CORTEX 185 (2025) 84–95

Available online at www.sciencedirect.com

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Journal homepage: www.elsevier.com/locate/cortex

Research Report

Clinical and metabolic profiles in behavioural frontotemporal dementia: Impact of age at onset

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ARTICLE INFO

Article history:
Received 11 June 2024
Revised 8 January 2025
Accepted 8 January 2025
Action Editor Stefano F. Cappa
Published online 11 February 2025

Keywords:
Behavioural frontotemporal dementia

ABSTRACT

Aim: Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disorder, with considerable variability of age-at-onset. We explored clinical and metabolic differences between early- and late-onset behavioural FTD (bvFTD), assuming that they might represent different disease phenotypes.

Materials and methods: We retrospectively studied consecutive patients diagnosed with prodromal or overt bvFTD with [^{18}F]FDG PET scan, neuropsychological assessment (NPS), and Neuropsychiatric Inventory (NPI) available at baseline. Patients were divided into three groups based on age-at-onset: early onset-bvFTD (EO-bvFTD, age<70), late onset-bvFTD (LO-bvFTD, age 70–75) and very late onset-bvFTD (vLO-bvFTD, age>75). NPS and NPI were compared between groups and in the subset of prodromal patients, to study different

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https://doi.org/10.1016/j.cortex.2025.01.011

Age at onset
FDG-PET
Cognition
Neuropsychiatric disorders

syndromic phenotypes. Voxel-based analysis compared brain [^{18}F]FDG PET of EO-bvFTD, LO-bvFTD and vLO-bvFTD independently, with respect to healthy controls, to explore metabolic differences. An inter-regional metabolic covariance analysis was performed in frontal lobe subregions, to explore differences in brain connectivity. Moreover, we supported our result using a correlation-based approach on clinical and metabolic variables.

Results: 101 bvFTD (62 prodromal bvFTD) were enrolled (EO-bvFTD: $n = 36$, prodromal $n = 21$; LO-bvFTD: $n = 36$, prodromal: $n = 22$; vLO-bvFTD: $n = 29$, prodromal: $n = 19$). Greater verbal memory deficit was evident in LO-bvFTD and vLO-bvFTD compared to EO-bvFTD (immediate recall: $p = .018$; $p = .024$; delayed recall: both $p = .001$, respectively), with similar results in the subset of prodromal patients. EO-bvFTD and LO-bvFTD had a higher behavioural severity than vLO-bvFTD. LO-bvFTD and vLO-bvFTD showed more widespread relative hypometabolism, with a greater involvement of posterior, subcortical and temporo-limbic regions compared with EO-bvFTD. Moreover, vLO-bvFTD showed a different pattern of intrafrontal metabolic covariance compared to EO-bvFTD and LO-bvFTD.

Discussion: The cognitive–behavioural profile of bvFTD differs between early- and late-onset, already from the prodromal stage of the disease. Both metabolic pattern and functional connectivity vary based on age-at-onset. Understanding these differences could contribute to improve diagnostic accuracy and understanding the underling pathological heterogeneity.

1. Introduction

Frontotemporal lobar degeneration (FTLD) is an umbrella term that includes the spectrum of those neurodegenerative disorders affecting the frontal and temporal lobes (Bang et al., 2015). These pathological conditions are highly heterogeneous, both from a clinical and neuropathological viewpoint (Boeve et al., 2022), with substantial overlap between syndromes and underlying pathological proteins (Boeve et al., 2022). This heterogeneity well mirrors the different clinical variants of frontotemporal dementia (FTD) that have been progressively described, ranging from primary progressive aphasias (PPA) (Gorno-Tempini et al., 2011), in which patients early manifest a predominantly language impairment, to the behavioural variant of frontotemporal dementia (bvFTD) (Rascovsky et al., 2011). The latter, which epidemiologically represents the most common syndromic subtype, mainly manifests with behavioural disturbances early-on in the disease course.

Traditionally, FTD is considered a predominant early onset disorder, but recently the maximum incidence was observed over 70 years of age (Borroni et al., 2024). Previous studies have investigated the differences between early onset and late onset subtypes in the spectrum of FTLD (AlWazan et al., 2023; Shimizu et al., 2011). Focusing on bvFTD, it was found that young and late onset phenotypes could be quite different in clinical presentation, although findings were not entirely homogeneous across available studies (Borroni et al., 2008; Fieldhouse et al., 2021; Seo et al., 2018) and were not explored in depth in prodromal subset of patients (Benussi et al., 2022).

Diagnostic accuracy of bvFTD can be improved by the use of biomarkers (Frisoni et al., 2024), in particular [^{18}F]FDG-PET (Minoshima et al., 2022; Peet et al., 2021; Vijverberg et al., 2016; Ward et al., 2023), along with MRI, genetic evaluation and fluid biomarkers (van der Ende et al., 2019). Previous studies has shown how [^{18}F]FDG-PET hypometabolism is able to track disease progression (Bejanin et al., 2020), can mirror underlying neuropathology (Peet et al., 2021) and correlated with survival time (El-Wahsh et al., 2021). Moreover, metabolic connectivity (Yakushev et al., 2017), explored by studying brain network alterations, has shown to be an added value to conventional [^{18}F]FDG-PET assessment, providing insights into the pathophysiology of dementing disorders (Carli et al., 2021; Morbelli et al., 2012).

It is still unclear whether early and late onset bvFTD might represent different clinical phenotypes and how age at onset could affect the pattern of hypometabolism and metabolic connectivity. The aim of this study is to explore clinical and metabolic differences between early and late onset bvFTD, both during the prodromal phase (Barker et al., 2022; Benussi et al., 2024) and in overt bvFTD, with the goal of delving into the underlying heterogeneity associated with different ages of onset. By thoroughly analysing these differences, we seek for enhancing our understanding of disease progression, and potentially identify distinct subtypes based on age at onset, as well as associated clinical and metabolic features.

