Original Article

Frontal hypometabolism in neurocognitive disorder with behavioral disturbance

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Running title: bvNCD

ABSTRACT

Criteria for the behavioral variant of frontotemporal dementia (bvFTD) include decreased frontal metabolism. FDG-PET was used to investigate whether patients with neurocognitive disorder and behavioral disturbance (bvNCD) who did not fulfill three bvFTD criteria had characteristic brain metabolic pattern.

Methods: Patients were referred from memory clinic to nuclear medicine for differential diagnosis of NCD with dysexecutive syndrome and predominant mild frontal atrophy. Patients were classified into two groups before FDG-PET, probable bvFTD (n = 25) or bvNCD (n = 27) when only two bvFTD criteria were met.

Results: Voxel-based and multivariate PLS analyses of FDG-PET did not show significant between-group difference at inclusion. After 4.8 years of follow-up, most patients with probable bvFTD received the same diagnosis, 3 remained very stable and one participant was given a psychiatric diagnosis. Five patients with bvNCD fulfilled criteria for probable bvFTD at 4.4 years mean follow up, while 2 participants remained very stable and 3 received alternative neurological or psychiatric diagnoses. When initial FDG-PET were compared between groups stratified at follow up (26 bvFTD versus 17 bvNCD), there was a trend ($p<.001$uncorrected) for lower prefrontal with relatively preserved premotor metabolism in bvFTD compared to bvNCD. Twelve bvNCD participants had neuropsychological testing before inclusion. They all presented executive dysfunction and normal visuospatial performance, and most (n=9) had memory encoding impairment.

Conclusion: Frontal hypometabolism was observed in a dysexecutive presentation of frontal neurodegenerative disorder (bvNCD) that did not fulfill all clinical criteria for bvFTD.

Keywords: FTD; behavioral variant; NCD; FDG-PET; neuroimaging

INTRODUCTION

Frontotemporal dementia (FTD) represents about 15% of all neurodegenerative dementias. The onset of the behavioral variant (bvFTD) is insidious and early diagnosis is difficult. Revised bvFTD clinical criteria were recently described (*1*). They state that bvFTD is characterized by progressive deterioration of behavior and cognition. The diagnosis is classified as possible when three of the following symptoms are present: early disinhibition, early apathy, loss of empathy, stereotyped or compulsive behavior, hyperorality, executive deficit with relative respect of memory and visuospatial functions. The diagnosis becomes probable when frontal and/or anterior temporal atrophy or hypometabolism can be demonstrated, and when significant functional decline is observed at follow-up. bvFTD diagnostic criteria are not achieved when only two of these symptoms are observed, irrespective of other factors including neuroimaging results. This study is performed to understand the outcome of patients with only two symptoms suggesting bvFTD. Exclusion criteria correspond to other neuropsychiatric diseases. Effectively, frontal involvement is observed in psychiatric conditions, in parkinsonian disorders or in frontal presentation of Alzheimer's disease (AD) for example. Among the inclusion criteria, the neuropsychological profile may be variable, since memory impairment is frequently reported in bvFTD when assessed with specific episodic memory tasks (*2*). Rascovsky et al. (*1*) reported 19 patients with pathologically confirmed frontotemporal lobar degeneration who did not meet all bvFTD criteria, and ten had important memory problems.

The sensitivity and specificity of neuroimaging for the bvFTD diagnosis have been assessed in several studies. One study using volumetric imaging and regions of interest compared bvFTD, semantic dementia and progressive non-fluent aphasia

