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# Radiomics feature similarity: A novel approach for characterizing brain network changes in patients with behavioral variant frontotemporal dementia

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ABSTRACT

*Introduction:* Network modeling is increasingly used to study brain alterations in neurological disorders. In this study, we apply a novel modeling approach based on the similarity of regional radiomics feature to characterize gray matter network changes in patients with behavioral variant frontotemporal dementia (bvFTD) using MRI data.

*Methods:* In this cross-sectional study, we assessed structural 3 T MRI data from twenty patients with bvFTD and 20 cognitively normal controls. Radiomics features were extracted from T1-weighted MRI based on cortical and subcortical brain segmentation. Similarity in radiomics features between brain regions was used to construct intra-individual structural gray matter networks. Regional mean connectivity strength (RMCS) and region-to-region radiomics similarity were compared between bvFTD patients and controls. Finally, associations between network measures, clinical data, and biological features were explored in bvFTD patients.

*Results:* Relative to controls, patients with bvFTD showed higher RMCS values in the superior frontal gyrus, right inferior temporal gyrus and right inferior parietal gyrus (FDR-corrected $p < 0.05$). Patients with bvFTD also showed several edges of increased radiomics similarity in key components of the frontal, temporal, parietal and thalamic pathways compared to controls (FDR-corrected $p < 0.05$). Network measures in frontotemporal circuits were associated with Mini-Mental State Examination scores and cerebrospinal fluid total-tau protein levels (Spearman $r > |0.7|$, $p < 0.005$).

*Conclusions:* Our study provides new insights into frontotemporal network changes associated with bvFTD, highlighting specific associations between network measures and clinical/biological features. Radiomics feature similarity analysis could represent a useful approach for characterizing brain changes in patients with frontotemporal dementia.

## 1. Introduction

Behavioral variant frontotemporal dementia (bvFTD) is the most common clinical subtype of frontotemporal dementia (FTD) affecting more than half of the patients with autopsy-confirmed FTD (Snowden et al., 2011). bvFTD is characterized by a progressive decline in social function and personality (Rascovsky et al., 2011) and is associated with specific morphometric changes involving cortical and subcortical brain areas, particularly the prefrontal cortex, anterior cingulate, temporal regions, striatum, and thalamus (Rosen et al., 2002; Boccardi et al.,

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2005; Whitwell et al., 2009; Filardi et al., 2024). Despite these typical patterns of brain atrophy and the peculiar clinical presentation, diagnosis of bvFTD remains challenging due to the high degree of overlap in clinical features with other neurological and/or psychiatric disorders (Bang et al., 2015). Therefore, over the past years several imaging metrics have been proposed as potential biomarkers for bvFTD, particularly in the early stages of the disease (Meeter et al., 2017; Chen and Kantarci, 2020; Nigro et al., 2022a; Rowe, 2022).

In the field of neurodegenerative diseases, network analysis has emerged as a promising analytical approach to depict the intricate wiring and functions of the brain thus providing a novel framework to understand the pathophysiology of these diseases (Bassett and Bullmore, 2009; Stam, 2014). Alterations in both functional and white matter brain networks have been documented in several neurodegenerative diseases and have been associated with the severity of clinical and cognitive symptoms (Pievani et al., 2014; Iturria-Medina and Evans, 2015; Nigro et al., 2015, 2016; Filippi et al., 2023). More recently, covariation in gray matter brain morphology has also been used to characterize structural connectivity alterations between brain regions in neurodevelopmental and neurodegenerative disorders (Li et al., 2017; Wagner et al., 2020; Yun et al., 2020; Chen et al., 2022; Nigro et al., 2022b). This approach relies on the assumption that morphological properties of interconnected brain regions covary due to shared developmental and maturational influences (Alexander-Bloch et al., 2013). Nonetheless, only a limited number of studies have examined gray matter covariance in patients with bvFTD (Hafkemeijer et al., 2016; Vijverberg et al., 2017; Nigro et al., 2021). The few available studies have considered different brain morphological features such as volume, cortical thickness, and gray matter density, documenting decreased network integrity in bvFTD patients compared to controls, particularly in regions such as the insular cortex, anterior cingulate and frontal cortex (Hafkemeijer et al., 2016; Vijverberg et al., 2017; Nigro et al., 2021).

In recent years, radiomic analysis has been proposed as a novel approach for assessing structural brain changes in different clinical populations (van Timmeren et al., 2020; Salvatore et al., 2021). Through the mathematical analysis of spatial signal distributions and pixel interrelationships, radiomics extracts quantitative textural information from various imaging modalities, providing insights into disease-specific processes (Mayerhoefer et al., 2020). Radiomics analysis has demonstrated the ability to capture novel gray matter properties by quantifying textural, shape and intensity pattern features. This information has proven effective in characterizing patients with neurodegenerative conditions, thereby supporting clinicians in the diagnostic work-up (Li et al., 2020; Tafuri B. et al., 2022a, b; Gore et al., 2023; Tafuri et al., 2024). Moreover, recent studies have investigated the potential application of radiomics features in defining gray matter networks (Zhao et al., 2021, 2022; Yu et al., 2023). Specifically, texture and intensity features from brain regions have been used to define single-subject regional radiomics similarity networks (Zhao et al., 2021). This novel approach has proven capable of quantifying subtle brain changes using structural MR images, thus representing a robust and reliable method for investigating brain changes associated with cognitive impairments and gene expression (Zhao et al., 2022; Yu et al., 2023). Moreover, alterations in radiomics feature similarity were more suitable for examining mild cognitive impairment subtypes than gray matter volume, allowing for better characterization of clinical subgroups using structural MRI data (Zhao et al., 2022).