2. Materials and Methods

We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. Patients

We retrospectively enrolled consecutive bvFTD patients evaluated at the memory clinic of IRCCS Ospedale Policlinico

San Martino (Genoa, Italy) between January 2011 and May 2023. At the time of the first diagnostic workup, patients underwent standard neurological, extensive neuropsychological evaluation, a brain [^{18}F]FDG-PET and an MRI within 6 months from first clinical assessment.

All patients in our cohort met the diagnostic criteria for probable bvFTD at baseline evaluation or during follow-up. At baseline diagnostic evaluation, patients were classified as overt bvFTD (so probable or definite bvFTD), according to current diagnostic criteria (Rascovsky et al., 2011), or prodromal bvFTD, according to recently proposed research criteria (Barker et al., 2022). Prodromal bvFTD patients have globally preserved instrumental activities of daily living. Of note, in this study we decided to encompass the full continuum of bvFTD, from prodromal to overt phases, in order to gain a comprehensive understanding of the age-specific phenotypic expression across the entire spectrum of disease severity. Patients with a borderline clinical stage between the prodromal and overt phases of bvFTD (minimal impairment in IADL, i.e., only one point lost on the IADL assessment) were assessed individually and were classified as prodromal bvFTD if this minimal loss did not significantly affect the patient's overall functional status in daily life, as reported by the patient, an informant, and the clinical judgement of two expert neurologists (MP, FM).

All subjects met the following inclusion criteria: symptoms duration less than 3 years at enrolment; confirmation of clinical diagnosis after at least two years of follow-up by expert neurologists (FM, MP); no comorbid psychiatric or neurological condition. Patients who satisfy diagnostic criteria at baseline (or at least during the first year from diagnosis) for PSP (Höglinger et al., 2017), CBS (Armstrong et al., 2013), language impairment totally or partially satisfying PPA diagnostic criteria (Gorno-Tempini et al., 2011), as well as those with right anterior temporal lobe-predominant degeneration (Younes et al., 2022) or possible bvFTD, were not included. Patients with positive biomarkers for AD (CSF or amyloid PET), even in the presence of [^{18}F]FDG-PET suggestive of bvFTD, were excluded, as well as patients with an [^{18}F]FDG-PET atypical for bvFTD (i.e. potentially suggestive of a behavioural variant of AD (Ossenkoppele et al., 2022), e.g. with relevant precuneus or posterior involvement), or with two-year follow-up findings not compatible with bvFTD. The presence of white matter hyperintensities at MRI was not an exclusion criteria if the Wahlund score (Wahlund et al., 2001) was lower than 2 in each site.

Patients were then divided into three groups based on age at symptoms onset, namely early onset-bvFTD (EO-bvFTD, age <70), late onset-bvFTD (LO-bvFTD, age range 70–75) and very late onset-bvFTD (vLO-bvFTD, age >75). These cut-offs were chosen given the need of having comparable groups in terms of sample size. Age at onset was deduced by clinical record, medical history, and confirmed by caregivers. Within these three groups, patients still in the prodromal phase of the disease (Barker et al., 2022) were identified and divided as follows: prodromal EO-bvFTD, prodromal LO-bvFTD and prodromal vLO-bvFTD. We also identified the subgroup of bvFTD patients who excluded AD with high likelihood (so performing CSF or amyloid PET, without evidence of cerebral amyloidosis).

For comparison, we selected 42 healthy controls (HC) who performed [^{18}F]FDG-PET scan during previous research (Orso et al., 2022). Their healthy condition was based on clinical history and examination, with MMSE score >27, CDR = 0, and a normal [^{18}F]FDG-PET scan according to visual assessment by an expert nuclear medicine physician (SM).

2.2. Standard protocol approval

All patients provided written informed consent before the enrolment in this study, in compliance with the Helsinki Declaration of 1975. The protocol was approved by the local Institutional Review Board (IRB). No part of the study analysis was pre-registered prior to the research being conducted.

2.3. Neuropsychological and behavioural assessment

A full neuropsychological (NPS) assessment within six months from the [^{18}F]FDG-PET scan was performed. The NPS aimed to evaluate the five main cognitive domains through the use of specific tests (i.e., Language: semantic verbal fluency and phonemic verbal fluency; Executive Functions: Trail Making Test A and B; Visuospatial Abilities: clock drawing test, constructional apraxia, simple copy and copy with guiding landmarks; Memory: Rey Auditory Verbal Learning Test–immediate and delayed recall- and Babcock story; Attention and Working Memory: Stroop colour word and Symbol digit, Corsi span, Digit span and Symbol digit) as previously described (Mattioli et al., 2021).

To assess behavioural and psychiatric disturbances overall, patients undertook the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). Specific items of the NPI were singularly explored in order to investigate the core behavioural features of bvFTD (Barker et al., 2022) (i.e., apathy, disinhibition, irritability, aberrant motor behaviour and appetite/hyperorality alterations). These selected items were then grouped into a composite behavioural score (NPI-FTD).

