

Investigating the Roles of Anterior Cingulate in Behavioral Variant Frontotemporal Dementia: A PET/MRI Study

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Abstract.

Background: The anterior cingulate cortex (ACC) seems to play an important role in behavioral deficits and executive dysfunctions in patients with behavioral variant frontotemporal dementia (bvFTD), while its specific and independent contribution requires clarification.

Objective: To identify whether ACC abnormalities in gray matter (GM) volume and standardized uptake value ratio (SUVR) images are associated with disease severity of bvFTD, by analyzing hybrid T1 and ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET).

Methods: We enrolled 21 bvFTD patients and 21 healthy controls in the study. Each subject underwent a hybrid PET/MRI study and a standardized neuropsychologic assessment battery. GM volume and SUVR are voxel-wise calculated and compared. Then we estimate the mean value inside ACC for further partial Pearson's correlation to explore the association between GM volume/SUVR of the ACC and severity of behavioral deficit as well as executive dysfunction.

Results: ACC was shown to be involved in both atrophy and hypometabolism patterns. The partial Pearson's correlation analysis showed that the SUVR of the ACC was strongly correlated with frontal behavior inventory total score (left $r = -0.85$, right $r = -0.85$, $p < 0.0001$), disinhibition subscale score (left $r = -0.72$, $p = 0.002$; right $r = -0.75$, $p < 0.0001$), and apathy subscale score (left $r = -0.87$, right $r = -0.85$, $p < 0.0001$).

Conclusion: These findings demonstrated decreased ACC activity contributes to behavioral disturbances of both apathetic and disinhibition syndromes of bvFTD, which can be sensitively detected using ¹⁸F-FDG PET.

Keywords: Anterior cingulate cortex, atrophy, ¹⁸F-fluorodeoxyglucose positron emission tomography, frontotemporal dementia, hypometabolism, magnetic resonance imaging

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INTRODUCTION

Behavioral variant frontotemporal dementia (bvFTD) is the most frequent subtype of frontotemporal lobe degeneration (FTLD), which primarily affects behavior regulation. It is characterized by early and prominent behavioral disinhibition, apathy or loss of sympathy, and impairment of executive function [1, 2]. bvFTD selectively impairs specific brain areas, particularly the frontal or temporal systems. In recent years, structural and metabolic research has found that the anterior cingulate cortex (ACC) is involved in bvFTD during both the prodromal and symptomatic stages, and in all subtypes of FTLD pathologies [3–14]. Also, abnormality of ACC can help discriminate bvFTD from other dementia such as Alzheimer's disease or semantic dementia on magnetic resonance imaging (MRI) with a high positive predictive value, which demonstrates its unique role in the development and progression of bvFTD [13, 15, 16].

ACC is considered as an epicenter, known for co-activation with frontoinsula as part of a “salience network” for homeostatic behavioral guidance, that may represent the initial target in bvFTD [17]. Also, ACC is located within a significant connection of the Papez circuit, where the frontal-temporal and limbic systems link, modulating motivation, goal-directed behaviors, emotional experiences and executive functions, and a significant predictor of self-conscious emotion [16, 18–24]. Additionally, ACC had been found regulating autonomic nervous system activity in bvFTD [25]. However, the specific contributions focusing on ACC in bvFTD remain to be elucidated.

Some structural or metabolic whole-brain analysis studies in bvFTD patients have investigated the correlation between specific brain areas and behavioral dysfunctions, most of which encompassed significant findings in ACC by voxel-wise analysis, demonstrating its potential importance [6, 26–31]. However, because of lacking consistency across studies due to single neuroimage modality, limited sample size, lenient statistical thresholds, and variable measurement scales, directly integrating clinical correlation results of previous structural and metabolic research is unreliable. Hypometabolism was found more severe than gray matter (GM) atrophy in ACC, which indicates that there may be some discrepancy in the implication of clinical correlations between different modalities [12, 32]. However, the clinical correlation of ACC has not been directly analyzed by multidimensional neuropsychiatric assessments matched with the hybrid neuroimaging method in

bvFTD patients. Integrated positron emission tomography (PET)/MRI is a recent technical innovation that allows anatomy and functional modalities to be obtained simultaneously, providing an available approach for exploring the clinical correlation [33].