In the present study, we explored the usefulness of regional radiomics features to define gray matter networks with the aim of characterizing structural connectivity alterations in patients with bvFTD. We hypothesized that individuals with bvFTD may exhibit changes in brain regions within the frontal and temporal circuits, which have been previously documented in bvFTD patients using functional and structural MRI (Meeter et al., 2017; Whitwell, 2019). To test this hypothesis, we first used regional radiomics feature similarity to construct intra-individual structural gray matter networks (Zhao et al., 2021). Next, we examined differences in regional mean connectivity strength (RMCS) between bvFTD patients and cognitively normal controls and compared region-to-region radiomics feature similarity between groups using network-based statistics. Finally, we investigated the association between network-based connectivity measures and clinical and biological features in patients with bvFTD.

## 2. Materials and methods

### 2.1. Participants

We enrolled twenty consecutive patients with bvFTD (mean age 65.95 ± 9.64 y) referred to the Center for Neurodegenerative Diseases and the Aging Brain of the University of Bari Aldo Moro in Tricase. All participants underwent a standardized diagnostic protocol which included: (1) neurological examination; (2) comprehensive neuropsychological assessment encompassing the main cognitive domains of attention, memory, executive functions, visuospatial abilities, and language; (3) brain MRI; and (4) lumbar puncture for CSF biomarker of neurodegeneration assay. More in detail, attention was assessed using the Digit Span Forward and Trail Making Test A, memory was evaluated with the Rey Auditory Verbal Learning Test (Immediate and Delayed Recall), executive functions were assessed with the Digit Span Backward and verbal fluency tests, visuospatial abilities were measured using the Clock Drawing Test and Figure Copy test, and language was evaluated through the Boston Naming Test. CSF $A\beta_{42}$, total tau, and phosphorylated tau levels were measured by chemiluminescent immunoassay (CLEIA) (Lumipulse G ß-amyloid 1–42, Lumipulse G Total Tau, Lumipulse G pTau181, Fujirebio Europe N.V., Gent, Belgium) on a fully automatic platform (Lumipulse G600II, Fujirebio Europe N.V., Gent, Belgium). Finally, the Goldman score was used to assess the likelihood of a genetic condition based on family history, with scores ranging from 1 (high likelihood of a genetic cause) to 4 (lower likelihood of a genetic cause) (Goldman et al., 2005; Beck et al., 2008). All patients fulfilled the current diagnostic criteria for probable bvFTD (Rascovsky et al., 2011). Exclusion criteria included comorbid neurological or psychiatric disease, drug abuse, clinical or neuroimaging evidence of focal lesions and/or inflammatory, infectious or vascular diseases. The control group consisted of twenty cognitively normal individuals (mean age 63.65 ± 4.49 y), showing no objective neuropsychological deficits and having unremarkable clinical, neuroimaging, and fluid biomarker examinations. The experimental protocol was approved by the ethics committee of ASL Lecce (verbale n°6, July 25th, 2017) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

### 2.2. MRI acquisition and processing

Cross-sectional structural MR images were acquired on a 3 T scanner (Philips Ingenia 3 T) using a three-dimensional T1-weighted sequence (repetition time = 8.2 ms, echo time = 3.8 ms, field of view = 256 × 256 $mm^2$, flip angle = 8°, isotropic 1 $mm^3$ voxels). T1-weighted images were inspected visually for scanner and motion artifacts and then processed through FreeSurfer (v. 7.0, https://surfer.nmr.mgh.harvard.edu/) to perform motion correction, intensity normalization, bias field correction, skull stripping and segmentation of cortical gray matter regions. Next, the non-uniform intensity corrected image (nu.mgz) and individual cortical segmentations based on the Desikan–Killiany Atlas were used to extract radiomics features on 68 cortical regions from both hemispheres (Desikan et al., 2006) (Fig. 1). Subcortical segmentation was also performed using an automated approach that estimates the probability of structure classification based on manually labeled templates (Fischl et al., 2002). We considered 12 subcortical areas, including the putamen, caudate, thalamus, pallidum, hippocampus, and amygdala for each hemisphere. For each brain region, 88 radiomics