2.4. [^{18}F]FDG-PET acquisition

Brain [^{18}F]FDG-PET scans were acquired according to the guidelines of the European Association of Nuclear Medicine that were in effect at the time (Guedj et al., 2022; Varrone et al., 2009). A SIEMENS Biograph 16 PET/CT hybrid system with a total axial field of view of 15 cm and no interplane gap space was used. To obtain blood glucose level lower than 7.8 mmol/L, patients had to fast for at least 6 h before the exam. Once blood glucose level was verified, after a 10-min rest in a silent and obscured room, with closed eyes and unplugged ears, 185–250 MBq of [^{18}F]FDG were injected via a venous cannula. Following injection, patients remained in the same room for 30 min before the image acquisition began, which started approximately 45 min later (±5 min). A low dose computed tomography transmission scan was performed for attenuation correction. Data were reconstructed using an ordered subset-expectation maximization (OSEM) algorithm, 16 subsets and 6 iterations, with a reconstructed voxel size of $1.33 \times 1.33 \times 2.00$ mm.

All [^{18}F]FDG-PET images were acquired in static mode and then subjected to affine and nonlinear spatial normalization into Montreal Neurological Institute (MNI) brain space using SPM12 (Wellcome Department of Cognitive Neurology,

London, UK). All the default settings of SPM were used and the specific [^{18}F]FDG-PET brain template was used as reference (Della Rosa et al., 2014). The spatially normalized set of images was then smoothed with a 10-mm isotropic Gaussian filter to account for individual anatomical variability and to improve the signal-to-noise ratio.

2.5. Regions of interest extraction

All ROIs were created using the WFUPickatlas toolbox in Montreal Neurological Institute (MNI) space. We selected those ROIs more typically involved in neurodegenerative disorders (Perani et al., 2020) and in bvFTD (Cerami et al., 2016), such as: anterior cingulate cortex, posterior cingulate cortex, dorsolateral prefrontal cortex, orbitofrontal cortex, angular gyrus, insula, inferior, middle and superior temporal gyrus, precuneus, parahippocampal gyrus, hippocampus, caudate, putamen, thalamus, amygdala; all the aforementioned ROIs were bilateral. ROIs values were extracted using MarsBaR toolbox implemented in SPM.

2.6. Statistical analysis

Categorical variables were compared using $\chi 2$ or Fisher's exact tests. Normal distribution of variables was checked using Shapiro–Wilk test. One-way analysis of variance (ANOVA) on the demographic, clinical and neuropsychological characteristics was then performed, followed by Tukey–Kramer post-hoc for pairwise multiple comparison. The same analyses were performed in the whole groups and in the subset of prodromal bvFTD patient. To support our results, a correlation-based approach using Pearson's correlations was used to examine the association between neuropsychological/neuropsychiatric measures and age at onset, adjusted for MMSE score and education level, both in the whole bvFTD group and in the prodromal bvFTD subgroup. For the analysis of bvFTD who excluded AD with high likelihood, a permutation test (with 10,000 samples) was performed on the Pearson's correlation, to account for the small sample size.

A voxel-wise two-sample *t*-test analysis of the [^{18}F]FDG PET scans was performed to investigate brain metabolic differences between the whole bvFTD group vs. HC using a height threshold $P < .001$ (uncorrected) at voxel level, $P < .05$ (family-wise error -FWE corrected) at cluster level, considering age, sex and education as nuisance variables. The same analysis was performed comparing the subgroups of patients divided by age-at-onset, separately, with HC, as well as in comparing male vs. female patients.

Ratios of Standard Uptake Values (SUVRs) of the previously identified ROIs were extracted from the [^{18}F]FDG PET images, to explore differences in brain metabolism of specific regions within the three separate subgroups. Raw ROIs SUVR were normalised using pons as a reference region, so to limit any age-related hypometabolic variability, as follows: (ROI-pons)/pons. A *p*-value lower than .05 was considered the threshold for significance. Subsequently, ANOVA on ROIs SUVr values of the three separate subgroups was performed, followed by Tukey–Kramer post-hoc analysis for pairwise-multiple comparison. Then Pearson's correlations was performed to examine the association between SUVr values and age at onset, adjusted for MMSE score and education level, both in HC, in the whole bvFTD group, in the prodromal bvFTD subgroup and in the subset of bvFTD who excluded AD with high likelihood (using a permutation test in this last group).

To assess the metabolic covariance between the dorsolateral (DLPFC), orbitofrontal (OFC) and medial subdivision of prefrontal cortices, we first extracted regional FDG counts, normalized on whole brain values for each subject. As a proxy measure of metabolic connectivity, we computed intracortical covariance analysis between the different aforementioned prefrontal regions, using Pearson's correlations, obtaining a score mirroring the strength of the correlation amongst regions (inter-regional covariance values). Lastly, we compared these resulting inter-regional covariance values between patients' groups and HC (Fisher-transformed correlation), to explore the differences in functional interaction between regions, using *Z*-test on the Fisher-transformed correlations.

Statistical analysis was performed using IBM SPSS Statistics 25 (Armonk, NY) and R (version 4.1.1; http://www.r-project.org/).

3. Results

Demographics and clinical characteristics are shown in Table 1. We enrolled 101 bvFTD patients, categorized as follow: definite bvFTD ($n = 5$), probable bvFTD ($n = 34$) and probable prodromal bvFTD ($n = 62$). Patients were then divided into three groups based on age at onset, namely EO-bvFTD ($n = 36$, mean age: 62.1 ± 7.4), LO-bvFTD ($n = 36$, mean age: 73.1 ± 1.5) and vLO-bvFTD ($n = 29$, mean age: 78.5 ± 1.9). To note, patients still in the prodromal phase of the disease were: prodromal EO-bvFTD ($n = 21$, mean age: 62.2 ± 8.1); prodromal LO-bvFTD ($n = 22$, mean age: 73.1 ± 1.4); prodromal vLO-bvFTD ($n = 19$, mean age: 78.1 ± 7.5). Indeed, 20 bvFTD patients (mean age at onset: 69.7 ± 7.8; 45% male; education 9.2 ± 4.4 years; MMSE 23.4 ± 4.0; 65% prodromal bvFTD) excluded AD with high likelihood. BvFTD patients were older than HC ($p = .043$), had a lower level of education ($p = .048$) and a lower MMSE ($p < .001$). Overall, 65% of patients were older than 70 years old at time of clinical onset.