In this study, patients with bvFTD underwent a hybrid PET/MRI scan and neuropsychological examinations, to explore the potential clinical contributions of ACC in bvFTD. We hypothesized that in patients with bvFTD, GM volume or standardized uptake value ratio (SUVR) changes of the ACC may have a strong correlation with the core manifestations, including behavioral disturbances and executive dysfunctions.

MATERIALS AND METHODS

Ethics

The study was conducted following the Declaration of Helsinki. The clinical protocols were approved by the ethics committee and local institutional review board of Xuanwu Hospital, Capital Medical University, China. The study was conducted following relevant guidelines and regulations for the use of human subjects in research. Written informed consent was obtained from all participants or their guardians before the start of the study.

Subjects

42 right-handed subjects are enrolled in this study, including 21 bvFTD patients and 21 healthy controls, from July 1, 2014, to December 31, 2019, in the Department of Neurology of Xuanwu Hospital. All patients were diagnosed as probable bvFTD, according to the consensus criteria published in 2011 [1]. Healthy controls were age- and sex-matched to patients and had no cognitive decline complaints, depression, or anxiety and performed within the normal range on neuropsychological tests (Mini-Mental State Examination [MMSE] score ≥ 24 and Frontotemporal Lobar Degeneration-Clinical Dementia Rating Scale [FTLD-CDR] score of 0).

Exclusion criteria for all participants were 1) any serious neuropsychiatric disorder that could affect cognitive functioning, such as substance abuse, alcoholism, schizophrenia, tumors, or cerebrovascular disease; 2) standard contraindications for MRI examinations; and 3) absence of a reliable informant.

Neuropsychologic assessment

Each participant underwent a standardized neuropsychologic assessment battery. Global cognitive screening was performed using the MMSE and disease severity was assessed using the FTLDCDR. Word-list memory was evaluated using Rey's Auditory-Verbal Learning Test (RAVLT). Executive function was evaluated using the Trail Making Test (TMT) and the Stroop I and II tests. Visuospatial skill was tested using the Rey complex figure test. The severity of behavioral abnormality was assessed using the Frontal Behavior Inventory (FBI), which can be separated into the negative apathy symptom subscale (first 12 items) and the positive disinhibition symptom subscale (last 12 items).

PET/MRI acquisition parameters

All images were acquired on a hybrid 3.0 T TOF PET/MRI scanner (SIGNA PET/MR, GE Healthcare, WI, USA) [34]. PET and MRI data were acquired simultaneously using a vendor-supplied 19-channel head and neck union coil. Three-dimensional (3D) T1-weighted sagittal images and ^{18}F -FDG PET volumes were acquired during the same session after administering 3.7 MBq/kg ^{18}F -FDG for each individual.

The parameters of the T1 data were as follows: repetition time (TR) = 6.9 ms, echo time (TE) = 2.98 ms, flip angle = 12° , inversion time = 450 ms, matrix size = 256×256 , field of view (FOV) = $256 \times 256 \text{ mm}^2$, slice thickness = 1 mm, 192 sagittal slices with no gap, voxel size = $1 \times 1 \times 1 \text{ mm}^3$, and acquisition time = 4 min 48 s. Static ^{18}F -FDG-PET data were acquired using the following parameters: matrix size = 192×192 , FOV = $350 \times 350 \text{ mm}^2$, and pixel size = $1.82 \times 1.82 \times 2.78 \text{ mm}^3$, including corrections for random coincidences, dead time, scatter, and photon attenuation. Attenuation correction was performed based on MR imaging of the brain (Atlas-based coregistration of 2-point Dixon) [35]. The default attenuation correction sequence was automatically prescribed and acquired as follows: LAVA-Flex (GE Healthcare) axial acquisition, TR = 4 ms, TE = 1.7 ms, slice thickness = 5.2 mm with a 2.6 mm overlap, 120 slices, pixel size = $1.95 \times 2.93 \text{ mm}$, and acquisition time = 18 s.