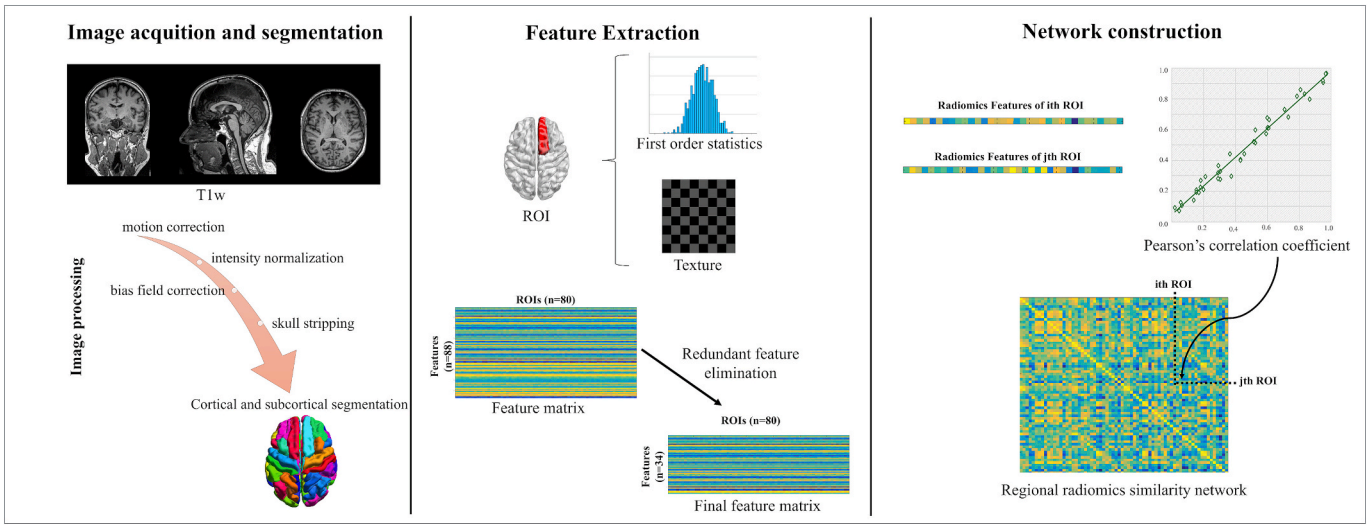


**Fig. 1.** Schematic illustration of the pipeline for constructing gray matter network. (Left panel) Preprocessing of the MR images and segmentation of brain regions based on the Desikan–Killiany Atlas. (Central panel) For each subject, radiomics features are extracted from each brain region and a feature matrix is created by removing redundant features. (Right panel) Construction of the regional radiomics similarity network.

features were extracted using Pyradiomics (van Griethuysen et al., 2017). First and second order textural measures that reflect the spatial distribution of voxels were computed using the gray level co-occurrence matrix (GLCM), gray level run length matrix (GLRLM), gray level dependence matrix (GLDM) and gray level size zone matrix (GLSZM). Detailed descriptions of the radiomics features are provided in Supplementary Materials (Table S1).

### 2.3. Network construction

A min–max approach was used to normalize the radiomics features across different brain regions at a single-subject level (Zhao et al., 2022; Yu et al., 2023). Redundant features were defined as features that showed a correlation coefficient exceeding 0.90 with other features (Zhao et al., 2021; Yu et al., 2023). Next, a final feature matrix (80 regions x 34 features) was obtained for each subject and used to define the regional radiomics similarity network (R2SN) (Fig. 1). In particular, network edges were defined by Pearson's correlation coefficient between interregional radiomics features (Zhao et al., 2022).

### 2.4. Statistical analysis

Data were explored using descriptive statistics (mean ± SD, or frequency). Differences between bvFTD patients and controls in demographic, clinical, biological data and network measures were analyzed through Fisher's exact test, Mann–Whitney *U* test or two-tailed independent samples *t*-test. Selection of the appropriate statistical test for each variable was determined by assessing normal distribution with the Shapiro–Wilk normality test. Group differences in network measures were examined considering age, sex and total intracranial volume as nuisance variables. False discovery rate (FDR) was used to correct for multiple comparisons (Benjamini and Hochberg, 1995), with FDR-corrected p-values $< 0.05$ considered statistically significant. The relationships between network metrics and clinical data (disease duration, FAB and MMSE scores) in bvFTD patients were investigated using Spearman correlation analysis corrected for age, sex, and education, while the association between CSF total-tau (t-tau) and network measures were assessed using Spearman correlation analysis corrected for age, sex, education, and disease duration. In order to mitigate the risk of detecting spurious correlations we considered only moderate to strong correlations (Spearman $r > |0.7|$) (Schober et al., 2018). Statistical analyses were performed using MATLAB R2021a version 9.10.0 (MathWorks). The brain figures were visualized using the BrainNet Viewer (https://www.nitrc.org/projects/bnv/)(Xia et al., 2013). Additionally, we conducted a voxel-based morphometry (VBM) analysis using SPM12 (fil.ion.ucl.ac.uk/spm/) and the CAT12 Toolkit (https://www.neuro.uni-jena.de/cat/). Group differences were assessed using a voxel-wise two-sample *t*-test, with total intracranial volume, age, and sex included as nuisance variables. Whole-brain statistical analyses were performed using the threshold-free cluster enhancement toolbox (dbm.neuro.uni-jena.de), a nonparametric permutation-based approach involving 5000 permutations and applying a family-wise error rate-corrected statistical threshold of $p < 0.005$. Detailed information on image processing is reported in the Supplementary Materials.

## 3. Results

### 3.1. Demographic and clinical characteristics

Demographic, clinical, cognitive, biochemical data and the Goldman score of patients with bvFTD and controls are reported in Table 1. There were no differences in age, sex, and years of education between bvFTD patients and controls (all $p > 0.05$). Patients with bvFTD had significantly lower MMSE and FAB scores ($p < 0.001$) (Table 1), as well as lower cognitive domain scores compared to controls ($p < 0.01$). All patients with bvFTD and controls were classified as amyloid-negative based on the CSF $A\beta_{42}$ cut-off value $> 599$ pg/ml as provided by the kit manufacturer.

