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Original Article

Diffusion tensor imaging of patients with behavioral variant frontotemporal dementia: a controlled study

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Abstract: Background: This study aimed to investigate the clinically important early symptoms of behavioral variant frontotemporal dementia (bvFTD) and the characteristics of bvFTD in structural imaging and to explore the value of diffusion tensor magnetic resonance imaging (MRI-DTI) in the early diagnosis of bvFTD. Material and Methods: Siemens 3T Verio MRI with echoplanar imaging (EPI) was employed in 8 patients with suspected bvFTD diagnosed according to the FTDC diagnostic consensus, 8 matched Alzheimer's disease (AD) patients and 8 healthy controls, and 3DT1 and DWI images were collected. Results: DTI showed the bilateral thalamic radiation, cingulate gyrus and hippocampus had significantly reduced FA ($P<0.001$). After FEW correction, FA in these regions was comparable between bvFTD patients and AD patients. The MD of the anterior frontal lobe and temporal lobe increased significantly in bvFTD patients, suggesting more severe white matter damage. Analysis of lateralization effect of FA showed lateralization distribution in the left thalamic radiation, inferior longitudinal fasciculus and cingulate gyrus in bvFTD patients as compared to healthy controls. Conclusion: MRI-DTI shows evident white matter lesions in bvFTD patients, and the injury to white matter at left thalamic radiation, left cingulate gyrus, forceps minor, left fasciculus occipitofrontalis inferior, right inferior longitudinal fasciculus and left uncinate fasciculus deteriorates. Moreover, the asymmetrical damage to the left thalamic radiation, left inferior longitudinal fasciculus and left cingulated is helpful for the early differential diagnosis.

Keywords: Diffusion tensor imaging, frontotemporal lobar degeneration, dementia

Introduction

Behavioural variant frontotemporal dementia (bvFTD) is a common type of frontotemporal lobar degeneration (FTLD). In USA, the prevalence of FTLD is about 20 cases per 100000 people younger than 65 years [1], which is about half of the prevalence of Alzheimer's disease (AD) in the same age group [2-4]. FTLD is frequently found in patients aged 40-65 years and accounts for 12-22% of pre-senile dementia (<65 years) [2, 5]. The clinical manifestations of bvFTD include loss of insight, affective blunting, impairment of interpersonal communication, compromised social competence and insidious onset, which are five core symptoms [6]. Although bvFTD patients have behavioral features, the early diagnosis of bvFTD is still difficult.

Typical bvFTD is progressive. However, in some patients meeting the diagnostic criteria for bvFTD, progression was not observed during the follow up, suggesting a "benign" course [7]. MRI of these patients fails to show atrophy of the frontal and temporal lobes. Currently, imaging examination is still a major tool used for the early diagnosis and the determination of prognosis of bvFTD. The imaging examinations of bvFTD include MRI, functional MRI, PET and others [8-12]. Structural imaging techniques have been mature and can be used to directly observe the location and severity of brain atrophy, for voxel-based morphometery (VBM) and for quantification [8, 13, 14].

Imaging and pathological studies have confirmed that mesial/orbitofrontal cortex and anterior insular cortex [15-17] are the regions of

grey matters closely related to the pathogenesis of bvFTD. Seeley et al. found these regions were involved in patients with very early bvFTD [17]. Recent study also reveals that the white matters around these regions are also associated with bvFTD, and of great importance, their changes occur earlier. Hornberger et al. found that the behavioral disinhibition was related to the orbitofrontal cortex, anterior temporal lobe, MPFC and white matter neural correlates [18]. Recent pathological study also confirms that white matter damage is a major feature of FTLD, frontal cortex is rich in connecting fibers, and a large amount of axons in the frontal cortex connect with other brain regions [9]. Diffusion tensor imaging (DTI) is a non-invasive imaging technique. Whitwell et al. investigated bvFTD with DTI and found that the mean diffusivity (MD) of grey matter (GM) increased, suggesting that cellular structure is damaged. They also noted that white matter tracts connecting with these GM structures were also injured [19]. Zhang et al. found the fractional anisotropy (FA) of white matter in the anterior brain regions reduced as compared to AD patients and healthy controls, suggesting that the white matter injury is more severe in FTD patients although there is also white matter injury in both AD patients and FTD patients [20]. Several studies on DTI have indicated that abnormalities in white matter tracts connecting with the frontal lobe or crossing the temporal lobe are more frequently found in bvFTD patients, which is helpful for the early differential diagnosis of bvFTD. In this study, patients with early bvFTD, matched AD patients and healthy controls were recruited to investigate the roles of DTI in the diagnosis and differential diagnosis of bvFTD.