(*3*). Each syndrome could be discriminated from each other with high sensitivity (86% to 100%) and specificity (89% to 100%). Characteristic frontal and temporal metabolic impairment on FDG-PET was shown in bvFTD with different statistical approaches (*4*,*5*). In a study of patients with suspected FTD but no characteristic changes on structural imaging, FDG-PET had a relatively low sensitivity of 47% for bvFTD, but a high specificity of 92% in a sample with diverse neurological and psychiatric diagnoses at follow up (*6*). Yet, FDG-PET was important by identifying bvFTD patients undiagnosed with structural imaging. Sensitivity and accuracy for detecting FTD are higher with FDG-PET than with MRI (*7*). Actually, the utility of FDG-PET to distinguish AD and FTD has long been recognized and the technique meets many of the ideal characteristics for a biomarker. Notably, it reflects a fundamental FTD pathological feature, i.e. the selective regional pathology in the anterior brain. Accordingly, frontal hypometabolism was already observed in carriers of progranulin mutation predating dementia (*8*). Interestingly, a « phenocopy » was described with a slow evolution and no decline in functional activities, where the initial diagnosis of possible FTD is not accompanied by frontal atrophy or hypometabolism (*9*). Among the differential diagnoses, frontal hypometabolism can be observed in schizophrenia, depression, or alcohol abuse for example (*10*,*11*). In the latter study, a group of patients with initial behavioral changes received after two-year follow up a diagnosis of probable/definite bvFTD (24%), other dementia (25%) or psychiatric disorder (40%). The specificity of frontotemporal atrophy on the baseline MRI for bvFTD was 95%, reflecting neurodegeneration. The sensitivity of FDG-PET frontal hypometabolism in participants with normal MRI was 90%, with a low specificity of 68% due to decreased frontal activity in primary psychiatric cases and other types of dementia (*11*).

In the present study, we examined successive patients referred to the nuclear medicine department for a differential diagnosis of neurocognitive disorder (*12*) with behavioral disturbance (bvNCD), no major psychiatric disorder and variable but predominant frontal atrophy on structural neuroimaging. Our objective was to investigate if patients with bvNCD who did not fulfill three bvFTD criteria had characteristic brain metabolic pattern. To do so, two main subgroups were identified according to clinical symptoms at inclusion and follow-up: patients with probable bvFTD (*1*) and participants with bvNCD. If there is a specific signature, lower glucose uptake in medial frontal regions was anticipated in bvFTD patients (*4*).

MATERIALS AND METHODS

Participants

Patients with NCD according to Diagnostic and Statistical Manual of Mental Disorders 5 criteria (*12*), behavioral and cognitive dysexecutive syndrome and no major psychiatric disorder were referred from memory clinic to the nuclear medicine department for differential diagnosis. Patients had difficulties in executive functions, frequent memory complaints, minor language or visuospatial disturbance and a variable number of behavioral symptoms (Table 1). Clinical evaluation of executive difficulties was based on caregiver's and patient's report of changes in initiative, planning, or organization of activities, and on report and clinical observation of impulsivity, lack of flexibility and deduction, and sometimes poor awareness of difficulties. Most participants had impaired effortful memory recall and improved performance when choice was given at recognition during medical screening. Neuropsychological testing was quite variable (from short screening to full neuropsychological battery), behavioral abnormalities reported by the patient and the

caregiver were recorded in a standard format according to recent criteria (*1*), but social cognition was not formally evaluated. We included 52 Caucasian participants (29 women and 23 men) with predominant frontal (versus posterior) atrophy at visual inspection of structural 3D brain images (Table 1). Participants without atrophy were not included to avoid phenocopy of behavioral disorder (*9*). Patients with probable AD (*13*) or parkinsonism were not included in the study. At the time of FDG-PET, the population was classified into 2 subgroups, probable bvFTD (n = 25) when three or more diagnostic criteria were met and bvNCD when only two bvFTD clinical criteria were recorded (n = 27). NCD diagnosis excluded psychiatric disease and addiction (*12*). Clinical dementia rating (CDR) allowed to assess the severity of dementia (*14*). Patients were subsequently followed in the memory clinic to record additional diagnostic symptoms, clinical deterioration or stabilization, or alternative neurological or psychiatric diagnosis.

For the sake of comparison with the literature, FDG-PET data from 32 healthy older participants and 52 patients with probable AD (*15*) were also gathered (supplementary Table 1). This study followed the Declaration of Helsinki on medical protocol and ethics and was approved by the Medical Ethical Committee of the University of Liege. All subjects gave informed consent for the use of their data for research purposes.

Neuroimaging

FDG-PET AND STRUCTURAL IMAGING. An FDG-PET was performed 30 minutes after intravenous injection of 150 MBq ± 10% FDG, with eyes closed, using Gemini TF scanner (Philips Medical Systems, Amsterdam, Netherlands) with a 18 cm axial field of view and a 4.8 mm resolution in air (axial resolution in the center of the

field of view). A low-dose CT was acquired for attenuation correction, followed by a 12-minute emission scan. Images were reconstructed using a list mode TOF algorithm including correction for attenuation, dead time, scatter and random events. Since some of the early healthy participants moved between CT and PET acquisitions, a RAMLA reconstruction assuming uniform attenuation was performed. Those images were used for all analyses. Reconstructed images had 2 mm isotropic pixel size and a 128x128x90 matrix size.