### 3.2. Voxel-based morphometry

Compared to controls, patients with bvFTD showed significantly lower gray matter density in the bilateral superior and middle frontal gyrus, insula, temporal pole, precentral gyrus, superior and middle temporal gyrus, fusiform, hippocampus, thalamus, putamen and angular gyrus (Fig. 2). No further statistically significant group differences were observed.

### 3.3. Differences in network metrics between bvFTD and controls

Patients with bvFTD showed higher RMCS values in the right superior frontal gyrus, right inferior temporal gyrus and right inferior parietal gyrus compared to controls (FDR-corrected p-value $< 0.05$) (Fig. 3, Table 2). Network analysis also identified several edges of increased

**Table 1**
Demographic, clinical, cognitive and biochemical data in controls and patients with bvFTD.

| | Controls ($n = 20$) Mean ± SD | bvFTD ($n = 20$) Mean ± SD | *t* or z | *p*-value |
|---|---|---|---|---|
| ***Demographic and clinical data*** | | | | |
| Age (years) | 63.65 ± 4.49 | 65.95 ± 9.64 | 0.81 | 0.41 |
| Sex (males/females) | 6/14 | 13/7 | 3.60 | 0.06 |
| Education (years) | 10.50 ± 4.88 | 11.15 ± 5.38 | 0.23 | 0.81 |
| MMSE | 27.55 ± 2.78 | 22.75 ± 5.81 | 3.55 | < 0.001 |
| FAB | 15.65 ± 2.01 | 11.30 ± 3.29 | 3.90 | < 0.001 |
| Duration (years) | – | 4.45 ± 4.81 | – | – |
| ***Main cognitive domains**** | | | | |
| Attention (z-score) | −0.03 ± 0.59 | −1.09 ± 1.41 | 4.35 | < 0.001 |
| Memory (z-score) | −0.44 ± 0.45 | −1.64 ± 0.99 | 4.00 | < 0.001 |
| Executive functions (z-score) | 0.11 ± 0.39 | −1.35 ± 0.96 | 5.33 | < 0.001 |
| Visuospatial abilities (z-score) | 0.30 ± 0.45 | −1.42 ± 1.54 | 2.49 | 0.01 |
| Language (z-score) | −0.01 ± 0.50 | −1.26 ± 1.13 | 4.31 | < 0.001 |
| ***Modified Goldman score***[b] | | | | |
| 1 | – | 15 % | – | – |
| 2 | – | 0 % | – | – |
| 3 | – | 5 % | – | – |
| 3.5 | – | 25 % | – | – |
| 4 | – | 55 % | – | – |
| ***Cerebrospinal fluid biomarkers*** | | | | |
| Amyloid-β ($A\beta_{42}$; pg/ml) | 1022.71 ± 118.21[a] | 985.50 ± 340.21 | 1.07 | 0.28 |
| Total tau (t-tau; pg/ml) | 230.57 ± 144.46[a] | 384.65 ± 152.78 | −2.29 | < 0.05 |
| Phosphorylated tau (p-tau; pg/ml) | 34.31 ± 10.27[a] | 41.56 ± 17.48 | 1.02 | 0.32 |

*Z-scores of cognitive domains based on normative data.

[a] Cerebrospinal fluid biomarker was performed in 7 out of 20 healthy controls, as the remaining participants declined to undergo lumbar puncture.

[b] 1 is an autosomal dominant family history of FTLD, MND,CBS, or PSP, defined as the presence of at least 3 affected people in 2 generations with 1 person being a first-degree relative of the other 2; 2 is familial aggregation of 3 of more family members with dementia but not meeting criteria for 1; 3 is 1 other affected family member with dementia (modified to give a score of 3 only if there is a history of young-onset dementia within the family, i.e., less than 65, and 3.5 if onset above 65), and 4 is no or unknown family history.

similarity in bvFTD patients compared to controls (FDR-corrected p-value $< 0.05$) (Fig. 3), primarily involving key components of the frontal, temporal and parietal pathways (Table 2). No significant decrease in RMCS values or edge similarity was observed in bvFTD patients compared to controls.

### 3.4. Association between network measures and clinical/biological data in bvFTD patients

Moderate-to-strong negative correlations emerged between MMSE scores and RMCS values in the left caudal middle frontal gyrus, right middle temporal gyrus, left pars opercularis, right isthmus of the cingulate gyrus and right banks of the superior temporal sulcus (Spearman $r > |0.7|$, p-values $< 0.002$) (Fig. 4). Negative associations were also found between edge weights and MMSE scores. No moderate-to-strong associations were observed between network measures and FAB scores. Positive correlations were observed between connectivity values and CSF total-tau in the frontal, temporal and occipital circuits (Spearman $r > |0.7|$, p-values $< 0.002$).

## 4. Discussion

In the present study we examined, for the first time, radiomics-based structural connectivity in patients with bvFTD. When compared with controls, bvFTD patients showed altered mean connectivity strength in several frontal, temporal, and parietal regions, including the superior frontal cortex, inferior temporal gyrus, and parietal cortex. Moreover, network analyses revealed an increased radiomics feature similarity in specific pathways involving frontal, temporal and thalamic regions. Noteworthy, network metrics were also associated with CSF neurodegeneration biomarkers and overall cognitive functioning in patients with bvFTD. Specifically, MMSE scores and CSF-total tau values correlated with connectivity values in network edges distributed within and among the frontal-temporal-parietal brain networks.