The ANOVA showed that there were no differences between the three groups of bvFTD in MMSE ($p = .33$), education level ($p = .39$) and percentage of prodromal patient ($p = .16$). Also, the prodromal subset of bvFTD showed no differences between the three groups in MMSE and education level ($p = .55$ and $p = .40$, respectively).

3.1. Cognitive profiles

Of 101 bvFTD patients, 86 underwent full NPS assessment. The ANOVA run on the NPS assessment showed a significant difference in performance at verbal memory test, both immediate recall ($p = .009$) and delayed recall ($p < .001$). In detail, LO-bvFTD and vLO-bvFTD groups had a greater impairment compared to EO-bvFTD group, both in immediate recall ($p = .018$; $p = .024$, respectively) and delayed recall ($p = .001$; $p = .001$, respectively). There was no significant difference between LO-bvFTD and vLO-bvFTD in verbal memory function (immediate recall $p = .34$; delayed recall $p = .43$–Fig. 1).

Table 1 – Demographics and clinical characteristics of bvFTD patients and HC. Values are shown as mean ± sd.

	bvFTD (n = 101)	HC (n = 42)	p value	bvFTD in the three subgroups			p value*	Prodromal bvFTD in the three subgroups			p value*
				EO (n = 36)	LO (n = 36)	vLO (n = 29)		EO (n = 21)	LO (n = 22)	vLO (n = 19)	
Age at onset, y	70.8 ± 8.2	/	/	62.1 ± 7.3	73.1 ± 1.5	78.5 ± 1.9	<.001	62.2 ± 8.1	73.1 ± 1.4	78.1 ± 1.5	<.001
Age at FDG, y	72.8 ± 8.3	69.6 ± 8.5	.043	64.4 ± 7.8	75.2 ± 1.8	80.4 ± 2.1	<.001	64.1 ± 8.11	74.8 ± 1.6	79.8 ± 1.7	<.001
Disease duration from onset, y	2.08 ± 1.23	/	/	2.28 ± 1.54	2.06 ± 1.15	1.86 ± .83	.369	1.90 ± .63	1.73 ± .77	1.68 ± .82	.569
Sex (% M)	36	35	/	47	25	35	/	48	27	37	/
MMSE at FDG	24 ± 3.9	29.2 ± .8	<.001	24.4 ± 3.6	23.9 ± 4.4	23.7 ± 3.5	.332	25.6 ± 2.5	25.4 ± 3.6	24.8 ± 2.7	.55
Prodromal status, %	61	/	/	58	61	64	.156	/	/	/	/
Lost IADL	2.01 ± 2.74	/	/	2.13 ± 2.88	2.18 ± 2.69	1.64 ± 2.71	.730	.14 ± .36	.15 ± .36	.06 ± .24	.531
Education level, y	9.2	10.7	.048	9.6	8.6	9.2	.391	9.8	8.5	10.6	.40

Legend: *p value calculated by performing ANOVA test. Abbreviations: bvFTD = Frontotemporal Dementia – behavioural variant; EO = Early Onset; FDG = [^{18}F]FDG-PET; IADL = Instrumental Activities of Daily Living. HC = Healthy Controls; LO = Late Onset; M = Male; MMSE = Mini Mental State Examination; n = number; vLO = very Late Onset; y = years.

Same results of a worse performance at verbal memory tests were found in the prodromal subset of LO-bvFTD and vLO-bvFTD compared to EO-bvFTD patients, particularly in delayed recall (p = .020; p = .013, respectively). No significant difference between prodromal LO and vLO-bvFTD were observed (p = .23).

Pearson's correlation in the whole bvFTD group showed a negative correlation between age at onset and performance at verbal memory test, both immediate recall (r = −.276; p = .012) and delayed recall (r = −.424; p < .001), with the same non-significant trend for Babcock story (r = −.209; p = .065). In the subset of prodromal bvFTD, we observed the same trend between age and performance at RAVLT delayed recall (r = −.367; p = .005). In the subgroup of bvFTD who excluded AD with high likelihood, we confirmed a negative correlation between age at onset and RAVLT immediate recall (r = −.502; p = .040), RAVLT delayed recall (r = −.580; p = .014) and Babcock story (r = −.738; p < .001).

3.2. *Behavioural profiles*

The ANOVA run on the single NPI items expressing the core clinical features of bvFTD did not show significant differences amongst groups, nor did the NPI global score. On the other hand, the ANOVA on the NPI-FTD score showed a significant difference between subgroups (p = .023). In detail, a higher presence of behavioural disturbances in EO-bvFTD and LO-bvFTD compared to vLO-bvFTD (p = .005; p = .013, respectively) was observed. The same trend was found in the prodromal subset of patients, but the results did not reach statistical significance (p = .061).

Pearson's correlation showed in the whole bvFTD group a negative correlation between age at onset and NPI score for apathy (r = −.295; p = .006) and NPI-FTD score (r = −.321; p = .003). Considering only prodromal subset of bvFTD, we found a similar non-significant trend between age at onset and NPI-FTD score (r = −.217; p = .086 in unadjusted analysis; p = .144 after adjusting for MMSE and education level). In the subgroup of bvFTD who excluded AD with high likelihood, we highlighted a negative correlation between age at onset and NPI disinhibition score (r = −.590; p = .012).