Subjects and methods

Subjects

Patients: Patients (n=8) diagnosed with probable bvFTD and receiving neuropsychological tests and MRI-DTI were recruited from the Shanghai Mental Health Center. Inclusion criteria: Informed consent was obtained and patients were willing to receive information collection, MRI and neuropsychological tests; patients were diagnosed with probable bvFTD according to the diagnostic criteria for bvFTD of International behavioural variant FTD criteria consortium [21]; there were no major and unstable physical illnesses; there were no central nervous system diseases including cerebrovascular disease and Parkinson's disease. Exclusion criteria: There were contradictions to MRI (such as presence of metal implants including cardiac pacemaker); there were severe physical illnesses.

AD patients: Eight patients with AD receiving MRI-DTI were recruited from the Shanghai Mental Health Center. Patients were diagnosed with probable AD according to the diagnostic criteria of National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [22]. These patients were matched with bvFTD patients in the age, gender, education level, score of mini mental state examination (MMSE) and score of clinical dementia rating (CDR), and also cooperated with MRI and neuropsychological tests.

Healthy controls (HC): Eight healthy controls also recruited from the Shanghai Mental Health Center and received MRI-DTI. They matched with bvFTD patients in age, gender and education level. Clinical examinations and scoring with MMSE failed to show cognition impairment and they cooperated with MRI.

Ethics

This was a parallel, controlled study which was approved by the Ethics Committee of Shanghai Mental Health Center.

Clinical information

General information was collected, and following information of bvFTD patients and AD patients was recorded: Number in our study, contact, name, gender, age, occupation, marriage status, education level, family history, past medical history, and personal history, age of onset, disease duration, incentives and diagnosis, and these characteristics were recorded in a specialized form. For healthy controls, following information was recorded: Number in our study, name, gender, occupation, marriage status and past medical history. The medical history was recorded by an experienced physician who mainly focused on the behavioral symptoms and age of onset. Scoring with MMSE, ADL and CDR was performed by qualified assessors.

Table 1. Demographics of bvFTD patients, AD patients and healthy controls

	bvFTD	AD	HC	Statistic	*P*
n	8	8	8		
Gender (M/F)	5/3	4/4	5/3	1.018*	0.601
Age	52.6±16.6	63.2±4.5	52.4±5.9	3.017**	0.069
Education	11.7±3.4	11±2.9	10.3±1.6	0.621**	0.546
MMSE	20.9±3.9	20.2±5.1	29.7±0.7	0.430#	0.522
ADL	27.1±8.9	24±4.5	15.6±1.9	0469#	0.504
CDR	2.0±0.8	1.3±0.6	0.0±0.16	2.131#	0.165

Notes: bvFTD: Behavioral variant frontotemporal dementia; AD: Alzheimer's disease; HC: healthy controls. *Chi square test, χ^2; **One way analysis of variance among three groups, F; #One way analysis of variance between bvFTD patients and AD patients, F.

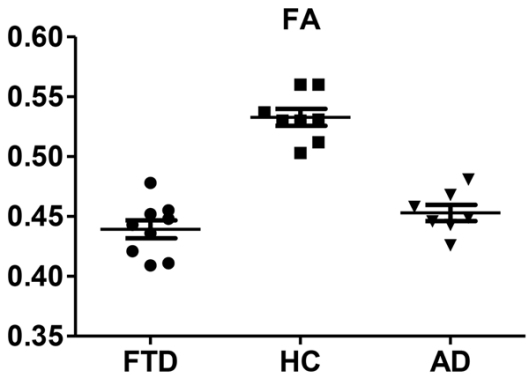

Figure 1. Massive white matter with significantly reduced FA in bvFTD patients as compared to HC. FA: Fractional Anisotropy; FTD: Behavioral variant frontotemporal dementia; AD: Alzheimer's disease; HC: healthy controls.

