Different FDG-PET metabolic patterns at single-subject level in the behavioral variant of fronto-temporal dementia.

Cerami C[1], Dodich A[2], Lettieri G[3], Iannaccone S[4], Magnani G[5], Marcone A[4], Gianolli L[6], Cappa SF[7], Perani D[8].

1 Vita-Salute San Raffaele University, Milan, Italy; Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy; Clinical Neuroscience Department, San Raffaele Turro Hospital, Milan, Italy.

2 Vita-Salute San Raffaele University, Milan, Italy; Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy.

3 Vita-Salute San Raffaele University, Milan, Italy.

4 Clinical Neuroscience Department, San Raffaele Turro Hospital, Milan, Italy.

5 Neurology Department, San Raffaele Hospital, Milan, Italy.

6 Nuclear Medicine Unit, San Raffaele Hospital, Italy.

7 Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy; NeTS Center, Istituto Universitario di Studi Superiori, Pavia, Italy.

8 Vita-Salute San Raffaele University, Milan, Italy; Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy; Nuclear Medicine Unit, San Raffaele Hospital, Italy. Electronic address: perani.daniela@hsr.it.

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DIFFERENT FDG-PET METABOLIC PATTERNS AT SINGLE-SUBJECT LEVEL IN THE BEHAVIORAL VARIANT OF FRONTOTEMPORAL DEMENTIA

Authors: Chiara Cerami [a,b,c], MD, Alessandra Dodich [a,b], PhD, Giada Lettieri [a], MD, Sandro Iannaccone [c], MD, Giuseppe Magnani [d], MD, Alessandra Marcone [c], MD, Luigi Gianolli [f], MD, Stefano F. Cappa [b,e], MD, and Daniela Perani [a,b,f], MD.

a) Vita-Salute San Raffaele University, Milan, Italy
b) Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy
c) Clinical Neuroscience Department, San Raffaele Turro Hospital, Milan, Italy
d) Neurology Department, San Raffaele Hospital, Milan, Italy
e) NeTS Center, Istituto Universitario di Studi Superiori, Pavia, Italy
f) Nuclear Medicine Unit, San Raffaele Hospital, Italy

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Corresponding Author: Daniela Perani, MD
Università Vita-Salute San Raffaele and San Raffaele Scientific Institute
Division of Neuroscience
Via Olgettina, 60 – 20134 Milan (Italy)
Tel: 0039 02 2643 2224
Fax: 0039 02 2643 5202
E-mail: perani.daniela@hsr.it

ABSTRACT

Background: The diagnosis of probable behavioural variant of fronto-temporal dementia (bvFTD) according to current criteria requires the imaging evidence of frontal and/or anterior temporal atrophy or hypoperfusion/hypometabolism. Different variants of this pattern of brain involvement may, however, be found in individual cases, supporting the presence of heterogeneous phenotypes. **Objective:** We examined in a case-by-case approach the FDG-PET metabolic patterns of patients fulfilling clinical criteria for probable bvFTD, assessing the presence and frequency of specific FDG-PET features. **Materials and Methods:** 52 FDG-PET scans of probable bvFTD patients were retrospectively analysed together with clinical and neuropsychological data. Neuroimaging experts rated the FDG-PET hypometabolism maps obtained at the single-subject level with optimized voxel-based Statistical Parametric Mapping (SPM). The functional metabolic heterogeneity was further tested by hierarchical cluster analysis and principal component analysis. **Results:** Both the SPM maps and cluster analysis identified two major variants of cerebral hypometabolism, namely the “frontal” and the “temporo-limbic”, which were correlated with different cognitive profiles. Executive and language deficits were the cognitive hallmark in the “frontal” subgroup, while poor encoding and recall on long-term memory tasks was typical of the “temporo-limbic” subgroup. **Discussion:** SPM single-subject analysis indicates distinct patterns of brain dysfunction in bvFTD, coupled with specific clinical features, suggesting different profiles of neurodegenerative vulnerability. These findings have important implications for the early diagnosis of bvFTD and for the application of the recent international consensus criteria.

1. Introduction

Diagnostic precision in dementia, particularly in the very early disease phase, highly depends on the presence of stringent syndromic symptoms and on the availability of valid information from disease biomarkers. The quest for accurate early and differential diagnosis in the field of fronto-temporal dementia (FTD) prompted the development of new criteria for the diagnosis of the main FTD subtypes (Rascovsky et al., 2011; Gorno-Tempini et al., 2011). In particular, an international consensus of experts provided a set of validated criteria for the diagnosis of the behavioural variant of fronto-temporal dementia (bvFTD) (Rascovsky et al., 2011), which have been quickly adopted both in research and clinical settings. These criteria define three levels of certainty: ‘‘possible’’, ‘‘probable’’, and ‘‘with definite fronto-temporal lobar degeneration (FTLD) pathology’’, according to the presence of supportive features to diagnosis. While the certainty of diagnosis is limited to cases with histopathological confirmation or *in vivo* evidence of a pathogenic gene mutation associated with FTLD, the “probable” level of diagnostic certainty is reached in the presence of from three up to six clinically discriminating features, with evidence of progression with functional disability, and supported by the identification of neuroimaging changes consistent with bvFTD.

While the new criteria are based on a flexible combination of clinical diagnostic features that might accommodate different initial clinical presentations, the imaging features required for the diagnosis of bvFTD are rather broad and unspecific. The presence of “frontal and anterior temporal lobe atrophy and/or hypometabolism” on brain imaging is the only requirement (Rascovsky et al., 2011). Damage to the frontal lobes, however, is present in other dementia conditions, such as the frontal variant of Alzheimer’s disease (AD) and

progressive supranuclear palsy, while anterior temporal lobe dysfunction characterizes the semantic variant of primary progressive aphasia.

It is increasingly recognized that bvFTD is a heterogeneous clinical syndrome resulting from a variable combination of key symptoms (e.g., dysexecutive syndrome, social cognition disorders and behavioural changes) and additional cognitive (e.g., memory or language disorders) or clinical (e.g., parkinsonism or motor neuron dysfunction) features (Piguet et al., 2011; Hornberger & Piguet, 2012; Cerami & Cappa, 2013).