Structural image preprocessing

Data were preprocessed using the computational anatomy toolbox 12 (CAT 12) toolbox, ([\[neuro.uni-jena.de/cat/\]\(http://www.neuro.uni-jena.de/cat/\)\), which is based on statistical parametric mapping 12 \(SPM12\).](http://www.</p></div><div data-bbox=)

First, the DICOM files were converted into nifti format, using MRICRON software (<http://people.cas.sc.edu/rorden/mricron/index.html>). Voxel-based morphometry (VBM) preprocessing was performed using the default settings of the CAT12 toolbox and the "East Asian Brains" ICBM template. T1-weighted 3D images were segmented into GM, white matter (WM), and cerebrospinal fluid partitions. Subsequently, the GM and WM partitions of each subject in native space were high-dimensionally registered and normalized to the standard Montreal Neurological Institute (MNI) space using diffeomorphic anatomical registration through exponentiated lie algebra normalization. The images were then smoothed using an 8-mm full-width half-maximum Gaussian kernel.

PET image preprocessing

PET images were preprocessed using SPM12, implemented in MATLAB (MathWorks, Natick, Massachusetts). After normalization of the structural MRI images, the transformation parameters determined by the T1-weighted image spatial normalization were applied to the co-registered PET images for PET spatial normalization. The images were then smoothed using an isotropic Gaussian kernel with an 8-mm full-width half-maximum. Finally, PET scan intensity was normalized using a whole cerebellum reference region to create standardized uptake value ratio (SUVR) images.

Voxel-based analysis and ROI analysis

The preprocessed structural and ^{18}F -FDG PET data were used to perform voxel-wise whole-brain comparisons between the bvFTD and control groups using Student's two-tailed *t*-test, with age, sex, and total intracranial volume as covariates. The correction threshold was set at $p < 0.05$ (FWE-corrected). Then we conducted the atlas-based ROI analysis of the structural and PET images to extract the regional GM volumes and SUVR of ACC from the AAL atlas for further correlation analysis.

Statistical analysis

Statistical analyses were carried out in SPSS 22.0 (IBM, Armonk, NY, USA). Continuous data are represented as means \pm standard deviations.

Table 1
Demographic data and neuropsychological performance in bvFTD patients ($n = 21$) and healthy controls ($n = 21$)

	bvFTD ($n = 21$)	Controls ($n = 21$)	p
Age (y)	61.00 \pm 11.32	57.95 \pm 8.00	0.320
Sex (male/female)	10/11	11/10	0.758
Years of education	10.76 \pm 4.94	11.62 \pm 3.14	0.506
Disease duration (y)	2.11 \pm 0.85		
MMSE	17.95 \pm 5.34	28.73 \pm 2.09	<0.001
FTLD-CDR sum of box	11.67 \pm 4.90	0	
Executive function			
TMT-A	108.07 \pm 37.47	48.47 \pm 17.66	<0.001
TMT-B	221.57 \pm 87.05	82.27 \pm 45.78	<0.001
Stroop I	85.44 \pm 53.43	19.13 \pm 3.14	0.006
Stroop II	135.00 \pm 128.30	29.07 \pm 5.80	0.004
Verbal memory			
RAVLT total	14.50 \pm 10.96	41.20 \pm 8.52	<0.001
RAVLT recall	1.78 \pm 2.07	8.20 \pm 2.01	<0.001
RAVLT recognition	3.54 \pm 5.09	11.73 \pm 2.49	<0.001
Visuospatial skill			
Rey complex figure test	10.71 \pm 4.51	15.00 \pm 1.41	0.004
Behavioral features			
FBI total score	31.62 \pm 11.02	1.57 \pm 3.04	<0.001
FBI disinhibition score	13.57 \pm 5.62	0.48 \pm 0.87	<0.001
FBI apathy score	18.05 \pm 6.09	1.10 \pm 2.23	<0.001

bvFTD, behavioral variant frontotemporal dementia; MMSE, Mini-Mental State Examination; FTLD-CDR, Frontotemporal Lobar Degeneration-Clinical Dementia Rating scale; TMT, Trail Making Test; RAVLT, Rey's Auditory-Verbal Learning Test; FBI, Frontal Behavior Inventory