MRI Acquisition and preprocessing

Sagittal 3DT1 sequences were acquired with the matrix of 256×256, 192 slices, Plane resolution of 1×1 mm^2, slice thickness of 1 mm, TR of 2300 ms, TE of 2.96 ms, TI of 900 ms and flip angle of 9°. DWI (diffusion weighted imaging, DWI) images were obtained with Siemens 3T Verio (Siemens, Erlangen, Germany) using EPI sequence with time repetition (TR)=7600 ms, time echo (TE)=97 ms, voxel size=2.3 mm×2.3 mm×2.3 mm, FoV=230 mm, matrix size=122×122 and 55 contiguous slices in the axial orientation. The protocol lasted 9 minutes including 64 gradient directions with b=1000 s/mm^2, and 1 gradient direction with b=0.

Raw DWI images were preprocessed using FDT (FMRIB's Diffusion Toolbox, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT). DWI images were first corrected for eddy currents using the Linear Image Registration Tool (FLIRT) in FSL 5.0.4. Then binary tensor masks for each individual were generated using BET. With eddy-corrected DWI images and tensor masks, the diffusion tensor was estimated for each voxel using probability tractography algorithm by the dtifit module [23]. The scalar FA and MD images were calculated for the following analysis.

Tract-based spatial statistics were used to perform the statistical analysis [24]. Each FA image was aligned into Montreal Neurological Institute (MNI) 152 standard space and generated the mean FA image. The mean FA skeleton was obtained with an FA threshold of 0.15. Then all the individual's FA images were projected onto the mean FA tract skeleton. MD images were similarly processed and also projected onto the mean FA tract skeleton using the tbss_non_FA module. Finally both skeletonized FA and MD images were obtained for each subject for the statistical analysis.

Statistical analysis

Permutation tests were used for group comparisons for each voxel on FA and MD measurements with the randomize tool in FSL (steps of random permutation: 5000). Multiple comparisons across space were corrected by family wise error (FWE) and the threshold for significance was set to $P<0.01$. Statistical analysis of demographic data was performed with SPSS version 11.5. Data for descriptive statistical analysis are expressed as mean ± standard deviation or rate (constituent ratio). Quantitative data were compared with one way analysis of variance for means among groups or independent sample t test between two groups when normal distribution was observed. Categorical data were compared with Chi square test or Fisher exact test.

Results

The demographics of bvFTD patients, AD patients and healthy controls are shown in **Table 1**. Results showed there were no marked differences in the gender, age and education level among three groups. In addition, significant dif-