3.3. *Brain metabolic profiles*

Compared to HC, bvFTD patients showed the typical anterior hypometabolic pattern involving the frontal and temporal lobes, and a relative hypermetabolism in the cerebellum (Fig. 2). When comparing males *vs.* females bvFTD patients' brain metabolic pattern, no significant clusters of difference in metabolism were displayed.

Within the three age-divided subgroups, compared to HC, voxel-wise analysis showed a partially overlapped pattern of hypometabolism in EO-bvFTD, LO-bvFTD and vLO-bvFTD. Visually, EO-bvFTD presents with a more prominent involvement of frontal and temporal lobes, while the hypometabolic clusters of LO-bvFTD and vLO-bvFTD extended more prominently to the parietal cortices (Fig. 3A, B, C).

ROIs analysis confirmed that vLO-bvFTD patients had a greater involvement of temporo-limbic structures compared to EO-bvFTD, namely hippocampus (p = .004),

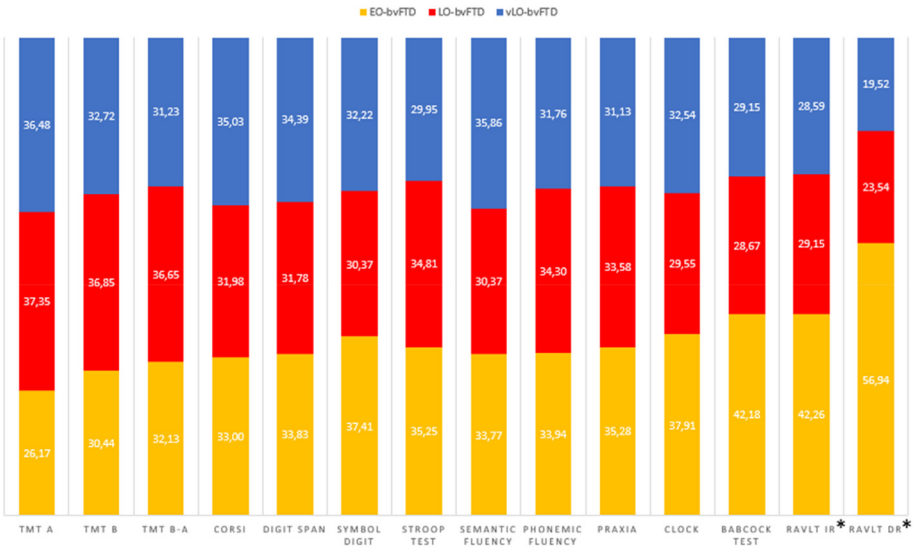

Fig. 1 – Boxplot shows the relative cognitive performance in three groups of bvFTD divided according to age at onset. Numbers within the boxes represents percentages. A higher percentage indicate a better relative cognitive performance in the test administered compared with other groups. Yellow = EO-bvFTD; Red = LO-bvFTD, Blue = vLO-bvFTD. * indicates statistical significant values. DR = Delayed Recall; EO = Early Onset; IR = Immediate Recall; LO = Late Onset; TMT = Trail Making Test; vLO = very Late Onset.

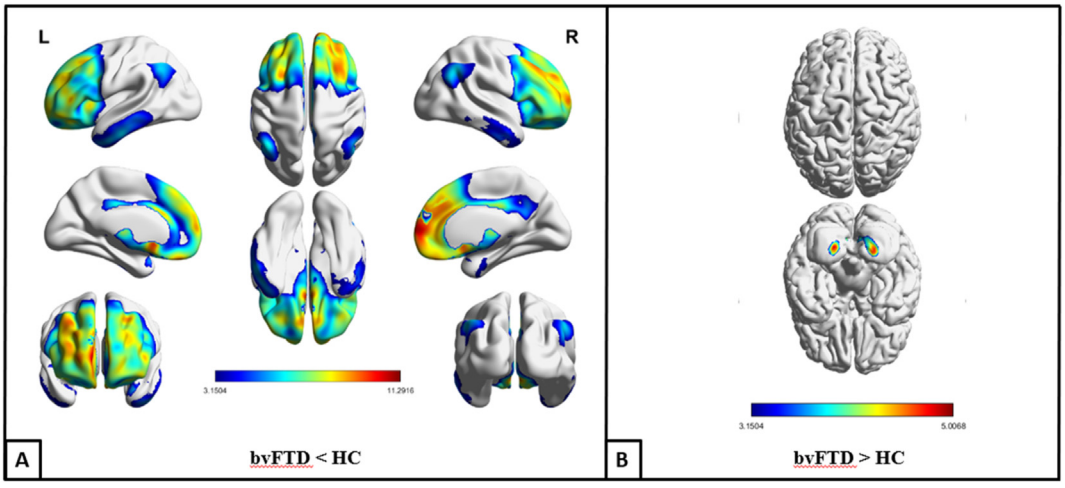

Fig. 2 – A) Pattern of relative hypometabolism in bvFTD patients compared to healthy controls. B) Pattern of relative hypermetabolism. Abbreviations: bvFTD = Frontotemporal Dementia – behavioural variant; HC = Healthy Controls; L = Left; R = Right.

parahippocampal gyrus ($p = .009$) and posterior cingulate cortex ($p = .020$). Moreover, a more prominent involvement of caudate nucleus was observed, although with a lower statistical reliability ($p = .048$). No significant differences were found between LO-bvFTD vs. EO-bvFTD patients, and LO-bvFTD vs. vLO-bvFTD.

