prominent hypoperfusion of the right frontal and lateral temporal lobes in the bvFTD. Furthermore, the differential hypoperfusion between the left and right parietal lobes can be capitalized on the clinical diagnosis of nflPPA. With respect to language, it was confirmed that subjects with bvFTD share several similar language deficits with individuals with semPPA, most notably impaired confrontation naming with relatively preserved verbal repetition.

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