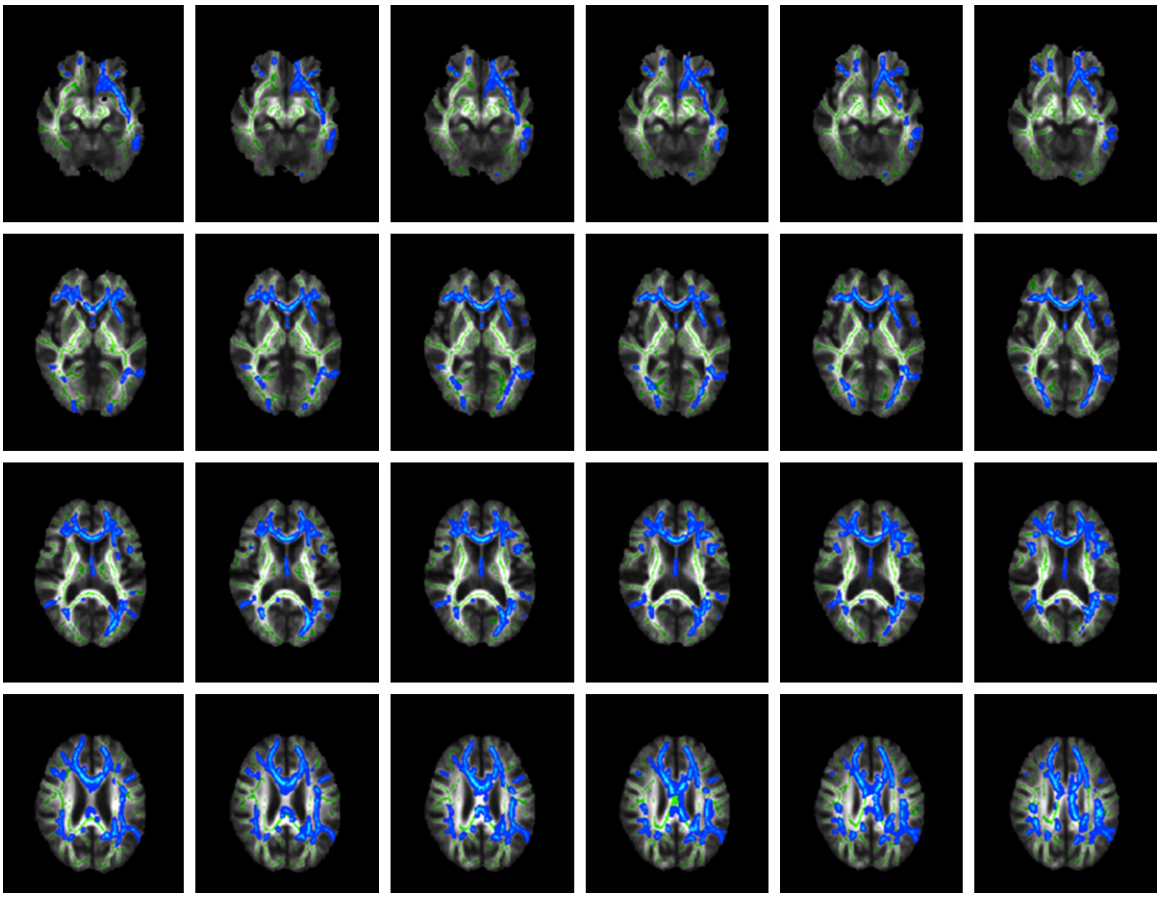

Figure 2. Massive white matter showed significantly decreased FA in bvFTD patients as compared to healthy controls (Mirror image, The right side is actually the left, FWE corrected, $P<0.01$).

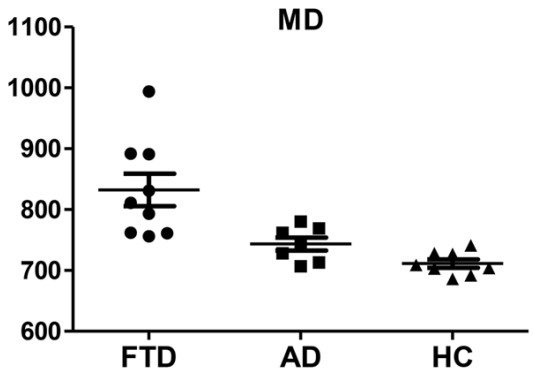

Figure 3. Significantly increased MD in bvFTD patients as compared to AD patients. MD: mean diffusity; FTD: Behavioral variant frontotemporal dementia; AD: Alzheimer's disease; HC: Healthy controls.

ferences were not observed in the scores of MMSE, ADL and CDR between bvFTD patients and AD patients, and the cognition score, severity of dementia and impairment of daily activity were also comparable between them (P>0.05) (**Table 1**).

FA reductions in bvFTD patients

Significant reductions of FA were observed in bvFTD patients as compared to HCs within extensive clusters including frontal lobe, temporal lobe and corpus callosum (P<0.01). The mean FA values were calculated within the clusters with significant between-group differences as shown in **Figure 1**. The mean FA was 0.44±0.02 in bvFTD patients, 0.54±0.02 in HC and 0.45±0.02 in AD patients. The mean FA values were comparable between bvFTD and AD patients, but lower than HCs.

The white matter (WM) tracts with reduced FA in bvFTD patients were localized using the JHU White-Matter Tractography Atlas. The alterations of WM tracts occurred in the anterior thalamic radiation, cingulate gyrus, hippocampus, forceps major, forceps minor, bilateral inferior fronto-occipital fasciculus, bilateral inferior longitudinal fasciculus, bilateral superior longitudinal fasciculus and uncinate fasciculus (**Figure 2**).