Overall, our findings provide consistent evidence that radiomics-based network connectivity measures could serve as a novel approach for characterizing brain structural changes in bvFTD patients. In recent years, several studies have investigated the usefulness of radiomic features in defining gray matter networks in neurogenerative diseases (Zhao et al., 2021, 2022; Yu et al., 2023). In particular, higher RMCS values in the temporal lobe, posterior cingulate, and hippocampus were observed in patients with Alzheimer's disease (AD) compared to controls (Yu et al., 2023). Additionally, increased RMCS values in the temporal, occipital, and frontal lobes were found in MCI patients relative to controls (Yu et al., 2023). Moreover, RMCS values in the amygdala, hippocampus, and cingulate gyrus were negatively associated with overall cognitive functioning (as assessed by the MMSE) and verbal learning performance (Yu et al., 2023). Significant correlations between R2SN connections and fluid intelligence were also found in healthy subjects from the Human Connectiome Project (HCP, https://www.humanconnectome.org/study/hcp-young-adult/document/) (Zhao et al., 2021). Similarly, we found that patients with bvFTD were characterized by an increased RMCS in the right superior frontal gyrus, right inferior temporal gyrus, bilateral inferior parietal gyrus and left parahippocampal gyrus. At the same time, RMCS values in the left caudal middle frontal gyrus, right rostral middle frontal gyrus, left pars opercularis, and right precuneus were negatively associated with MMSE scores. Patients with bvFTD also exhibited increased connectivity between frontal and temporal cortical brain regions. Alterations in network properties of frontotemporal regions have been previously reported in functional and structural networks of patients with bvFTD compared to controls (Filippi et al., 2017; Vijverberg et al., 2017; Nigro et al., 2021; Liu et al., 2023). Specifically, network analysis showed that patients with bvFTD are characterized by a focal pattern of functional connectivity alterations, including frontotemporal pathways and connections to the motor cortex and basal ganglia, relative to controls (Filippi et al., 2017). Aberrant metabolic connectivity within the limbic cortico-striato-thalamic-cortical circuit has also been described in symptomatic and presymptomatic patients with bvFTD (Liu et al., 2023). Regarding gray matter networks, lower connectivity density was also reported in bvFTD patients compared to controls (Vijverberg et al., 2017). Moreover, decreased network integrity involving the anterior cingulate cortex, insular cortex, paracingulate gyrus, and frontal medial cortex was reported in patients with bvFTD relative to controls (Hafkemeijer et al., 2016; Nigro et al., 2021). Notably, we found that frontotemporal regions had significantly higher RMCS and connectivity values in bvFTD patients compared to controls. One possible explanation for the increased network connectivity in these areas may be related to the coordinated process of gray matter changes underlying bvFTD pathology, which may lead to increased similarity in radiomic features. This hypothesis is supported by correlation analyses between connectivity measures and cognitive performance, which revealed a negative association between MMSE scores and RMCS values. Additionally, we found positive associations between connectivity values and CSF total-tau protein levels.

Several studies have reported associations between MMSE scores and occipital, parietal, and frontal gray matter structural changes in patients