Dichotomous data are represented as absolute values. Group differences were tested using Student's t -test for continuous data and chi-square and Fisher's exact tests for categorical data. For the bvFTD group, partial Pearson's correlations between GM volume, ^{18}F -FDG SUVR of the ACC, and neuropsychiatric assessment scores were calculated. Statistical significance was set at $p < 0.05$.

RESULTS

Participant demographics and neuropsychological performance

Detailed demographic data and neuropsychological performance are summarized in Table 1. Twenty-one bvFTD patients were recruited, which included 10 men and 11 women. There were no group differences in age (61.00 \pm 11.32 versus 57.95 \pm 8.00, $p = 0.320$), sex (10/11 versus 11/10, $p = 0.758$), or years of education (10.76 \pm 4.94 versus 11.62 \pm 3.14, $p = 0.506$). Behavior problems were prominent in bvFTD patients, which was shown by an FBI score of 31.62 \pm 11.02, an apathy subscale score of 18.05 \pm 6.09, and a disinhibition subscale score of 13.57 \pm 5.62. Patients had poor neuropsychological performance for general mental status,

shown by a mean MMSE score of < 24 and an average FTLD-CDR score of 11.67 \pm 4.90. Moreover, executive functions were found impaired in patients: TMT-A completion time 108.07 \pm 37.47 s, TMT-B completion time 221.57 \pm 87.05 s, Stroop I completion time 85.44 \pm 53.43 s, and Stroop II completion time 135.00 \pm 128.30 s.

GM atrophy and hypometabolism of the ACC

The atrophy and hypometabolism pattern of the ACC in the bvFTD group compared with the healthy control group is shown in Fig. 1A and 1B. GM volume and SUVR of the bilateral ACC were significantly lower in patients compared with healthy controls (FWE corrected, $p < 0.05$). Spatial coordinates and peak values of brain areas of GM atrophy and hypometabolism in bvFTD patients were shown in Table 2.

Correlation analysis

Pearson's correlation analysis of mean GM volume and SUVR values of the ACC and neuropsychological scale scores showed no significant correlations between ACC GM volume and executive function ($p > 0.05$) or behavioral deficit ($p > 0.05$). As shown

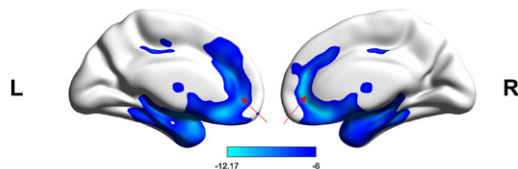
Table 2

Spatial coordinates and peak values of brain areas showing significant GM Volume and metabolism differences between bvFTD patients and healthy controls

Region	Anatomical location	Side	Cluster Size	MNI coordinate	T value
GM atrophy					
Anterior cingulate	Anterior cingulum	R	1659	9 45 18	-12.14
	Anterior cingulum	L	2352	-4 35 13	-12.30
Frontal lobe	Inferior orbital frontal	L	2339	-31.5 31.5 -7.5	-9.32
	Medial orbital frontal	R	1096	11 39 -9	-12.17
	Middle orbital frontal	R	985	30 52.5 -4.5	-9.08
Temporal lobe	Middle temporal	L	4642	-46.5 -6 -13.5	-8.38
	Middle temporal	R	4112	55 -33 -2	-8.77
	Superior temporal pole	L	1357	-39 15 20	-8.27
Limbic lobe	Hippocampus	L	1860	-32 -12 -14	-12.10
	Insula	R	3640	39 6 2	-9.07
	Insula	L	2649	-30 -9 13.5	-8.97
Subcortical	Caudate	L	1492	-12 11 10	-8.99
	Putamen	R	1139	28 5 3	-9.54
GM hypometabolism					
Anterior cingulate	Anterior cingulum	L	1135	-4 35 13	-9.24
	Anterior cingulum	R	1040	2 20 26	-11.82
Frontal lobe	Middle frontal	L	2644	-34 33 36	-8.23
	Superior medial frontal	L	2461	-5 50 31	-11.83
	Superior frontal	R	1763	16 70 10	-11.11
	Superior medial frontal	R	1623	38 34 35	-8.35
Temporal lobe	Superior temporal pole	L	2252	-39 15 -20	-9.07
Limbic lobe	Insula	R	711	46 18 -10	-8.64
Subcortical	Thalamus	R	736	6 -20 10	-8.90
	Putamen	L	519	-25 4 3	-9.26
	Caudate	L	710	-12 11 10	-10.43