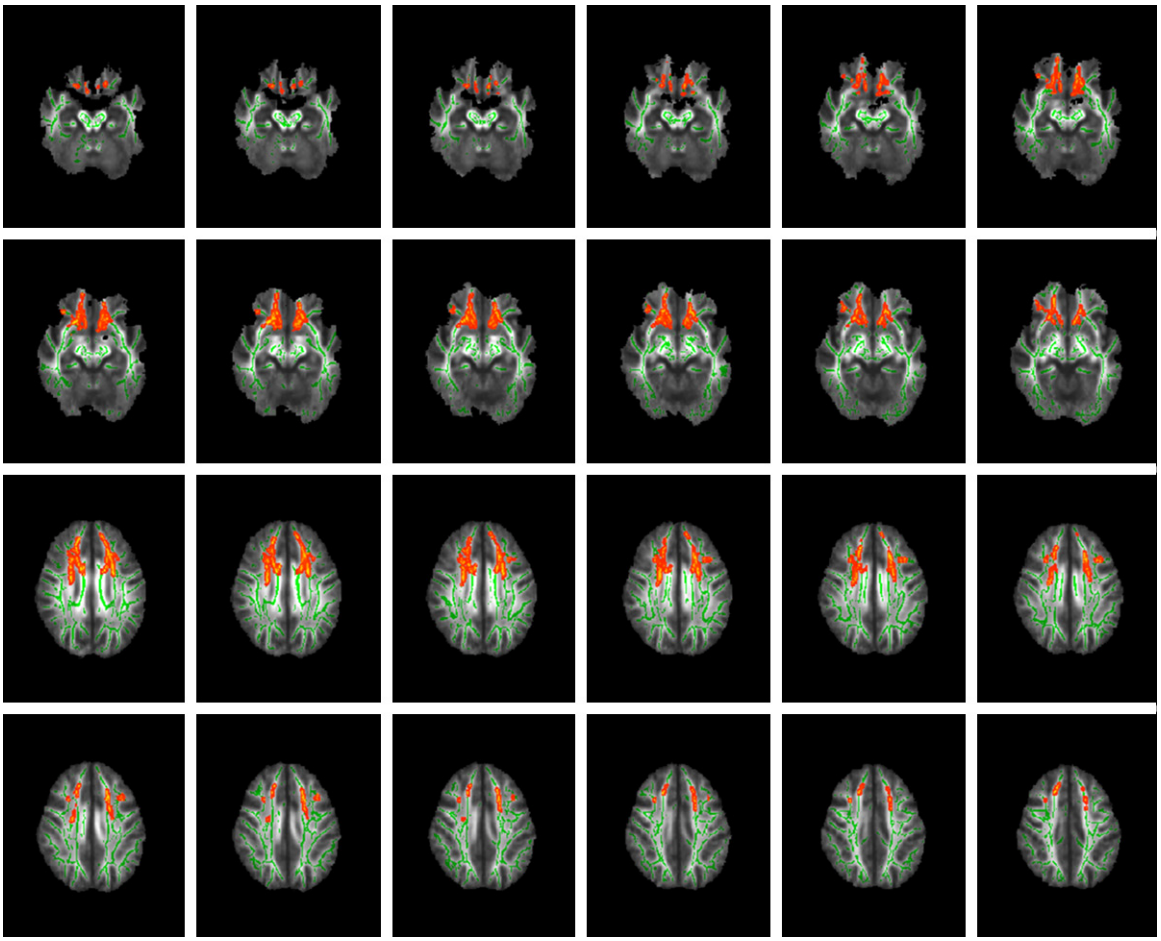

Figure 4. White matter with increased MD in bvFTD patients as compared to AD patients (Mirror images, The right side is actually the left, FWE correction, $P<0.05$). Note: It displays brain sections with increased MD; red: regions with increased MD; red area: size of voxel with increased MD.

Increased MD in bvFTD patients

There were significant differences on MD between bvFTD and AD patients (P<0.01). MD in bvFTD patients was significantly higher than in AD patients after FWE correction. Mean MD values were calculated within the clusters with significant difference. MD was 832±80 10^{-6} mm^2/s in bvFTD patients, 743±28 10^{-6} mm^2/s in AD patients and 711±19 10^{-6} mm^2/s in HC as shown in **Figure 3**.

After matching with JHU White-Matter Tractography Atlas template and localization, the WM tracts that had increased MD were almost consistent with those with reduced FA and included right anterior thalamic radiation, bilateral cingulate gyrus, forceps minor, right inferior fronto-occipital fasciculus, bilateral uncinate fasciculus and bilateral superior longitudinal fasciculus (**Figure 4**).

Hemisphere asymmetry of FA in bvFTD patients

According to the FA distribution in both hemispheres of bvFTD patients, there was hemisphere asymmetry in FA of some regions between two hemispheres. Thus, we further calculated the lateralization effect, but no significant difference was observed between bvFTD patients and AD patients. After multiple comparison FWE correction and matching with standard template, significant difference was only observed in following regions: anterior thalamic radiation, left inferior longitudinal fasciculus and left cingulate gyrus (**Figure 5**).