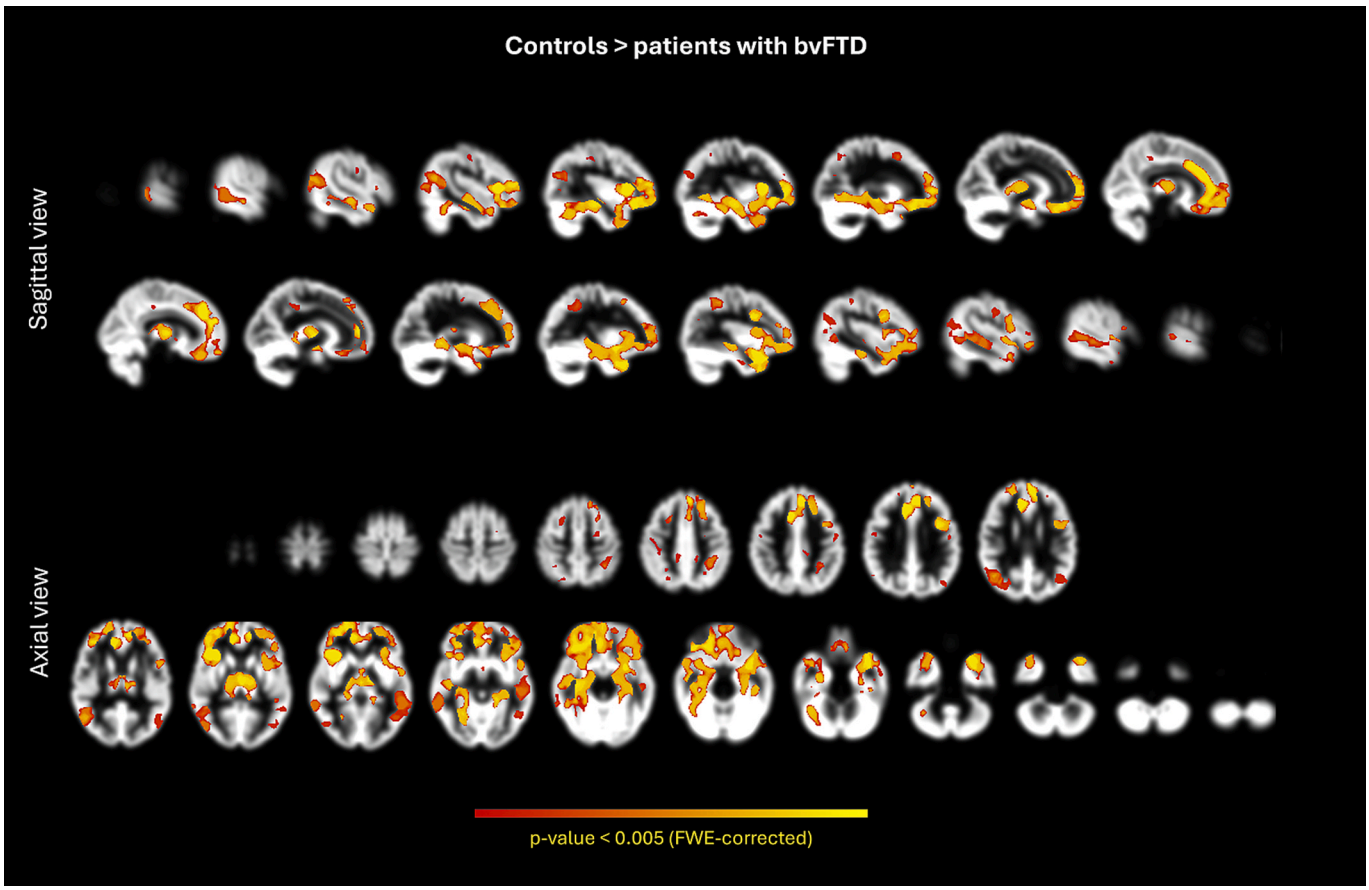


**Fig. 2.** Group comparison of gray matter density between patients with behavioral variant frontotemporal dementia (bvFTD) and controls.

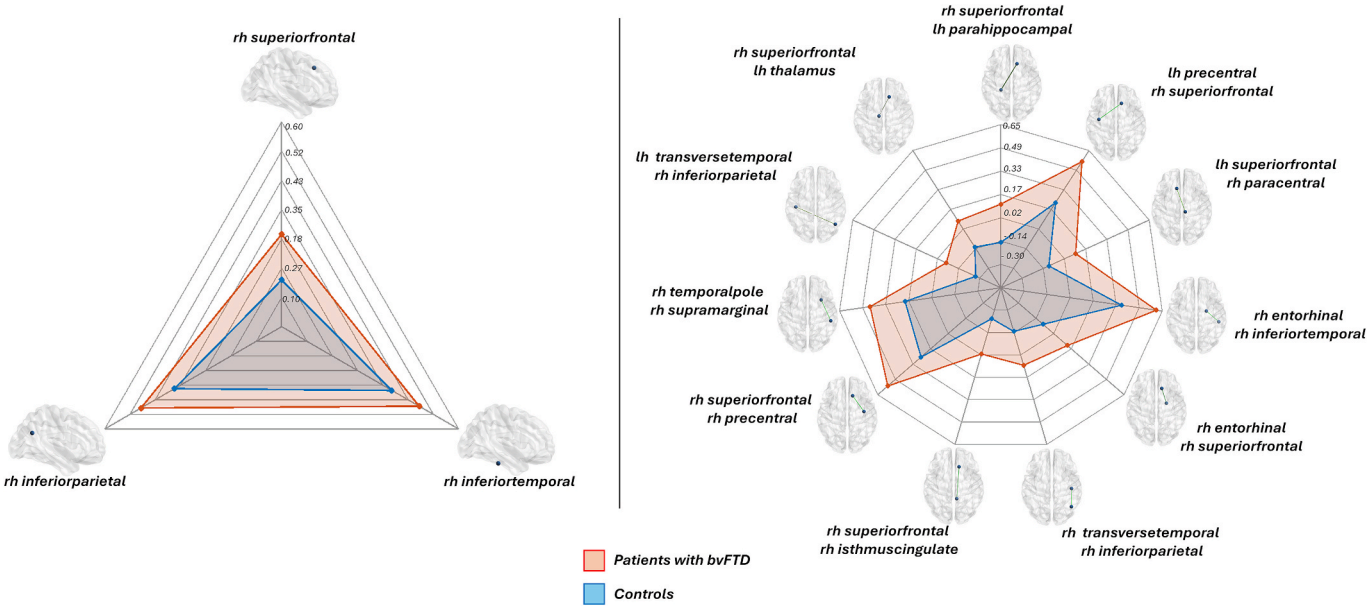


**Fig. 3.** Differences in network measures between controls and patients with bvFTD. (Left) Brain nodes showing significant differences in RMCS between controls and bvFTD patients (FDR corrected p-values $< 0.05$). (Right) Edges showing significant differences between controls and bvFTD patients (FDR corrected p-values $< 0.05$).

with mild cognitive impairment and Alzheimer's disease (Arlt et al., 2013). A significant association between MMSE scores and cortical thickness was also found in the left caudal middle frontal gyrus, left lateral orbitofrontal gyrus, left medial orbitofrontal gyrus, and left rostral middle frontal gyrus (Zhao et al., 2015). Consistent with these studies, we observed a robust correlation between MMSE scores and RMCS values in several frontal, temporal and occipital brain regions of bvFTD patients. Additionally, we observed that specific connections linking the caudal middle frontal gyrus to temporal regions were associated with cognitive performance, indicating that gray matter changes