Consistent but scattered evidence accumulated in the last 20 years supports the presence of different FDG-PET imaging findings in bvFTD (see Perani, 2008; Cerami & Cappa, 2015; Cerami et al., 2015). In particular, FDG-PET imaging studies at the group level analysis reported an early metabolic damage of the limbic system, in line with the well-known selective disease-specific vulnerability of the frontal basal-insular-temporal networks (Seeley et al., 2012), and with the dysfunction of the connected subcortical structures (Salmon et al., 2003; Grimmer et al., 2004; Ibach et al., 2004; Franceschi et al., 2005; Jeong et al., 2005; Schroeter et al., 2008; Seeley et al., 2008).

FDG-PET neuroimaging is considered to be more sensitive than conventional MRI at the individual level, and, crucially, at the earliest disease phase, allowing an early support to the diagnosis of neurodegeneration (Perani et al., 2014, 2016; Kerklaan et al., 2014; Jacova et al., 2013). Conventional MRI *per se* has low sensitivity in bvFTD (Perani et al., 2016; Kipps et al., 2007), and the application of voxel-based methods (e.g., Statistical Parametric Mapping–SPM) for the analysis of FDG-PET imaging data is showing its fundamental role to improve the diagnostic accuracy at the individual level (Perani et al., 2014; Frisoni et al., 2013). Recently, a FDG-PET SPM method has been validated for the detection of specific metabolic

patterns associated with different neurodegenerative conditions, including the FTLD spectrum (Perani et al., 2014, 2016).

While the clinical heterogeneity has been reported in patients belonging to research and clinical settings, the associated case-to-case variability in functional metabolic patterns has not been explored yet. Although some authors previously proposed possible classifications for bvFTD based onto distinct anatomical subtypes, as revealed by brain MRI or FDG-PET imaging studies (Whitwell et al., 2009; Salmon et al., 2006), these reports are based only on group level classifications not allowing the detection of cognitive-functional bvFTD endo-phenotypes at the individual level.

In the present study, we aimed to evaluate in a large retrospective study of probable bvFTD patients (n=52) the consistency of the individual clinical profiles and the case-to-case variability in FDG-PET imaging patterns, as assessed by an optimized voxel-based method already validated and standardized at the single-subject level (Della Rosa et al., 2014; Perani et al., 2014, 2016).

2. Materials and Methods

2.1 Participants

The sample included subjects belonging to the database of the Neurology Centres for Cognitive Disorders of San Raffaele Hospital (Milan, Italy), referred as suspected bvFTD to the Nuclear Medicine Department of San Raffaele Hospital for an FDG-PET scan in the years between 2011 and 2014 and fulfilling Rascovsky criteria (Rascovsky et al., 2011) for “probable bvFTD”. It means that we included only patients with at least three

behavioural/cognitive symptoms from Rascovsky et al. (2011), significant functional decline and imaging results consistent with bvFTD. Patients carrying known autosomal dominant gene mutations as well as subjects presenting signs or symptoms of motor neuron dysfunction were excluded from the present study.

The entire clinical (medical history, neurological examination and neuropsychological assessment) data and the available information on CSF and imaging biomarkers (MRI and FDG-PET), acquired at baseline, were considered by three neurologists (SI, GM, AM) expert in dementia diagnosis in making the clinical diagnosis. A follow-up of two-years was also considered in each case.

From an initial set of 64 individuals, twelve subjects were excluded since 5 patients were classified by the experts as early-onset AD, 2 as bvFTD with Amyotrophic Lateral Sclerosis, 2 as phenocopy bvFTD syndrome, and 3 as “possible bvFTD” (but not “probable”). On this basis, 52 cases finally were included in the study (age = 69.57±8.01 years; education = 10.9±4.5 years; CDR sum of boxes = 5.15±2.86; disease duration = 30.9±21.7 months; MMSE raw score = 22.4±5.7). A family history of neuropsychiatric conditions was reported by the majority of patients. See Table 1 for demographic and clinical details.

The neuropsychological battery administered at the time of the initial diagnosis included measures of global cognitive efficiency (i.e., Mini Mental State Examination), memory (i.e., Digit Span Forward, immediate and delayed recall of Rey Auditory Verbal Learning, recall of copy of the Rey-Osterrieth figure), attention and executive functions (i.e., Attentional Matrices, Raven Colored Progressive Matrices; Digit Span backward; letter (P-F-L) and category (animals-fruits-car brands) fluency tests; Cognitive Estimation Test; Stroop Interference Test or Wisconsin Card Sorting Test), language abilities (i.e., Token test, picture naming and single word comprehension tests) and visuo-spatial abilities (i.e., copy of the Rey-Osterrieth

figure). Standardized neuropsychological measures assessing social cognition abilities (Serafin & Surian, 2004; Dodich et al., 2014, 2015) were also obtained in 33% of the patients. Behavioural changes were assessed with caregiver questionnaires (e.g., Neuropsychiatric Inventory (Cummings et al., 1994) and Frontal Behavioural Inventory (Alberici et al., 2007)).

Conventional MRI was available in all cases to exclude the presence of white matter hyper intensities and lacunes of presumed vascular origin. On the basis of the neuroradiology report, only moderate or mild fronto-temporal atrophy was present in about the half of the sample (n=22/52), with relative asymmetric atrophy pattern in some cases. No evidence of relevant changes was reported at the conventional MRI assessment in 30 cases. FDG-PET scan was obtained in each included case as part of the diagnostic algorithm performed in our academic centre. CSF β-Amyloid, Tau and p-Tau values were also sampled whenever possible (i.e., 34/52 patients). As expected, β-Amyloid and Tau changes typical of AD (i.e., low β-Amyloid and high phospho- or total-Tau levels) were not found in any of these cases.

All subjects, or their informants/caregivers, gave written informed consent to the experimental procedures previously approved by the Ethical Committee of San Raffaele Hospital.