MNI, Montreal Neurological Institute. All regions survived the most stringent whole-brain FWE correction for multiple comparisons at $p < 0.05$ (minimum cluster size 100 voxels).

A GM volume bvFTD<NC



B FDG-SUVR bvFTD<NC

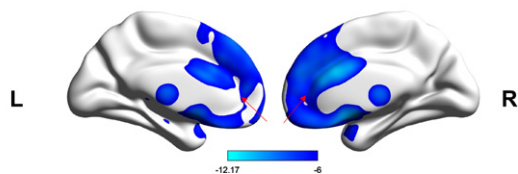


Fig. 1. GM atrophy and hypometabolism profiles. A) Regions of GM loss and B) hypometabolism in bvFTD patients. ($p < 0.05$, FWE-corrected, minimum cluster size 100 voxels). T values are color-coded from cyan to blue. The red arrow indicates the location of ACC.

in Fig. 2, SUVR of the ACC was significantly correlated with the FBI total score (left $r = -0.85$, right $r = -0.85$, $p < 0.0001$), disinhibition subscale score (left $r = -0.72$, $p = 0.002$; right $r = -0.75$, $p < 0.0001$), and apathy subscale score (left $r = -0.87$, right $r = -0.85$,

$p < 0.0001$). No significant correlations were found between SUVR of the ACC and scales targeting executive function ($p > 0.05$). The detailed r -values were shown in Table 3.

DISCUSSION

For the first time, our study explored the specific role the ACC plays in the severity of behavioral disturbances and executive dysfunction in bvFTD patients, using hybrid PET/MRI imaging. A strong significant correlation was found between SUVR of the ACC and behavioral disturbance. The findings provide *in vivo* evidence for the contributions of the ACC in the development of bvFTD disease dysregulation and indicate that ^{18}F -FDG PET can offer a sensitive biomarker that reflects the severity of the disease.

Regional variability between hypometabolism and atrophy had been revealed. The voxel-wise analysis showed predominant ACC involvement in both the atrophy and hypometabolism patterns, however, hypometabolism was observed more predominant than atrophy. This phenomenon can also be observed