As per protocol, all patients had variable frontal atrophy on structural neuroimaging (brain CT or brain MRI) performed as part of the clinical routine. The global cortical atrophy-frontal subscale scores were visually rated on transverse sections of structural cerebral images (*16*).

FDG-PET PROCESSING NAD STATISTICAL ANALYSES. PET data were subjected to an affine and non-linear spatial normalization onto the MNI space using the SPM12 standard PET brain template (SPM12, Wellcome Department of Cognitive Neurology, London, UK) and smoothed using an isotropic Gaussian kernel of 8-mm full-width at half-maximum (FWHM). A mean image was generated that served as a study-specific brain template. Each PET image was then spatially normalized onto this brain template and smoothed with an isotropic Gaussian kernel of 12-mm FWHM. Partial volume effect could not be taken into account because MRI was not obtained in all participants. The normalized FDG-PET images were entered in a general linear model with a factorial design including the frontal groups, controls and AD patients, using proportional scaling by cerebral global mean values to take into account the individual variation in global FDG uptake. Reference tissue was not used because none is recommended in bvFTD. The analyses consisted in

comparisons: frontal groups versus control volunteers, frontal groups versus AD patients and bvFTD versus bvNCD, using age and sex as confounding variables. Significant group difference in regional metabolism was tested with a statistical threshold of p< .05 FWE corrected for multiple comparisons at the voxel level, and trends were also searched for (p<.001 uncorrected, k>10). We performed a second analysis on groups defined at follow-up (bvFTD versus bvNCD), entering patients with other diagnoses as variables of no interest.

We also provide a multivariate approach using spatiotemporal partial least square (PLS) analysis (*17*), that operates on voxel metabolic covariance to identify one component (latent variable, LV) that optimally distinguishes two groups. We used non-rotated task PLS where a design matrix comparing 2 conditions (bvFTD versus controls, bvNCD versus controls, bvFTD versus bvNCD) and the image data matrix (one mean-centered PET image per subject) were submitted to singular value decomposition. The resulting LV has a singular value which represents the amount of covariance between the design matrix and the image matrix. Each brain voxel has a weight (a salience) on the LV, that indicates how that voxel is related to the LV. The salience is positive for one group and negative for the other. The significance for the LV was determined by a permutation test. The singular value of each newly permuted LV was compared to the singular value of the original LV, yielding a probability of the number of occurrences that the permuted values exceed the original value. 600 permutations were conducted and the statistical significance level was set at $p < .05$. Finally, the reliability of the saliences for the brain voxels characterizing LV was assessed by a bootstrap analysis of the standard errors using 150 bootstrap samples (*18*). A reliable contribution for a given voxel was defined as a ratio of salience to standard error superior or equal to 3 (cluster size > 5, $p < .005$).

Demographic and clinical data at inclusion were compared between frontal groups using two-sample t-tests or Chi-squared tests ($p<.05$) in Statistica (StatSoft, Inc.). Additionally, the frequency of clinical bvFTD symptoms was compared between the two groups by means of Mann-Whitney tests, with an alpha level of .05.

RESULTS

Clinical Data

We compared clinical manifestations in the cohort of 52 patients, contrasting the bvFTD versus the bvNCD group (Table 1).

Patients with bvFTD were younger than patients with bvNCD [$t(50) = 2.9$, $p < .01$]. There was a majority of men in the bvFTD group and a majority of women in the bvNCD group [$\chi^2 = 4.85$, $p < .05$]. The symptom duration did not differ between-groups ($p = .21$). Dementia severity was more important in the bvFTD group than in the bvNCD group according to CDR [$t(50) = -3.89$, $p < .001$]. However, there was no difference in MMSE score at FDG-PET time between the two groups. A familial history of dementia was reported in 10 bvFTD patients and 6 bvNCD patients. Vascular risk factors were less frequent in the bvFTD group.

Table 1 presents also the frequency of behavioral symptoms in the frontal groups. Comparison revealed that bvFTD patients exhibited more symptoms of disinhibition, apathy, loss of empathy, stereotypes and hyperorality than bvNCD patients. BvFTD patients showed more frequently anosognosia than bvNCD patients (all significant p values < .05). There was no between-group difference for initial complaints of executive functioning, memory and visuo-spatial impairment. bvNCD participants appeared to have more cognitive than behavioral symptoms (Table 1).