2.2 FDG-PET imaging acquisition and pre-processing

FDG-PET acquisitions were performed **in the early disease phase at the time of the initial clinical evaluation** at the Nuclear Medicine Unit, San Raffaele Hospital (Milan, Italy) according to the guidelines of the European Association of Nuclear Medicine (EANM) following standardized procedures (Morbelli et al., 2012; Varrone t al., 2009). Before radiopharmaceutical injection of FDG (185–250 Mbq: usually, 5-8 mCi via a venous cannula),

subjects were fasted for at least 6 hours and their blood glucose level was <120 mg/dL. All images were acquired with a Discovery STE (GE Medical Systems, Milwaukee, WI) multi-ring PET tomography (PET-CT) system (time interval between injection and scan start = 45 minutes; scan duration = 15 minutes). For each PET scan, 47 transaxial tomographic slices of 4.25 mm were acquired. Images were reconstructed using an ordered subset expectation maximization (OSEM) algorithm. Attenuation correction was based on CT scan. Specific software integrated in the scanner was used for scatter correction. All subjects gave written informed consent, following detailed explanation of the FDG-PET procedure.

Image processing and statistical analysis were performed according to standardized and validated procedures (Della Rosa et al., 2014; Perani et al., 2014, 2016). In particular, normalization procedure was performed at the single-subject level to a dementia-specific SPM FDG-PET template (Della Rosa et al., 2014). Each patient scan was then tested for relative “hypometabolism” based on a validated procedure that includes comparison with a large normal image database (n=112) of FDG-PET images on a voxel-by-voxel basis (Perani et al., 2014). Age was included as a covariate. Proportional scaling was used to remove inter-subject global variation in PET intensities. The threshold was set at p=0.05, FWE-corrected for multiple comparisons at the voxel level. Only clusters containing more than 100 voxels were deemed to be significant.

Whole-brain group analysis (i.e., two-sample t-test) was done to evaluate the FDG-PET hypometabolic patterns in bvFTD subgroups (see results) compared with the normal image database (n=112) of FDG-PET images, including age as covariate. The threshold was settled at p<0.05 FWE-corrected with a minimum cluster size of 100 voxels.

Finally, to explore the commonalities in the FDG-PET hypometabolic patterns of the resulting bvFTD subgroups, we computed a conjunction analysis between the statistical maps

representing the significant hypometabolism of the metabolic variants resulting from cluster analysis (Nichols et al., 2005). The threshold is settled at $p<0.05$ FWE corrected, minimal cluster extent = 100.

2.3 FDG-PET images rating

Three raters (CC, LG, DP), with an extensive experience in the neuroimaging of dementia, blinded to clinical-neuropsychological data, biomarkers information and clustering analysis classification assessed the voxel-based SPM hypometabolic maps of each bvFTD patient (see examples of FDG-PET SPM single-subject maps in Figure 1). They were only informed that the study included patients who had a clinically confirmed diagnosis of “probable bvFTD”.

Before the study, each rater followed a training session to familiarize with the materials provided and the requested evaluation procedure. For this training, we used the FDG-PET SPM maps of 3 patients with a diagnosis of possible bvFTD, which were excluded from the experimental data set. The procedure adopted for the training was the same used in previous published studies (Perani et al., 2014, 2016).

The raters were then independently presented with the FDG-PET SPM maps for each subject. Each image was displayed in a 5x5 matrix of transaxial images (i.e. 25 axial slices) from rostral to ventral brain sections in neurological convention. Each axial slice covered 4 mms on the z-axis ranging from -40 to +56. SPM maps showed statistically significant reductions of metabolism with the significant t-values in yellow/red scale. Raters were first instructed to report details on brain hypometabolism, including the involved brain lobes and the cortical and subcortical structures, and to decide whether the hypometabolic pattern was bilateral or asymmetrical (i.e., > left or > right hemisphere). Finally, they were asked to group the FDG-PET SPM maps according to the regional distribution of brain hypometabolism. This

resulted in two FDG-PET SPM patterns, categorized as, respectively, prevalent dorsolateral frontal and temporo-limbic involvement (see examples of FDG-PET SPM maps on Figure 1).

2.4 Cluster and principal component analyses

Preliminarily, we selected the region of interests (ROIs) for the cluster analysis from AAL (Tzourio-Mazoyer et al., 2002) and IBASPM116 Atlas (Alemán-Gómez et al., 2006). The regions of relative hypometabolism in the single-subject SPM maps were: dorsolateral, medial frontal, ventromedial and orbitofrontal cortices, anterior/middle cingulate cortex (ACC/MCC), insula, temporal pole, hippocampal structures, amygdala, superior, middle and inferior temporal gyrus, posterior cingulate cortex, nucleus accumbens, caudate, and thalamus bilaterally. A hierarchical agglomerative cluster analysis was performed by a researcher (AD), blind to both clinical-neuropsychological information and FDG-PET SPM rating, following the procedure applied by Whitwell et al. (2009) using the Ward's clustering linkage method of combining clusters. Such hierarchical method gives a sequence of nested clusters and allows the researcher to choose the number of clusters to work with. Additionally, we used principal component analysis (i.e., PCA) to validate the results of clustering analysis.

2.5 Statistical comparisons

Demographic, clinical and neuropsychological variables were compared among bvFTD subgroups (see results). Demographic-corrected scaled neuropsychological scores were used for statistical comparisons. Since executive functions were evaluated in single cases either with the Wisconsin Card Sorting Test or with the Stroop Colour-Word Test, we compared patients' performances by classifying them as normal or impaired according to the

Italian normative standards (Caffarra et al., 2004; Venturini et al., 1983). Pearson Chi-squared statistic was used in order to compare the distribution of cognitive disorders between subgroups. Additionally, we correlated neuropsychological data and PCA scores. Correlation analyses between social cognition performances and PCA scores were not performed because of the poor number of patients tested (approximately 33% of the entire sample). Due to the non-normal distribution of neuropsychological data we used non parametric statistics (i.e., Wilcoxon rank-sum, Mann–Whitney U-tests and Spearman rho index). The results were corrected for multiple comparisons using false discovery rate (FDR). Statistical analyses were performed Cohen's κ coefficient was used to evaluate the inter rater agreement between FDG-PET experts with the SPSS software.