Using Pearson's correlation between SUVr values and age at onset, in the whole bvFTD group, we observed a negative correlation between age at onset and metabolism of hippocampus ($r = -.330$; $p < .001$), parahippocampal gyrus ($r = -.312$; $p = .002$), caudate nucleus ($r = -.291$; $p = .003$), posterior cingulate cortex ($r = -.234$; $p = .020$) and amygdala ($r = -.215$; $p = .032$), with a borderline significant correlation with thalamus ($r = -.204$; $p = .051$). Considering only prodromal bvFTD subgroup, we found a significant negative correlation between age and SUVr values of caudate nucleus ($r = -.326$; $p = .011$) and borderline significant with thalamus ($r = -.237$; $p = .068$). In the subgroup of bvFTD who excluded AD with high likelihood, we confirmed a negative correlation between age at onset and posterior cingulate cortex ($r = -.730$; $p < .001$), parahippocampal gyrus ($r = -.616$; $p = .003$), hippocampus ($r = -.462$; $p = .041$), thalamus ($r = -.501$; $p = .026$), caudate nucleus ($r = -.535$; $p = .016$), but the same association emerged also with angular gyrus ($r = -.827$; $p < .001$), precuneus ($r = -.684$; $p < .001$) and the whole temporal lobe involvement ($r = -.762$; $p < .001$).

Performing the same analysis in the HC group, no significant correlation between age and SUVr values were found.

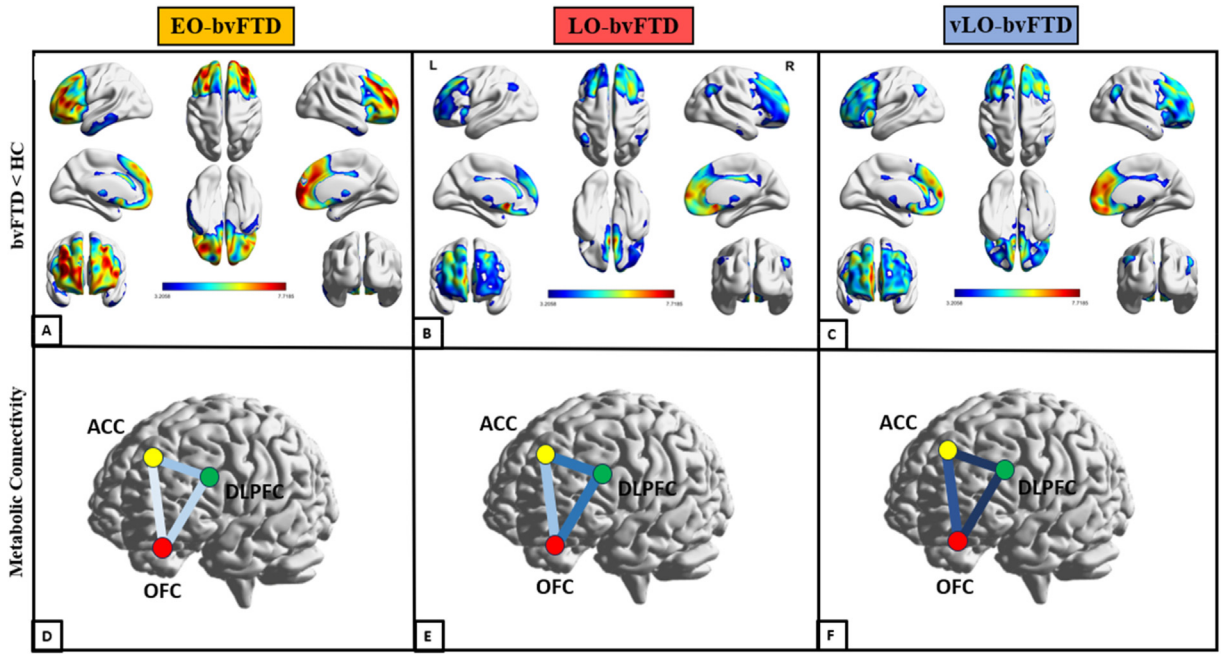

Fig. 3 – A, B, C: Pattern of hypometabolism in the three groups of bvFTD patients compared with HC. D, E, F: Graphic representation of metabolic covariance: lighter colours represent disaggregated connectivity compared to HC values. Yellow dot represents anterior cingulate cortex, as indicated. Green dot is dorsolateral prefrontal cortex; Red dot is orbitofrontal cortex. Abbreviations: ACC = anterior cingulate cortex; bvFTD = Frontotemporal Dementia – behavioural variant; DLPFC = dorsolateral prefrontal cortex; EO = Early Onset; HC = Healthy Controls; L = Left; LO = Late Onset; OFC = orbitofrontal cortex; R = Right; vLO = very Late Onset.

3.4. *Metabolic connectivity*

When comparing with HC, z-test revealed a significant difference in metabolic covariance in EO-bvFTD patients within the prefrontal regiones explored ($p = .03$), especially between the OFC and the anterior cingulate, while there was no difference in metabolic covariance in vLO-bvFTD ($p = .25$). The difference between LO-bvFTD and HC was borderline significant ($p = .05$) (Fig. 3D, E, F).

On the other hand, when comparing metabolic covariance between patients' subgroups, there was no difference between EO-bvFTD and LO-bvFTD ($p = .22$). Conversely, there was a significant difference in intrafrontal metabolic covariance between EO-bvFTD and vLO-bvFTD ($p < .001$), with the former showing a more aberrant OFC-DLPFC connectivity compared to vLO-bvFTD ($p = .006$).