Frontal atrophy was mild to moderate in most patients, and severe in only few of them. The global cortical atrophy-frontal subscale scores did not differ between-groups [t(49) = 0.12, p = .89]. Genetic testing (comprising C9orf72) was obtained in 7 bvFTD and 5 bvNCD participants and no mutation was observed.

The mean clinical follow-up duration was 4.8 ± 3.1 years for bvFTD patients and 4.4 ± 2.4 years for bvNCD patients. This duration did not differ between groups [t(50) = -0.50, p = .61]. Follow-up did not much modify group attribution for bvFTD, with one psychiatric diagnosis (depression) and three participants with no or very slow progression (stable cases). The behavioral symptoms and dependence tended to worsen in the remaining 21 bvFTD patients who met diagnosis criteria for probable bvFTD at follow-up. Follow up provided few additional information for a differential diagnosis in the bvNCD group with 5 participants reaching 3 diagnostic criteria for bvFTD, 2 stable cases, one vascular dementia, one psychiatric disorder (depression), and one alcohol addiction. The other bvNCD cases (n = 17) could not be more precisely defined following bvFTD criteria. All participants with unexpected evolution are identified in the graphical representation of frontal FDG uptake in the following result section. Twelve patients with a bvNCD diagnosis at follow up (70%) had a full neuropsychological examination during their diagnostic assessment. Forward and backward digit span was normal in 11 cases. Long term memory impairment concerned effortful (executive) retrieval in 11 and encoding in 9 cases, while intrusions were observed in 4 patients (*19*). Slowness was recorded in 6 cases when assessing simple conditions in Stroop experiment (*20*). Dysexecutive function corresponded to impaired verbal inhibition (*20*), and/or planning difficulties for remembering Rey's figure (*21*) and/or perseverations in graphical or motor sequences and/or impaired verbal fluency. Visuospatial performance was normal,

while naming was impaired in 3 patients. In summary, the main results of the neuropsychological evaluation in this sample were dysexecutive functioning in all patients and memory encoding impairment in 9 cases.

Brain Metabolism

Visual reading reported frontal hypometabolism in each patient (see Supplementary figure 1).

SPM12 statistical analyses contrasting FDG-PET in each frontal group with healthy controls at inclusion revealed a significant reduction of frontal metabolism in both patients' groups (Figure 1 and Table 2). Compared with the control group, the bvFTD group seemed to have a more extended decrease of cerebral activity in bilateral frontal areas than bvNCD, but the direct group comparison did not reveal any significant difference. There was only a trend ($p < .001$ uncorrected for multiple comparisons) for the bvFTD patients having a more important hypometabolism than bvNCD patients in the dorsal anterior cingulate cortex (MNI coordinates: x= 15, y = 41, z = 19, Z = 3.72, k = 56), a region belonging to the salience network (*22*), and in the inferior temporal pole (x=33, y=5, z=-44, k=49). There was a trend ($p < .001$ uncorrected) for the bvNCD to have a lower metabolism than the bvFTD group in the left intraparietal sulcus (x=-33, y=-37, z=46, k=41). Adding frontal atrophy measure as confounding covariate in the contrast did not modify the result.

We also confirmed that the two frontal groups demonstrated reduced frontal activity compared to AD (Table 2).

Multivariate PLS analysis showed that one latent variable (LV) represented a significant group difference ($p<.001$) for both bvFTD versus controls and bvNCD versus controls. The brain metabolic involvement was very similar in both groups

(Figure 2). There was no significant LV between bvFTD and bvNCD groups, confirming univariate results.

Since few patients had unexpected follow-up, plots of FDG-PET uptake for the bvFTD and bvNCD groups were generated for regions with the maximum SPM12 voxel significance in order to identify potential outliers (Figure 3). A single patient had higher left prefrontal FDG-PET uptake than the others in the bvNCD group, and the diagnosis for this patient was a slowly progressive form of bvNCD. Of note, other patients whose follow-up diagnosis changed to alternative diagnosis (e.g., stable cases, vascular, psychiatric) had frontal metabolic values within the ranges of patients whose diagnosis was confirmed at follow-up.

We compared participants with a diagnosis of bvFTD (n=21 + 5) and bvNCD (n=17) at follow-up. There was no significant difference in FDG-PET distribution. We observed a trend ($p<.001$ uncorrected) for lower metabolism in the medial frontal cortex (x=13, y=32, z=28, k=12) and relatively higher metabolism in the premotor cortex (x=-24, y=-16, z=61, k=68 and x=29, y=-20, z=61, k=18) for bvFTD compared to bvNCD.