3. Results

3.1 FDG-PET SPM maps rating

The neuroimaging expert raters split the bvFTD sample into two subgroups according to the functional metabolic patterns. Notably, the raters identified either a predominant "frontal" or a predominant "temporo-limbic" FDG-PET pattern. The "frontal" pattern was characterized in each individual by a widespread hypometabolism in the prefrontal cortex (i.e., dorsolateral, medial and ventromedial frontal). In contrast, the "temporo-limbic" pattern by a predominant hypometabolism in the temporal lobes, including temporal poles, hippocampal structures and amygdala, and lateral temporal cortex with a selective sparing of the dorsolateral prefrontal cortex. Both pattern subgroups shared a common hypometabolic pattern within the limbic system (i.e., anterior/middle cingulate cortex (ACC/MCC), ventromedial frontal cortex, and

insula), the basal ganglia (i.e., nucleus accumbens and caudate) and thalamus. In addition, a minority of patients showed hypometabolism in the posterior cingulate cortex, probably due to neural disconnection. Inter-rater agreement within the experts' classifications for the FDG-PET imaging resulted in an "almost perfect agreement" ($\kappa>0.85$).

Notably, there was also a case-to-case variability in the FDG-PET SPM maps at individual level. Expert raters reported indeed variable extent and degree of hypometabolism both in the "frontal" and the "temporo-limbic" metabolic patterns. This heterogeneity, however, particularly characterized the "temporo-limbic" subgroup. While the most of "temporo-limbic" patients showed a selective or predominant reduction of brain metabolism in the limbic system structures, a minority of such patients showed a major damage in the lateral portions of the temporal cortex.

A prevalent right hemispheric asymmetry **(i.e., right > left hypometabolism)** was present in a high proportion of cases (~40%) belonging to both subgroups.

See examples of "frontal" and "temporo-limbic" FDG-PET SPM single-subject patterns on Figure 1.

3.2 Cluster and principal component analyses

Two clusters of comparable size (cluster #1, n=27 and cluster #2, n=25) emerged at the final step of the cluster analysis (Figure 2 and 3). This two-cluster level defined divergent FDG-PET patterns corresponding to those recognized by the expert raters at the evaluation of the FDG-PET SPM single-subject maps. The conjunction analysis between the patterns of brain hypometabolism of patients belonging to the two clusters revealed areas of regional commonalities involving the ACC/MCC, the superior medial frontal gyrus, the ventromedial

frontal cortex extending to orbitofrontal cortex, the insula, the nucleus accumbens and the thalamus bilaterally (Figure 2).

Notwithstanding the above-mentioned two final clear-cut divergent FDG-PET SPM patterns, four additional sub-clusters were evident at the preceding step of the cluster analysis (Figure 3). By revising the SPM maps of the single included cases, we found that the four-cluster level was further informative on the asymmetry and topographical distribution of the brain glucose metabolism. In particular, patients within the “temporo-limbic” subgroup was subdivided by clustering into two sub-clusters according to the predominant involvement of limbic structures (n=20) or lateral temporal cortex (n=7) (see Figure 1 and 3). Patients within the “frontal” subgroup were split according to the symmetric or left-predominant (n=16) or right-predominant (n=9) hypometabolism in the dorsolateral prefrontal cortex (Figure 3).

The first four principal components of the PCA analysis were represented by: 1) the bilateral frontal lobes, 2) the right and 3) the left temporal lobes, and 4) the subcortical brain structures. They captured the 80% of the variance and can thus be considered as the best dimensional representations of the full data set. The first three components well distinguished the two bvFTD clusters, further validating the identification of the different metabolic profiles (Figure 4).

3.3 Behavioural and neuropsychological profiles

“Frontal” and “temporo-limbic” metabolic subgroups did not differ in gender and education, global cognitive efficiency and clinical severity (Table 1). The “temporo-limbic” subgroup was significantly older and with a longer disease duration (Table 1).

Although at the time of the initial clinical evaluation (baseline), all bvFTD patients showed behavioral disturbances, in some cases the first/presenting symptom was not of behavioral-type (see Table 1). In such cases, behavioral alterations appeared some months after the onset of cognitive impairments (i.e., anomia, memory disorders or prosopagnosia). Such cognitive presenting symptoms differed between the two subgroups. Language symptoms (i.e., word finding difficulties) were present only in the "frontal" subgroup, while memory difficulties only in the "temporo-limbic" subgroup (Table 1).

Disinhibition and apathy were simultaneously present in the majority of patients belonging to both subgroups (i.e., 56% "frontal" and 67% "temporo-limbic" patients), while isolated apathy was prevalent in the "frontal" (i.e., 40%) compared to the "temporo-limbic" subgroup (i.e., 26%). Isolated disinhibition was present only in the "temporo-limbic" subgroup (i.e., 7%).

Scores at the executive and fluency tasks, as well as the performance in the immediate recall of the Rey auditory verbal learning test (RAVLT), were significantly lower in the "frontal" subjects compared to the "temporo-limbic" (Table 2). No significant difference on delayed recall was found between the two subgroups. After controlling for levels of immediate recall, however, the number of patients with selectively impaired delayed recall was significantly higher in the "temporo-limbic" subgroup (i.e., 4% "frontal" vs. 19% "temporo-limbic" subjects; $\chi^2(1) = 4.72$, $p<0.05$) (Table 2).

Loss in empathy/sympathy skills were reported by caregivers in the majority of patients (i.e., 72% and 70%). Standardized socio-emotional tasks were available only for a part of the patients (i.e., 32% and 33%). Severe deficits in emotion recognition and empathy/theory of mind abilities were present in patients belonging to both subgroups. Notably, all the "temporo-limbic" patients that were tested were impaired.

3.4 Correlation analysis

Correlation analyses between neuropsychological data and PCA scores revealed significant negative correlations between the first PCA component (i.e., bilateral frontal lobes) and attentional matrices ($r = -0.486$, $p=0.008$), semantic ($r = -0.363$, $p<0.05$), phonemic verbal fluency ($r = -0.451$, $p<0.01$), digit span forward ($r = -0.424$ $p<0.01$), Raven's progressive matrices ($r = -0.306$, $p<0.05$) and RAVLT immediate recall ($r = -0.413$, $p<0.05$).