4. Discussion

This retrospective, single-centre study performed on a large cohort of bvFTD patients, highlighted the heterogeneity of clinical and metabolic phenotype of this syndrome, which arises in different age at onset subgroups. Overall, the cognitive–behavioural profile varies in bvFTD across age of symptoms onset, with greater verbal memory deficit in late onset bvFTD and a more severe behavioural symptomatology in early onset bvFTD. This appears to be present from the prodromal stages of the disease. From a metabolic point of view, vLO-bvFTD had a more widespread neurodegeneration involving deep grey structures and posterior areas compared to EO-bvFTD and LO-bvFTD, while EO-bvFTD showed aberrant intrafrontal metabolic connectivity compared to both controls and vLO-bvFTD. Thus, age at symptoms onset seems to modulate the clinical heterogeneity of bvFTD patients, with EO-bvFTD presents with a more behavioural phenotype, paired with prefrontal metabolic connectivity abnormalities, while vLO-bvFTD being with a more cognitive phenotype, paired with a widespread pattern of neurodegeneration.

In line with our findings, it has been highlighted that cognitive–behavioural profile differs between EO-bvFTD and LO-bvFTD (Fieldhouse et al., 2021). Younger age-at-diagnosis was associated with more severe behavioural symptoms, while older age-at-diagnosis was associated with more severe memory impairment. Episodic memory impairment has been described as a possible manifestation of bvFTD (Hornberger & Piguet, 2012), and in some cases could be as severe as AD patients (the so called "amnestic-FTD (Bertoux et al., 2014)"). Also, it has been previously correlated with hypometabolism in the anterior parahippocampal and inferior temporal gyri (Fernández-Matarrubia et al., 2017). The preponderance of amnestic deficit in elderly subjects with bvFTD was formerly associated neuropathologically with hippocampal sclerosis (Baborie et al., 2011, 2012). This is in agreement with our results, in which late onset bvFTD seems to be more significantly

impaired in delayed recall. The presence of memory impairment, particularly in the older subset of patients, could be misleading if it is considered as an exclusion criterion for diagnosis.

In recent years, the focus has shifted considerably towards prodromal and preclinical forms of FTD (Benussi et al., 2022), as in other neurodegenerative disorders. The high prevalence of prodromal forms of bvFTD in our sample allowed us to explore the entire spectrum of the disease continuum, not limiting the age-specific peculiarities to the overt stage of the disease. A similar result of cognitive–behavioural profile emerged in the prodromal subset of patients, highlighting that the observed peculiarities could be present from the early clinical stages of the disease.

In the bvFTD population, there are some differences in metabolic pattern according to age-at-onset, with a greater involvement of temporo-limbic structures (hippocampus, parahippocampal gyri), parietal cortex (posterior cingulate cortex and angular gyrus) and subcortical structures (caudate nuclei and thalamus) in late onset bvFTD. Indeed, different anatomical subtypes can be recognized in bvFTD patients (Ranasinghe et al., 2016, 2021) and, in particular, Cerami et al. (2016) described two distinct [^{18}F]FDG-PET patterns subtypes: a frontal pattern and a temporo-limbic pattern; the latter was most frequently observed in patients with a long disease duration and an older age. We could speculate that anatomical spreading of neurodegeneration is differently distributed according to age at onset, with a preponderance of the temporo-limbic and posterior involvement in elderly patients. Moreover, posterior cingulate cortex is an important hub of default mode network, and it is profoundly linked with the medial temporal lobe. Hypometabolism of this region was previously described as not restricted to AD, but also to more advanced and amnestic forms of bvFTD (Scheltens et al., 2018), probably mediated by age at onset, according to our results.

It has been described that alteration in subcortical structure and cerebellum have a contribution to clinical manifestations of FTD (Bussy et al., 2023; Chen et al., 2019, 2020; McKenna et al., 2021). In [^{18}F]FDG-PET studies, it has been shown that there is a relative hypermetabolism in the brainstem and cerebellum of bvFTD patients compared with healthy controls (Rajagopalan & Pioro, 2023; van Engelen et al., 2023), as confirmed in our cohort. It is possible that hypermetabolism in these regions might represent a compensatory mechanism in response of brain dysfunction, or to an early phase of neurodegeneration, with prominent neuroinflammation and microglial proliferation (van Engelen et al., 2023).

Caudate nucleus and deep grey matter (such as thalamus) are considered one of the main foci of neurodegeneration in ALS-FTD continuum (Machts et al., 2015; Masuda et al., 2016; Sobue et al., 2018), and it has been shown in previous studies that atrophy of the caudate nuclei can discriminate FTD from AD and HC (Möller et al., 2015). Our results seem to support the idea that, in the older bvFTD patients, there is a greater functional damage of the deep grey matter structure, which could be related to poorer performance in the immediate recall of the Rey Auditory Verbal Learning Test, as demonstrated in other diseases (Yoo et al., 2022).

Another explanation that can be invoked to explain the different metabolic involvement according to age is the co-presence of underlying multiple proteinopathies, or comorbid disorders (such as small vessel disease), usually seen in late onset forms (Seo et al., 2018). It must be pointed out that our focus was on the phenotypic presentation of bvFTD, irrespective of the possible underlying misfolded protein presence, also taking into account the retrospective nature of this clinical dataset. Nevertheless, correlations-based analysis performed in the subset of bvFTD who excluded AD with high likelihood showed similar results, ruling out a major influence of AD pathology in our findings.

Previous studies investigated resting state metabolic connectivity in neurodegenerative conditions (such as AD (Morbelli et al., 2012) and FTD (Boccalini et al., 2022; Liu et al., 2023)), focusing in some works on different age at onset (Chung et al., 2016). Indeed, changes in intraregional connectivity have been shown to represent an early marker of neurodegeneration both using resting state fMRI and metabolic data. The EO-bvFTD population presented an aberrant intrafrontal connectivity compared to controls and vLO-bvFTD, while there was no significant difference in the frontal regional FDG values between groups. This observation suggests a possible anatomical correlation for the increased behavioural burden observed in EO-bvFTD compared to vLO-vbFTD and points to the relevance of regional network properties assessments to study the phenotypic heterogeneity of subjects with neurodegenerative conditions, such as FTD.