DISCUSSION

Frontotemporal decrease of metabolism is considered as an important criterion for a diagnosis of probable bvFTD (*1*). Accordingly, we studied a group of patients referred for a differential diagnosis of neurocognitive and behavioral dysexecutive disorder, who had some degree of frontal atrophy on structural brain images. Patients either fulfilled criteria for probable bvFTD, or they presented with bvNCD and did not fulfill the three required clinical diagnostic criteria (*1*). Statistical analysis of FDG-PET revealed that both bvFTD and bvNCD patients presented with

a pattern of frontal hypometabolism compared to controls and AD patients. When groups of bvFTD and bvNCD were compared at inclusion and at follow up, there was only a trend for lower dorsomedial prefrontal metabolism in bvFTD. bvNCD participants had more cognitive than behavioral symptoms and they all had memory impairment. Although we do not have neuropathological or genetic confirmation, they may correspond to a subgroup of bvFTD patients already described by Rascovsky (*1*).

Patients first came to the memory clinic with memory and executive complaints. At follow-up, only two bvNCD and one bvFTD patients were diagnosed with psychiatric disease or addiction. None received a diagnosis of parkinsonism, but one bvNCD patient had vascular dementia, that correspond to an alternative diagnosis (*23*). A differential diagnosis for the bvNCD patients would have been AD as the proportion of patients with FTD syndrome and AD neuropathology is not negligible (*24*). However, our bvNCD patients did not have a typical AD-related hypometabolic pattern in posterior associative cortices. Effectively, dysexecutive variant of AD was reported to be characterized by temporoparietal greater than frontal atrophy (*25*), even if medial and orbital frontal hypometabolism was greater in “frontal” than in more typical AD cases (*26*). Early cognitive disorder was already reported in bvFTD (*27*-*29*). Our patients with bvNCD were older than bvFTD ones, and they were slightly less demented using the CDR scale. This might be consistent with early onset being more affected than late onset FTD (*30*). Mild frontal, insular or temporal atrophy was recently reported in few patients with bvFTD phenocopy (*31*), but frontal hypometabolism in our stable bvNCD cases is not consistent with this diagnosis. Of note, some patients with C9ORF72 mutations can present with a slow progression phenotype of bvFTD (*32*). Only few participants in our sample had

genetic testing and results were negative for the main FTD mutations. More interestingly, in Rascovsky et al's report (*1*), patients with FTLD neuropathology who did not meet behavioral variant criteria were older and presented with memory impairment, as in our bvNCD group. The main limitation of our study is that there was no biomarker of AD amyloid or tau pathology in our sample and no pathological diagnosis.

The main finding of the current clinical study was that frontal hypometabolism was as important in bvNCD as in bvFTD. More precisely, there was no significant metabolic difference between the groups, using univariate and multivariate analyses or displaying plots of FDG-PET frontal uptake. Even if that was our expectation, based on the literature, there was only a trend for a greater dorsomedial prefrontal glucose hypometabolism in the bvFTD group. This might indicate that bvNCD is an early stage of FTLD with mild dysexecutive syndrome at onset. The last limitation of our study is that a longer follow-up (with post-mortem brain analyses) would be required to better characterize patients with bvNCD.

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KEY POINTS

QUESTION: Does brain metabolic pattern and clinical evolution characterize patients with neurocognitive disorder and behavioral/dysexecutive syndrome (bvNCD) who do not fulfill three bvFTD criteria.

PERTINENT FINDINGS: In this cohort study, we could not demonstrate significant difference in FDG-PET distribution between bvNCD and bvFTD patients. bvNCD patients were slightly older, and they all complained from memory impairment.

IMPLICATIONS FOR PATIENT CARE: Frontal hypometabolism may characterize a subgroup of bvFTD patients described by Rascovsky, with memory impairment and not all bvFTD criteria.