4. **Discussion**

In this study, we assessed FDG-PET metabolic patterns at the individual level in a large sample of probable bvFTD patients, testing for the presence of specific metabolic signatures supporting the existence of subgroups. FDG-PET scans were analysed in single subjects with a standardized and validated SPM voxel-based method (Della Rosa et al., 2014; Perani et al., 2014, 2016). The raters, blinded to clinical information, identified two major and different metabolic patterns, namely, a widespread hypometabolism in the prefrontal cortex and a predominant hypometabolism of limbic structures and temporal lobe with selective sparing of the dorsolateral prefrontal cortex. The analysis of cognitive and behavioural profiles indicated commonalities as well as differences between the two subgroups. We observed longer disease duration and an older age at the time of diagnosis in the "temporo-limbic" group, suggesting a more benign neurodegenerative course in these subjects.

Previous neuroimaging studies indicate an overall consistency in neuroanatomical subtyping of bvFTD in subgroups with prevalent frontal or temporal involvement (e.g., Salmon et al., 2003, 2006; Whitwell et al., 2009, 2011, 2013), and with a relative asymmetry or

symmetry in the pattern of brain damage (Salmon et al., 2003, 2006; Whitwell et al., 2009, 2013; Josephs et al., 2009). This has suggested different pathological substrates, leading to specific neuroanatomical endo-phenotypes (Whitwell et al., 2012; Snowden et al., 2015). The present FDG-PET metabolic study adds further evidence, with a measure of early neural dysfunction at single-subject level, to the previous findings largely based on measures of late structural changes, such as MRI atrophy, at a group level. It further indicates that a possible bvFTD classification based on the recent diagnostic criteria (Rascovsky et al. 2011) is compatible with different clinical-neuropsychological phenotypes that are related to specific FDG-PET patterns at the individual level.

The analyses of metabolic changes and cognitive profiles in these two metabolic subgroups suggest different network vulnerability associated with specific neuropsychological features. Notably, the significantly lower executive and fluency scores in the “frontal” subgroup are correlated to the predominant hypometabolism in the prefrontal cortex, whereas the medial temporal lobe hypometabolism in the “temporo-limbic” patients accounted for the presence of delayed recall deficits in memory testing. These anatomo-clinical findings might explain previous evidence indicating that bvFTD patients may present with memory deficits comparable to those of AD (Hornberger & Piguet, 2012; Bertoux et al., 2014, 2015; Irish et al., 2013, 2014). In particular, Bertoux and colleagues (2014) showed that not even the performance on cued recall tasks (i.e., Free Cued Selective Reminding Task) can differentiate bvFTD from AD patients. Half of their bvFTD sample had indeed impaired free and total (free + cued) recall, and delayed recall performances as severely impaired as AD patients. Notably, the authors questioned the utility of episodic memory assessment in the differential diagnosis between bvFTD and AD (Bertoux et al., 2015). Further studies, however, focused on

comparison of episodic memory performances between bvFTD subgroups with different FDG-PET metabolic profiles and typical AD patients, will contribute in clarifying this issue.

A subset of “temporo-limbic” patients (n=7) showed a major involvement of the lateral temporal cortex, mainly on the right side (Figure 1 and 3). This dysfunctional pattern is compatible with the definition of the right temporal variant of FTD (Josephs et al., 2009). The clinical profiles of the patients with lateral temporal cortex hypometabolism in our series include prosopagnosia, word-finding and comprehension difficulties, and topographical disorientation, all typical features of this syndrome (Josephs et al., 2009).

The presence of a right-hemispheric predominant hypometabolism in our bvFTD sample is supported by previous findings of selective involvement of the right frontal basal-insular-temporal structures in the early stages of this condition (see Seeley et al., 2012 for a review). The predominant role of the right temporal and limbic structures in mediating socio-emotional cues recognition and processing in bvFTD has been extensively investigated (e.g., Eslinger et al., 2011; Lee et al., 2014; Cerami et al., 2014, 2015). A major involvement of limbic structures was overall present at the individual level. A common core of metabolic dysfunction of the ACC/MCC, the ventromedial frontal cortex, the insula, the nucleus accumbens and the thalamus represented the shared dysfunctional feature of the whole bvFTD group (Figure 1 and 2). This FDG-PET evidence supports the key involvement of brain regions other than the reported “frontal and anterior temporal lobes” in probable bvFTD. Of note, the insula, a crucial component of the large-scale functional salience network involved in socio-emotional processing (Ibañez & Manes, 2012), was found to be consistently hypometabolic among the patients of our sample.

Behavioural disorders (i.e., disinhibition and apathy, perseverations, and dietary changes) as well as loss of empathy/sympathy did not distinguish between the two subgroups. The

shared metabolic involvement in the above-mentioned fronto-limbic structures, core hubs of the socio-emotional processing and behaviour controls networks, may explain the lack of differences between the “frontal” and the “temporo-limbic” patients in these main behavioural core dimensions. While the present results do not support the classic dichotomy between apathetic and disinhibited syndromes in bvFTD, isolated apathy was more frequent in the “frontal” subgroup and disinhibition in the “temporo-limbic” subgroup. This is in accordance to the well-established neuroanatomical correlates of these behavioural symptoms. Disinhibition is mainly associated with hypometabolism in the interconnected fronto-limbic structures, while apathy is mostly related to dorsolateral and medial frontal hypometabolism (Franceschi et al., 2005; Rosen et al., 2005; Peters et al., 2006; Zamboni et al., 2008; Massimo et al., 2009; Hornberger et al., 2011; Schroeter et al., 2011).