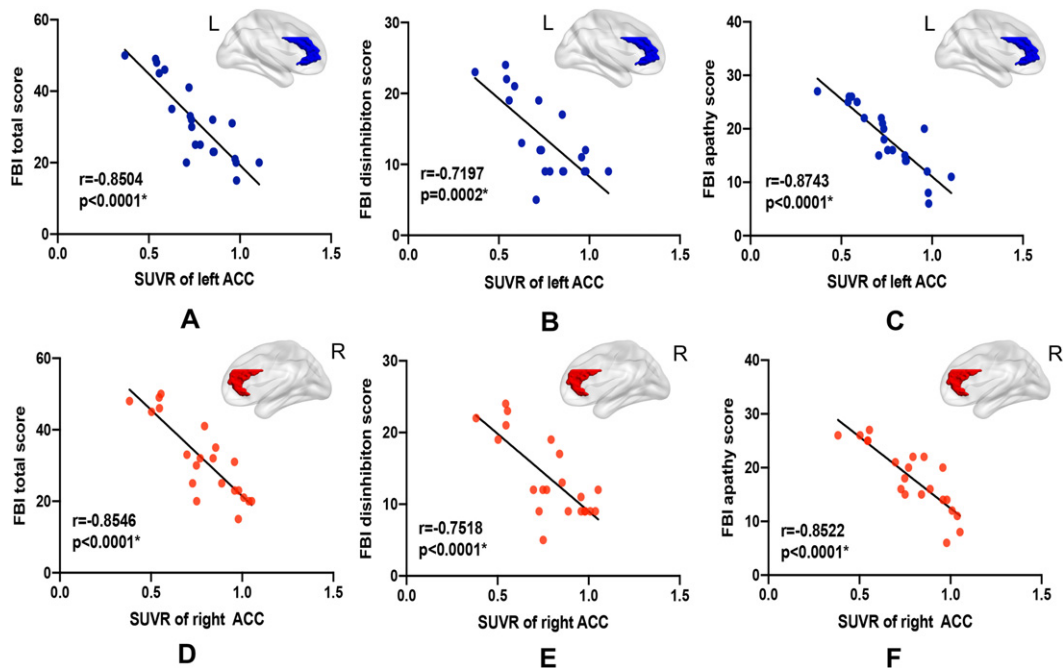


Fig. 2. Scatter plots of significant correlations in the bvFTD group. Strong correlations were found between SUVR of the left (A-C) and right ACC (D-F) and FBI total score, FBI disinhibition subscale score, as well as FBI apathy subscale score.

Table 3
Results of the partial Pearson's correlation analysis

	TMT-A	TMT-B	Stroop I	Stroop II	FBI Total	FBI Apathy	FBI Disinhibition
GM volume							
RACC	0.0253	-0.2167	-0.5115	-0.4185	-0.1987	-0.2677	-0.0975
LACC	-0.1826	-0.4360	-0.4648	-0.3992	-0.2116	-0.3301	-0.0542
SUVR							
RACC	0.2330	0.0576	0.5891	0.6436	-0.8546*	-0.7518*	-0.8522*
LACC	-0.0380	-0.1532	0.5256	0.5704	-0.8504*	-0.7197*	-0.8743*

GM, gray matter; RACC, right anterior cingulum; LACC, left anterior cingulum; SUVR, standardized uptake value rate; TMT, Trail Making Test; FBI, Frontal Behavior Inventory *of statistical significance ($p < 0.05$).

in other bvFTD hybrid PET/MRI studies [12, 32]. This may be because ^{18}F -FDG PET is more associated with functional changes, hypometabolism is not only related to GM atrophy but also proteinaceous aggregation and disposition (e.g., tau, TAR DNA-binding protein 43, or FUS protein), which may cause genuine and more widespread functional alterations than atrophy does [36]. Another study targeting Alcoholic Korsakoff's Syndrome suggests that the hypometabolism may not only be due to local neural damage but also reflect synaptic dysfunction remote from morphological damage in other components of the functional circuit [37]. In our study, we found hemispheric asymmetry that atrophy more frequently lateralized to the left and hypometabolism to the right,

which has some discrepancy with the previous study [38, 39]. This may be due to the limited sample size with diverse disease severity and different statistical thresholds settings, which need further validation in a large cohort study.

The correlation analysis showed that SUVR of the bilateral ACC was strongly associated with behavioral disturbance. However, GM volume was not found any significant correlation. This may be attributed to the distinct pathophysiological representations of brain atrophy and cerebral hypometabolism, whereby atrophy indicates neuronal loss or reduction in the number of connections between neurons and a functional compensatory phenomenon may appear, whereas ^{18}F -FDG PET is a

type of molecular imaging that is based on astrocyte/neuronal glucose consumption, and ^{18}F -FDG uptake is considered a direct indicator of synaptic dysfunction [40, 41]. Hypometabolism reflects genuine functional damage because glucose is vital for the brain to participate in various critical functions, such as adenosine triphosphate production, oxidative stress management, and synthesis of neurotransmitters, neuromodulators, and structural components [41]. Coupling between function network and cognition was found stronger in presymptomatic carriers, also provide evidence that the independent and synergistic effects exist in different image modalities [42].