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Figure 1. SPM12 analysis of FDG-PET of frontal patients overlaid on MRI template ($p < .05$ FWE-corrected for multiple comparisons)

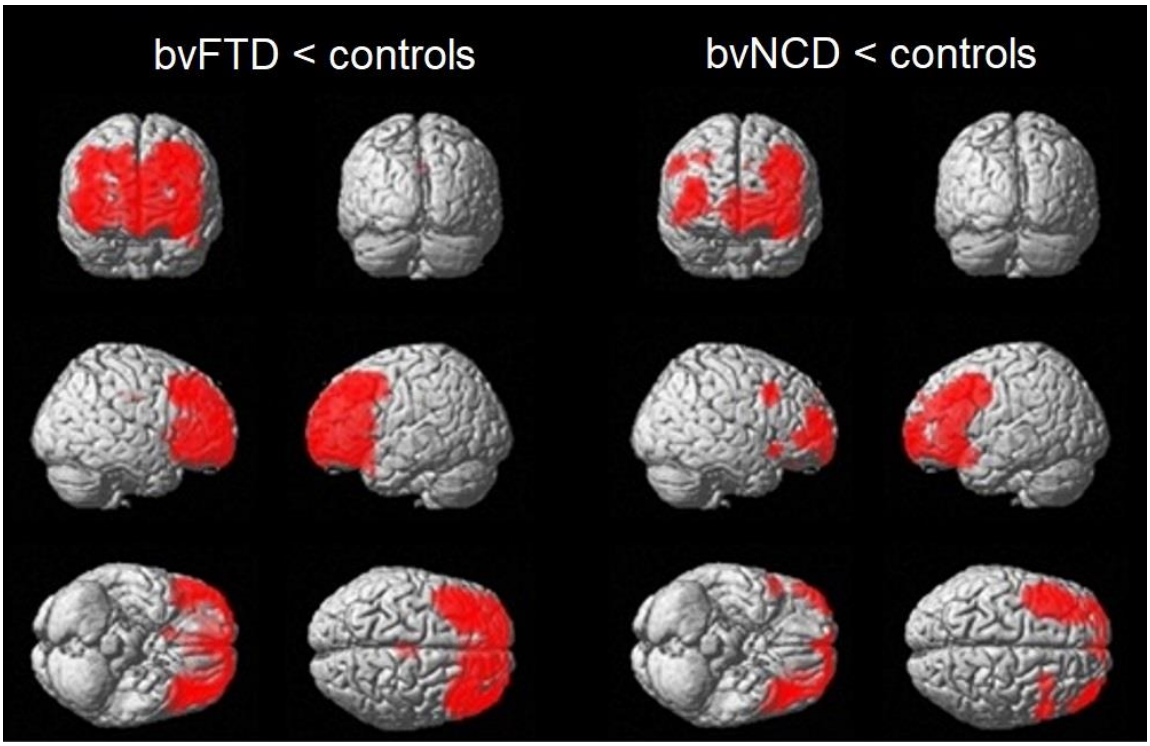


Figure 2. Multivariate PLS results: Topography of cerebral hypometabolism in bvFTD patients and frontal bvNCD patients when compared to controls. The color scale represents bootstrap ratio (hot colors for areas with decreased metabolism in patients compared to controls; cold color for the reverse contrast).