In conclusion, our data indicate the presence of at least two distinct metabolic patterns in bvFTD patients at single-subject level, resulting in different cognitive profiles and possibly reflecting different pathways of neurodegeneration. In the absence of pathological information we cannot speculate on any link to the multiple underlying pathologies that cause bvFTD (e.g., Tau or TDP-43 pathology). Specific imaging signatures have been reported in FTLD patients according to the pathological substrates (Whitwell et al., 2012; Hornberger et al., 2012; Warmus et al., 2014; Snowden et al., 2015). In particular, Hornberger et al. (2012) showed greater hippocampal loss in FTLD-TDP post-mortem cases compared to those with tau pathology, suggesting that episodic memory deficits in conjunction with marked hippocampal atrophy may be potential biomarkers for TDP-43 pathology in FTLD. Further neuropathological studies are needed to confirm this hypothesis.

Finally, our findings may contribute to the discussion on the international consensus criteria for bvFTD, suggesting that FDG-PET may be useful to define specific imaging profiles related

to different clinical presentations (Joseph et al., 2011). This functional metabolic study at the single-subject level goes beyond the previous results, which were based on group analysis, showing that specific metabolic patterns reflected in different clinical syndromes can be observed at the single-subject level. The effective identification in clinical settings of different bvFTD endo-phenotypes is critical for management considerations and prognostic evaluations.

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Figure Legend:

Figure 1. Examples of single-subject FDG-PET SPM maps for the two bvFTD variants (i.e., “frontal” and “temporo-limbic” hypometabolic patterns). While the patients with the “frontal” pattern (#1-3) show a widespread damage of the prefrontal cortex, either symmetrically (#1) or asymmetrically (#2-3), the patients with the “temporo-limbic” pattern show variable degrees of hypometabolism in the fronto-limbic structures (i.e., ventromedial and orbitofrontal cortices) and/or the anterior lateral temporal cortex, with a relative sparing of the dorsolateral prefrontal cortex (#4-6). Additional involvement of subcortical structures is also evident. The threshold is settled at $p<0.05$ FWE-corrected, minimal cluster extent = 100.

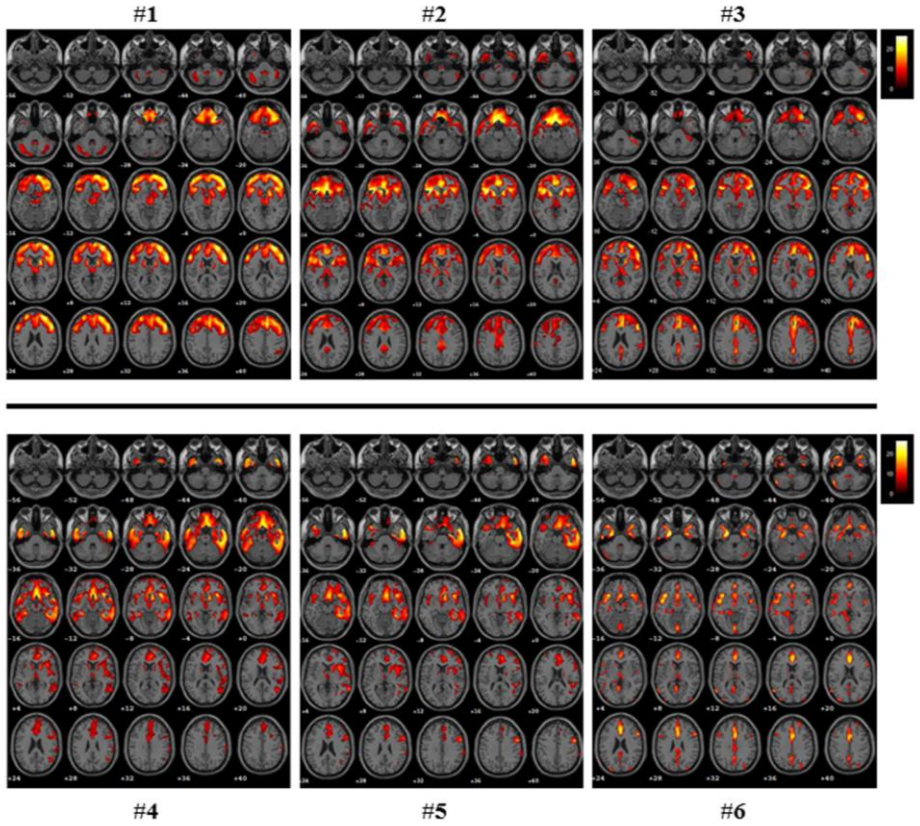

Figure 2. The upper left panel shows the one-sample t-test FDG-PET hypometabolic SPM map of the “temporo-limbic” bvFTD subgroup, the lower left panel the SPM map of the “frontal” subgroup. The right panel shows the hypometabolic SPM map resulting from conjunction analysis of the two patterns. All results are overlaid on the SPM structural MNI single-subject template and displayed on axial view. For graphical purposes, the threshold is settled at $p<0.001$ uncorrected, minimal cluster extent = 100.