**Table 2**
Differences in network measures between controls and patients with bvFTD.

| RMCS | Controls ($n = 20$) Mean ± SD | bvFTD ($n = 20$) Mean ± SD | $t$ or z | FDR p-value |
|---|---|---|---|---|
| **Nodes** | | | | |
| rh superior frontal | 0.15 ± 0.11 | 0.28 ± 0.07 | −4.52 | 0.005 |
| lh inferior parietal | 0.38 ± 0.07 | 0.47 ± 0.08 | −3.60 | 0.037 |
| rh inferior temporal | 0.37 ± 0.09 | 0.48 ± 0.08 | −3.47 | 0.037 |
| **Region-to-region connectivity Edges** | | | | |
| lh parahippocampal − rh superiorfrontal | −0.15 ± 0.14 | 0.11 ± 0.19 | −4.70 | 0.029 |
| lh precentral − rh superiorfrontal | 0.23 ± 0.22 | 0.56 ± 0.22 | −4.29 | 0.043 |
| lh superiorfrontal − rh paracentral | −0.10 ± 0.15 | 0.10 ± 0.23 | −4.10 | 0.047 |
| rh entorhinal − rh inferiortemporal | 0.37 ± 0.18 | 0.61 ± 0.17 | −4.27 | 0.039 |
| rh entorhinal − rh superiorfrontal | −0.08 ± 0.12 | 0.14 ± 0.19 | −4.52 | 0.030 |
| rh transvervtemporal − rh inferiorparietal | −0.15 ± 0.11 | 0.09 ± 0.22 | −4.85 | 0.028 |
| rh superiorfrontal − rh isthmuscingulate | −0.24 ± 0.15 | 0.01 ± 0.16 | −4.51 | 0.026 |
| rh superiorfrontal − rh precentral | 0.26 ± 0.24 | 0.56 ± 0.18 | −4.13 | 0.047 |
| rh temporalpole − rh supramarginal | 0.20 ± 0.15 | 0.44 ± 0.15 | −5.16 | 0.021 |
| rh superiorfrontal − lh thalamus | −0.27 ± 0.14 | −0.05 ± 0.15 | −4.64 | 0.026 |
| lh transvervtemporal − rh inferiorparietal | −0.13 ± 0.13 | 0.08 ± 0.02 | −4.18 | 0.046 |

in this brain region might play a key role in driving cognitive symptoms in bvFTD patients. Regarding CSF biomarkers, our results show that brain connectivity between frontal, temporal and occipital brain regions is associated with CSF total-tau, which is considered a biomarker of neurodegeneration (Giuffrè et al., 2023). In recent years, CSF biomarkers have been proposed as tools to discriminate between various clinical FTD forms and the underlying pathogenetic mechanism (Swift et al., 2021). Reduced cortical thickness in the lateral occipital cortex, lateral orbitofrontal cortex, and temporal lobe has recently been associated with higher CSF total-tau values in patients with FTD (Fenu et al., 2022). In line with this study, our findings provide supporting evidence regarding the association between CSF biomarkers and gray matter degeneration in patients with bvFTD.

Several limitations of the present study must be acknowledged. First, our analysis was conducted on a relatively small sample of bvFTD patients; therefore, it is mandatory to replicate our findings in a larger cohort of patients to ensure robustness and generalizability of our results. Second, screening for causative mutations for FTD, including chromosome 9 open reading frame 72 (C9ORF72), progranulin (GRN), and microtubule-associated protein tau (MAPT) genes, was not routinely performed at the time of data collection. Specifically, genetic assessment was conducted in 11 out of 20 bvFTD patients, and all tested negative for mutations in the C9ORF72, GRN, and MAPT genes. Third, CSF biomarker of neurodegeneration assay was performed in 7 out of 20 controls, as the remaining participants declined to undergo lumbar puncture. This issue is relatively common in clinical practice, as, despite lumbar puncture's general tolerability, many individuals perceive the procedure as painful and lengthy (Umemura et al. 2022). Fourth, the radiomics-based method did not capture the real connections between brain regions, unlike diffusion tensor imaging and functional MRI. However, this approach has proven to be a complementary method for exploring and understanding the organization and integrity of gray matter networks when only T1-weighted images are available. Structural MRI has unique advantages over diffusion and functional MRI, including widespread availability, higher signal-to-noise ratio, and higher spatial resolution (Wang and He, 2024). Additionally, network construction is less affected by artifacts, such as head motion, and requires relatively lower computational resources. Fifth, longitudinal studies are warranted to investigate whether the connectivity changes observed in bvFTD patients can be used as predictive markers of clinical-pathological progression. At the same time, it may be of interest to compare network measures derived from regional radiomic feature similarity networks with those obtained using alternative brain network construction methods, such as diffusion-based tractography or fMRI connectivity, and/or different network analysis approaches, such as graph theory. Finally, further studies are required to ascertain whether the RMCS and connectivity alterations documented in bvFTD patients by radiomics feature similarity analysis could serve as potential biomarkers to distinguish between different clinical subtypes of FTD.

## 5. Conclusion

Regional radiomics feature similarity represents a promising approach for investigating gray matter network alterations in patients with bvFTD, capturing intricate patterns in brain images beyond classical morphometric measures. Changes in brain network metrics may aid in differentiating bvFTD from other neurodegenerative disorders, contributing to earlier and more precise diagnoses. Additionally, alterations in network connectivity could enhance our understanding of the neural mechanisms underlying the cognitive and biological alterations observed in patients with bvFTD. Finally, radiomics similarity analysis may play a pivotal role in improving diagnostic accuracy and developing tailored therapeutic approaches for individuals with bvFTD.