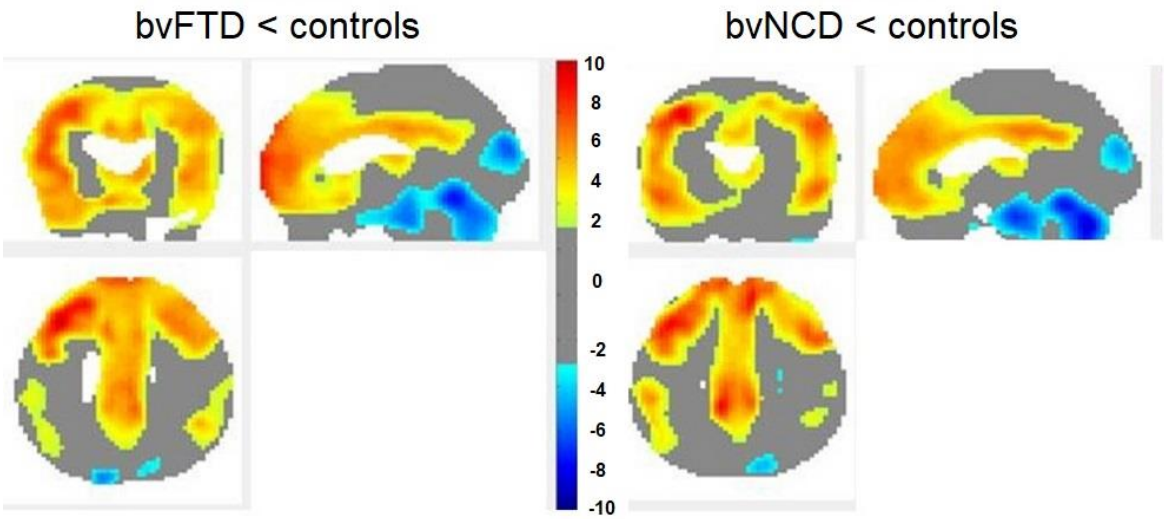
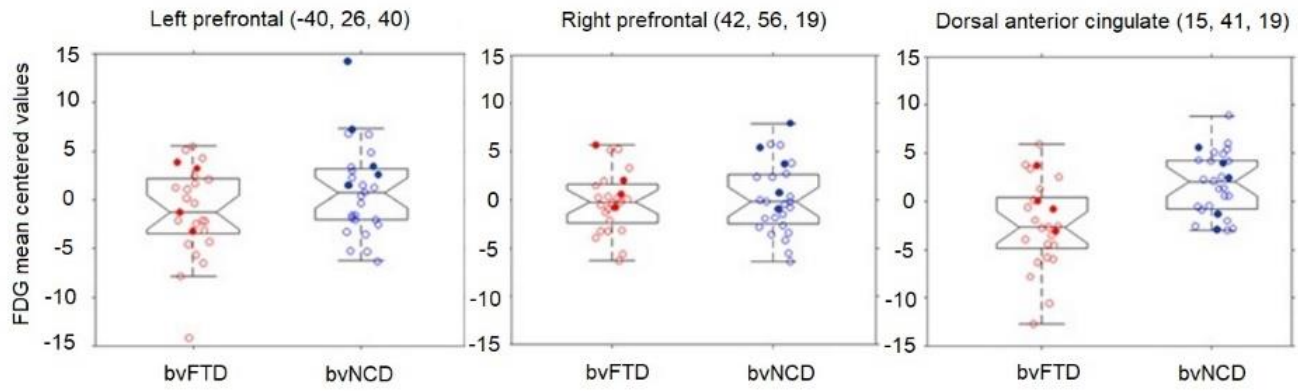


Figure 3.Plots of FDG-PET uptake values in frontal patients. Full circles show patients with alternative diagnosis at follow-up.



Supplementary figure 1. Transverse and sagittal FDG-PET images of frontal patients