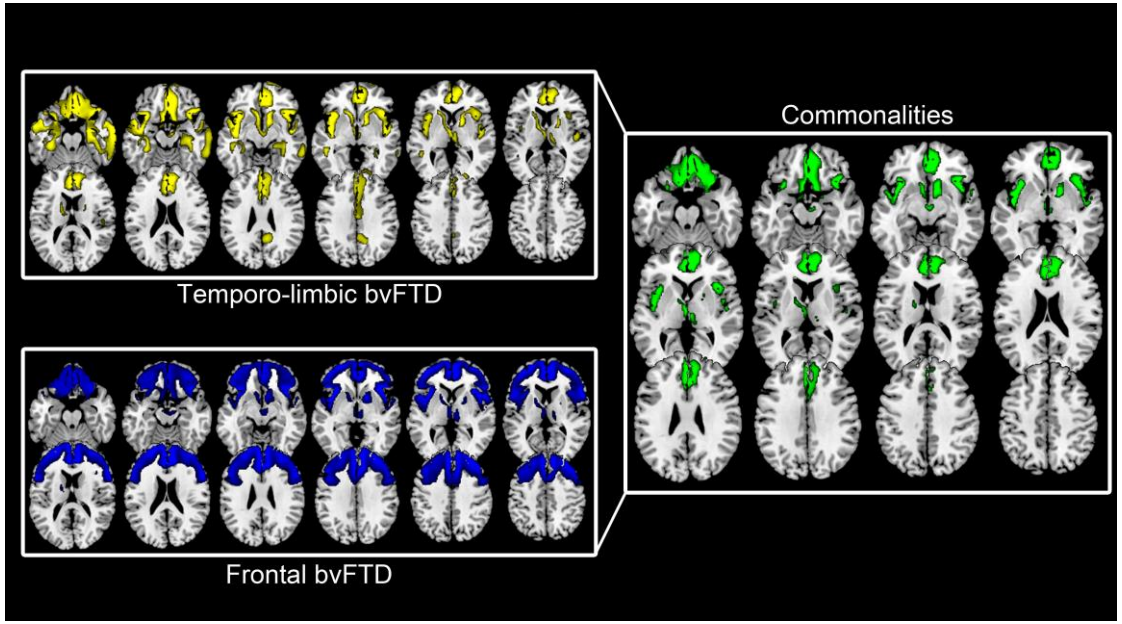

Figure 3. This figure reports the dendrogram of the cluster analysis. The closer the distance along the x-axis the greater the similarity between the subjects. At the final step, the clustering split the cases into two clusters of comparable size (i.e., cluster #1 (n=27), i.e., “temporo-limbic pattern” patients, and cluster #2 (n=25), i.e., “frontal pattern” patients). At the step before, these two major clusters were split into four clusters: cluster #1 into “limbic pattern” (n=20) and “temporal pattern” (n=7), and cluster #2 into “bilateral/left predominant frontal pattern” (n=16) and “right predominant frontal pattern” (n=9).

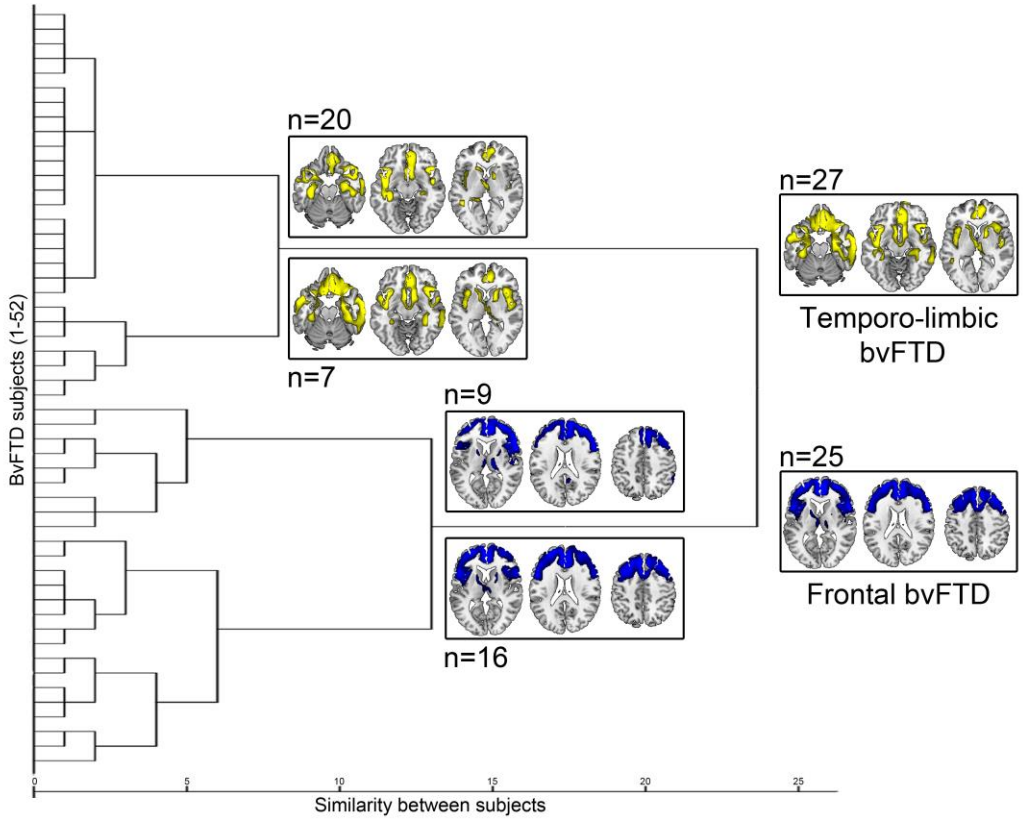

Figure 4. Scatterplots showing the distribution of patients belonging to FDG-PET clusters #1 and #2 according to the scores on the first three components of the PCA. Notably, subjects belonging to the cluster #2 (i.e., the “frontal” subgroup) showed high first principal component scores suggestive of predominant involvement of frontal lobes (left panel), while those belonging to the cluster #1 (i.e., the “temporo-limbic” subgroup) a low first principal component scores and high second (i.e., right temporal lobe) and third (i.e., left temporal lobe) principal component scores.