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## CRediT authorship contribution statement

**Salvatore Nigro:** Writing – original draft, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Marco Filardi:** Writing – review & editing, Software, Formal analysis. **Benedetta Tafuri:** Writing – review & editing, Software, Formal analysis. **Roberto De Blasi:** Writing – review & editing, Investigation, Data curation. **Maria Teresa Dell'Abate:** Writing – review & editing, Investigation, Data curation. **Alessia Giugno:** Writing – review & editing, Investigation, Data curation. **Valentina Gnoni:** Writing – review & editing, Investigation, Data curation. **Giammarco Milella:** Writing – review & editing, Investigation, Data curation. **Daniele Urso:** Writing – review & editing, Investigation, Data curation. **Chiara Zecca:** Writing – review & editing, Investigation, Data curation. **Stefano Zoccolella:** Writing – review & editing, Investigation, Data curation. **Giancarlo Logroscino:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

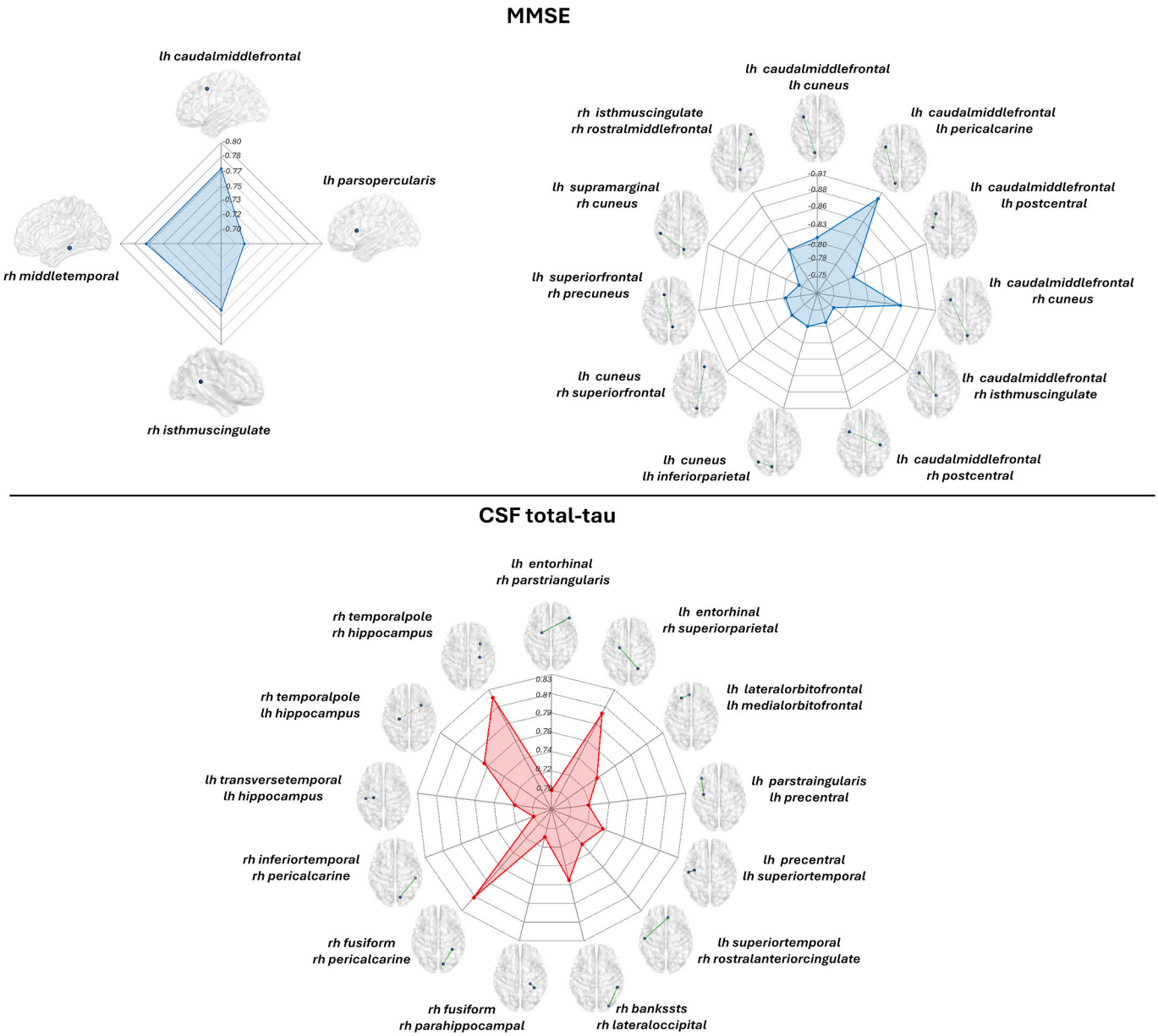


**Fig. 4.** Associations between network measures and neuropsychological/biological data in patients with bvFTD. (Upper panel) Brain nodes and edges showing moderate to strong associations with MMSE scores in bvFTD patients. In order to facilitate visualization of the results, we focused on associations with Spearman r > 0.75, results for the remaining measures are shown in Table S2. (Lower panel) Edges showing moderate to strong associations with CSF total-tau in bvFTD patients.

the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2025.103780.

## Data availability

Data will be made available on request.

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