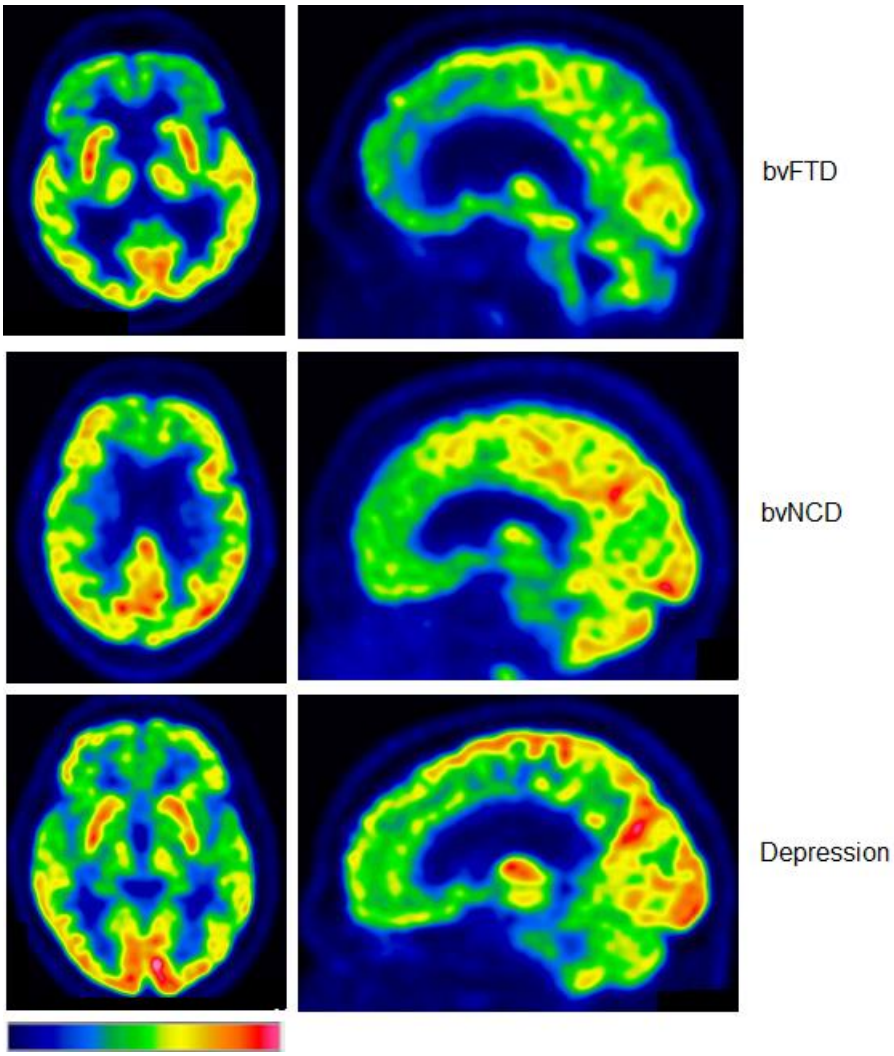


Table 1. Demographic and clinical characteristics of the frontal patient groups

	bvFTD (n=25)	bvNCD (n=27)
Gender (% women)	40	70*
Age (years)	68.2 (11.3) range 47 – 88y	75.8 (7.2)* range 51 - 86y
Family history of dementia (%)	32	22
Vascular risk factors (%)	44	81*
Symptoms duration (years)	5.3 (4.0)	4.1 (2.9)
MMSE (0-30)	24.7 (3.7)	24.9 (3.5)
CDR (0-3)	1.86 (.76)	1.15 (.55)*
Number of CDR 0.5, 1, 2, 3	1/7/12/5	6/14/7/0
Impaired memory (%)	84	100
Impaired spatial abilities (%)	4	15
Impaired executive functions (%)	80	78
Decreased inhibition (%)	52	15*
Apathy (%)	80	44*
Loss of empathy (%)	52	11*
Perseveration/compulsion (%)	92	33*
Hyperorality (%)	60	15*
Number of criteria/6 (SD)	4.2 (.9)	2 (0)
Anosognosia (%)	64	41*
Frontal atrophy (GCAF 0-3)	1.35 (.69)	1.38 (.73)

bvNCD= behavioral variant of neurocognitive disorder; bvFTD=behavioral variant of frontotemporal dementia ; MMSE= mini mental state exam; CDR= clinical dementia rating; GCAF= global cortical atrophy-frontal scale. Values in parentheses are SD. * significant difference at $p<.05$

Table 2. FDG-PET SPM12 analysis: regions showing metabolic differences between groups

	Regions	MNI coordinates			Z score	Cluster size
		x	y	z		
bvFTD< bvNCD; bvNCD<bvFTD	Nihil					
bvFTD< controls	Bilateral frontal	-39	26	40	6.99	4649
	Right caudate	12	14	1	5.11	25
	Cingulate cortex	0	-22	34	4.82	41
bvNCD < controls	Right frontal	42	56	19	6.97	234
	Left frontal	-42	23	37	6.14	1763
	Right insula	54	17	-11	5.24	27
	Right frontal	33	14	43	5.07	55
	Right frontal	60	11	40	4.96	62
bvFTD< AD	Bilateral frontal	48	32	-14	6.43	2024
bvNCD < AD	Left frontal	-12	68	-5	6.37	290
	Right frontal	45	56	13	5.67	328
	Left orbitofrontal	-24	20	-23	5.67	209
	Right orbitofrontal	30	23	-14	5.46	74
	Right precentral	60	8	43	5.28	47

MNI=Montreal Neurological Institute; $p < .05$ FWE-corrected for multiple comparisons at the voxel-level.

Supplementary Table 1. Main characteristics of all groups

	Controls (n=32)	bvFTD (n=25)	bvNCD (n=27)	AD (n=52)
Age at PET date (years)	62.0 (13.0)	68.2 (11.3)	75.8 (7.2)	78.6 (7.3)
Gender (women/men)	19/13	9/16	19/8	24/28
MMSE	>26	24.1 (3.4)	24.9 (7.9)	22.1 (4.4)
Percentage of familial history	N/A	32%	22%	17%

bvFTD= frontotemporal dementia behavioral variant ; bvNCD=neurocognitive disorder behavioral variant ; AD= Alzheimer's disease ; N/A= not available ; mean (SD)

Graphical abstract