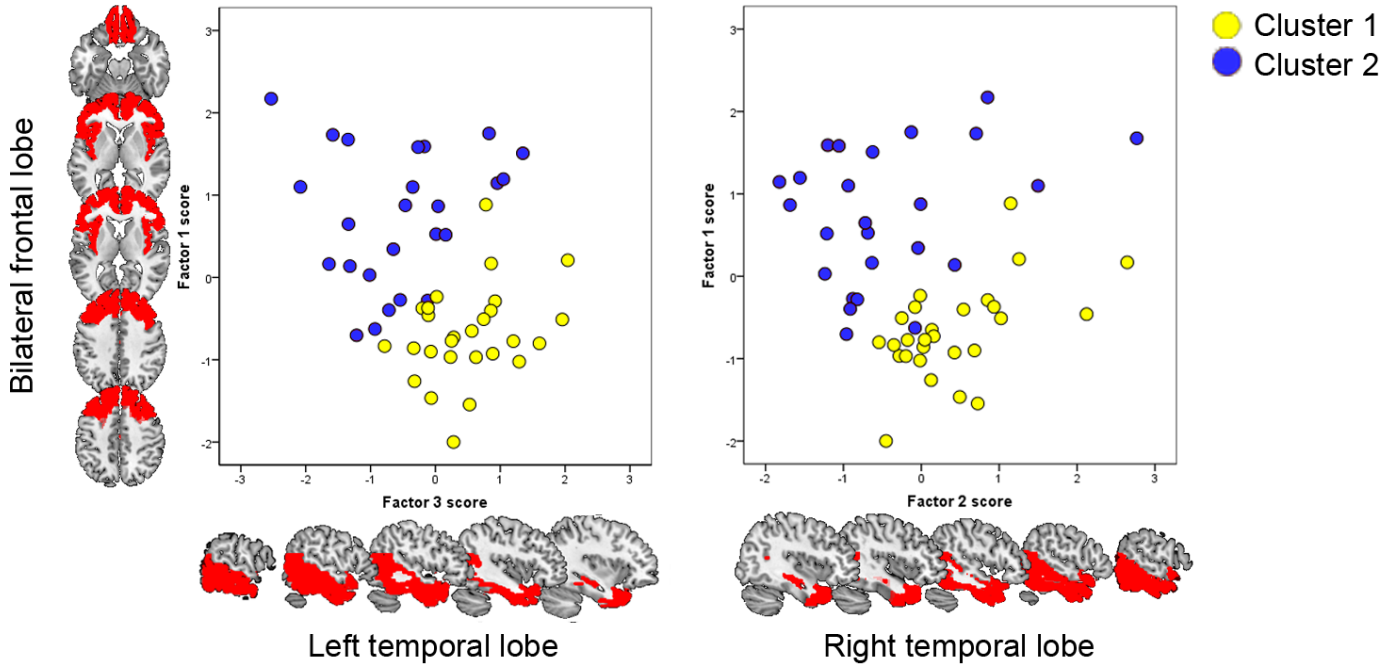

Table 1. Demographic and clinical features of the two bvFTD subgroups

	Frontal	Temporo-limbic	Statistics
Number of subjects	25	27	-
Gender *(female/male)*	11/14	12/15	n.s.
Age in years *(mean/st.dev.)*	65.96±7.50	72.9±7.083	F<TL *
Education in years *(mean/st.dev.)*	11.12±4.51	10.78±4.61	n.s.
CDR sum of boxes *(mean/st.dev.)*	4.84±2.06	5.48±3.57	n.s.
Months from symptoms' onset at baseline *(mean/st.dev.)*	26.8±13.54	34.81±27.15	n.s.
MMSE raw score *(mean/st.dev.)*	22.04±5.76	22.67±5.74	n.s.
Presenting symptoms *(n. of cases)*	Behavior n=16 Behavior + Language n=8 Language n=1	Behavior n=11 Behavior + Memory n=9 Memory n=6 Prosopagnosia n=1	-
Family history of neuropsychiatric conditions *(n. of cases)*	21	22	n.s.
History of bipolar syndrome or depression *(n. of cases)*	4	4	n.s.
Behavioral disinhibition *(n. of cases)*	1	2	F≠TL ∫ *
Apathy or inertia *(n. of cases)*	10	6	
Both disinhibition and apathy *(n. of cases)*	14	19	
Loss of empathy or sympathy *(n. of cases)*	18	19	n.s.
Perseverative, stereotyped, or compulsive/ritualistic behaviors *(n. of cases)*	14	20	n.s.
Hyperorality and dietary changes *(n. of cases)*	8	9	n.s.
Executive deficits *(n. of cases)*	24	16	F≠TL ₽ *
Immediate recall memory impairments *(n. of cases)*	0	0	
Delayed recall memory impairments *(n. of cases)*	1	5	F≠TL § *
Both immediate and delayed recall memory impairments *(n. of cases)*	14	7	
No immediate and delayed recall memory impairments *(n. of cases)*	8	6	

*CDR = Clinical Dementia Rating Scale; MMSE = Mini Mental State Examination; F = Frontal; TL = Temporo-Limbic; * = p<0.05; n.s. = not significant; ∫ = the comparison between the frequency of subjects with an isolated behavioral symptom (either apathy or disinhibition) and the frequency of subjects with mixed behavioral profile showed a significantly higher number of subjects with isolated apathy within the "frontal" sub-group; ₱ = the comparison between the frequency of subjects with impaired Modified Card Sorting Test or Stroop-Colored Task in the two sub-groups significantly differed, namely the frequency of subjects with such deficit was higher in the "frontal" sub-group; § = the comparison between the frequency of subjects with isolated delayed recall deficit and subjects with combined delayed and immediate deficits showed a significantly higher number of subjects with isolated delayed recall deficit in the "temporo-limbic" sub-group*

Table 2. Neuropsychological features of the two bvFTD sub-groups

	Frontal	Temporo-limbic	Statistics
Number of subjects	25	27	-
FBI *(mean/st.dev.)*	26±8.29	30.22±8.12	n.s.
NPI *(mean/st.dev.)*	26.45±17.61	35.77±21.48	n.s.
Token task *(mean/st.dev.)*	22.12±8.16	27.82±5.73	F<TL *
Semantic verbal fluency *(mean/st.dev.)*	19.85±10.65	28.84±13.88	F<TL *
Phonemic verbal fluency *(mean/st.dev.)*	8±7.16	18.19±9.74	F<TL **
Modified Card Sorting Test *perseverative errors (mean/st.dev)*	13.82±8.34	9.18±6.41	-
Stroop Colour Task interference score *(mean/st.dev.)*	39.79±11.86	37.5±44.22	-
Attentional matrices *(mean/st.dev.)*	29.60±8.70	37.93±9.47	F<TL**
Raven matrices *(mean/st.dev.)*	20.31±6.97	23.65±5.78	n.s.
Digit forward *(mean/st.dev.)*	4.18±0.66	5.34±0.87	F<TL ***
Rey list immediate recall *(mean/st.dev.)*	21.73±10.43	31.78±12.70	F<TL *
Rey list delayed recall *(mean/st.dev.)*	2.79±2.64	6.17±4.85	n.s.
*FBI = Frontal Behavior Inventory; NPI Neuropsychiatric Inventory; F = Frontal; TL = Temporo-Limbic; * = p<0.05; ** = p<0.01; *** = p<0.001 n.s. = not significant*			