Some patients with bvFTD primarily present with negative symptoms, which include apathy, inertia, and loss of volition, whereas other patients predominantly present with positive symptoms, such as impulsiveness, disinhibition, and hyperactivity [1, 2, 43]. These two profiles have been termed “apathetic” and “disinhibited,” and may overlap as the disease progresses [44]. In our study, behavioral deficits in bvFTD patients were assessed using the FBI, which is a scale specifically designed for FTD to accurately capture the severity of apathy and disinhibition, including symptoms of restlessness, irritability, and aggression as well as those related to aphasia and comprehension deficits; these provided greater sensitivity for measurements of symptoms of FTD [43, 45].

We found that disinhibition was associated with the bilateral ACC. Hypometabolism of the ACC is thought to impact the projection and communication of the orbitofrontal-subcortical circuit, for which its dysfunction is characterized by disinhibition symptoms, such as irritability and impulsivity [46]. In addition, other brain regions within this circuit, such as the medial prefrontal cortex, insula, and basal ganglia, were also impaired in the patients in our study. Apathy is a debilitating syndrome that is associated with numerous neurological disorders, and ACC is an anatomical correlate [47]. This is consistent with the *in vivo* findings of the bvFTD patients in our study. The ACC is a hub node in the ACC-subcortical circuit, which is associated with apathy [48]. Other brain areas in the ACC-subcortical circuit also showed abnormalities in our patients, such as the insula and subcortical structures, which indicated that the circuit is involved in the development of apathy in bvFTD. This requires confirmation in a further functional MRI study in a larger cohort.

We found no significant correlation between executive function and ACC both in GM volume and

SUVR, which may be due to the limited sample size and the incomprehensive assessments of executive function. However, other studies employing various methods, such as lesions, electrical stimulation, microelectrode recording, and PET, have defined ACC as a region involved in the modulation of attention in executive functions, and impairment of the ACC has been shown to result in a host of symptoms, which include inattention and executive dysfunction [22]. Fronto-striatal circuits, especially those involving the ACC, have also been shown to be related to executive functions [48, 49]. Therefore, further research in a larger bvFTD patient cohort focused on the involvement of the ACC in executive functions using assessment tools, such as the imitation sorting task, tower building, and reverse categorization, is needed to confirm whether the ACC is associated with executive function in bvFTD patients.

Moreover, ACC had been demonstrated to participate in various functions in many other studies targeting bvFTD. The integrity of gray matter areas and white matter tracts of the subcortical Papez circuit region including ACC affecting the degree of amnesia [16]. A study found that right pACC neurodegeneration played an important role in both the physiological and behavioral aspects of self-consciousness emotion in bvFTD [24]. In addition, abnormal connectivity of ACC had been found causing integrity attenuation of salience network then lead to resting parasympathetic and sympathetic disruption [25]. All these findings suggest that ACC is quite an essential construct of bvFTD; however, with limited conditions, we did not perform these functional validations. Further studies are needed to validate, refine, and extend the comprehensive function of ACC.

Our study has several limitations. First, the sample was relatively small because of the challenges to enroll a large group of patients who have undergone both metabolic and structural neuroimaging. Second, a longitudinal study is warranted to observe ACC atrophy and hypometabolism and understand how they correspond to symptom progression. This will allow a deeper understanding of the ACC's role in behavioral disturbances during the natural disease course. Finally, although our bvFTD phenotypes were defined using stringent diagnostic criteria, we did not perform pathological verification. Therefore, our findings may differ slightly from those of other studies, which highlights the heterogeneity of the disease again.

CONCLUSION

Our preliminary study provided *in vivo* evidence that the ACC alteration was strongly correlated with the core clinical symptoms of behavioral deficits, which demonstrates the essential role of the ACC in bvFTD disease development. Furthermore, these findings may have important implications for the use of ¹⁸F-FDG PET to establish a biomarker for the assessment of behavior alteration severity.

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All listed authors agree with the submission and the final manuscript has been approved by all authors. The authors wish to acknowledge Kun Yang and Bin-Bin Nie for dedicating their time helping us in the methods.

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