Some limitations need to be acknowledged. Deficit in social cognition is an hallmark of bvFTD (Dilcher et al., 2023) and it is not assessed in this cohort. Therefore, further studies will be needed in the future to evaluate its relationship with age in bvFTD. A high mean age at onset (notably 65.1% of patients exceeded 70 years of age at onset) was observed in our cohort, although in line with epidemiological data (Logroscino et al., 2019, 2023). This could have been influenced by two factors. The specific demographic traits of the Ligurian region affected the high prevalence of relatively older FTD patients. This was an opportunity for the sake for present aims, but it also influenced the prevalence of late-onset forms. Second, it is likely that patients with early onset forms are more frequently identified in psychiatric outpatient clinics and currently are not included in our cohort. Although, considering only chronological age could profoundly limits our findings. It would be interesting instead to categorize patients based on biological age parameters, independently of demographic age, and to understand whether this intrinsically influence disease phenotype. In addition, the higher prevalence of prodromal bvFTD may have blunted some of the differences between the groups, in particular regarding metabolic pattern. It is known from neuropathological studies that bvFTD is more commonly associated with tau or TDP-43 pathology (Perry et al., 2017), but in absence of pathological confirmations, it is not possible to speculate on any link to underlying aetiology. It must be noted, however, that the focus of the study was not on a specific pathological underpinning of FTD, but on the syndromic presentation of bvFTD, associated with a neurodegeneration pattern suggestive for this condition. Future studies are

warranted regarding the replication of these findings in an independent cohort or unravel similar age-related differences in other FTLD-spectrum syndromes (such as PPA).

5. Conclusion

In conclusion, our study shows that, in presence of the same overall clinical severity, late-onset bvFTD presents with a more widespread hypometabolism and wider involvement of cognitive domains, whereas early onset forms have a more pronounced syndrome-specific behavioural disorders. Exploring heterogeneity in bvFTD has direct implications in clinical trials, as late-onset patients may be wrongly excluded, given the less suggestive clinical features and lower sensitivity of current diagnostic criteria. This study places emphasis on the fact that considering bvFTD as a purely early-onset disorders is somehow limiting. Summing up, metabolic and clinical phenotype differ in bvFTD depending on the age at onset. Understanding these differences may contribute to improved diagnosis and treatment strategies, particularly in late-onset cases with overlapping features of Alzheimer's Disease.

CRediT authorship contribution statement

Mattia Losa: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Sara Garbarino:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Alessio Cirone:** Writing – review & editing, Methodology, Formal analysis. **Lucia Argenti:** Writing – review & editing. **Lorenzo Lombardo:** Writing – review & editing. **Francesco Calizzano:** Writing – review & editing. **Nicola Girtler:** Writing – review & editing, Data curation. **Andrea Brugnolo:** Writing – review & editing, Data curation. **Pietro Mattioli:** Writing – review & editing. **Matteo Bauckneht:** Writing – review & editing. **Stefano Raffa:** Writing – review & editing. **Gianmario Sambuceti:** Writing – review & editing. **Antonio Canosa:** Writing – review & editing. **Stefano Caneva:** Writing – review & editing. **Michele Piana:** Writing – review & editing. **Giulia Bozzo:** Writing – review & editing. **Luca Roccatagliata:** Writing – review & editing. **Gianluca Serafini:** Writing – review & editing. **Antonio Uccelli:** Writing – review & editing. **Fabio Gotta:** Writing – review & editing. **Paola Origone:** Writing – review & editing. **Paola Mandich:** Writing – review & editing. **Federico Massa:** Writing – review & editing. **Silvia Morbelli:** Writing – review & editing. **Dario Arnaldi:** Writing – review & editing. **Beatrice Orso:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Matteo Pardini:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Financial disclosure

BO: received research support from G.E. Healthcare. FM: received speaker and consultant honoraria from Roche Diagnostics and Eli Lilly S. p.A. MP: received research support from Novartis and Nutricia, received fees from Novartis, Merck and Biogen.

Fundings

The study was supported by the European Union—Next Generation EU—NRRP M6C2—Investment 2.1 Enhancement and strengthening of biomedical research in the NHS, by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022) [to MP and CL].

Declaration of competing interest

None.

Acknowledgment

This work was developed within the framework of the DINOGMI Department of Excellence of MIUR 2018–2022 (law 232–2016). SM was supported by RF-2018-12366238—In vivo assessment of demyelination and remyelination in patients with Multiple Sclerosis: computational approach to brain and spinal cord amyloid PET.

Scientific transparency statement

DATA: No raw or processed data supporting this research are publicly available.
CODE: All analysis code supporting this research is publicly available: https://github.com/sgarbarino/stats_bvFTD-cortex.
MATERIALS: No study materials supporting this research are publicly available.
DESIGN: This article reports, for all studies, how the author(s) determined all sample sizes, all data exclusions, all data inclusion and exclusion criteria, and whether inclusion and exclusion criteria were established prior to data analysis.
PRE-REGISTRATION: No part of the study procedures was pre-registered in a time-stamped, institutional registry prior to the research being conducted. No part of the analysis plans was pre-registered in a time-stamped, institutional registry prior to the research being conducted.
For full details, see the *Scientific Transparency Report* in the supplementary data to the online version of this article.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2025.01.011.

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