Discussion

Frontotemporal dementia has been a focus in recent studies. Pathological studies indicate that white matter damage is one of major fea-

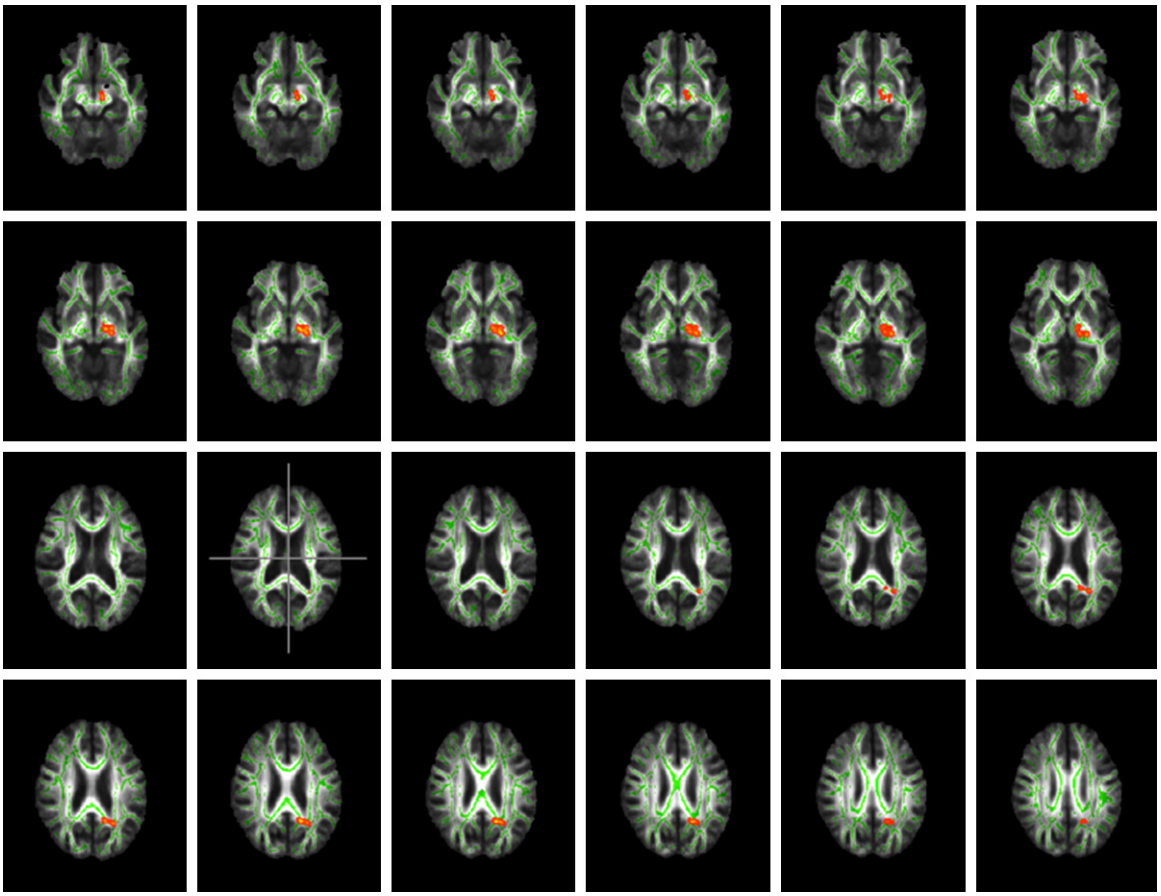

Figure 5. Dominant regions with reduced FA value in the left hemeisphere of bvFTD patients as compared with HC (Mirror image, The right side is actually the left, uncorrected, $P<0.05$). Note: It displays brain sections with reduced FA; Red: regions with reduced FA; red area: size of voxel with reduced FA.

tures of FTLD [9, 24, 25]. In addition, there are a large amount of connection fibers in the frontal cortex and a variety of axons which connect with other brain regions. The pathology of FTLD is characterized by the formation of inclusions containing tau, TDP-43 or FUS in the neurons and glial cells, demyelination and axonal damage of the white matter and excess gliosis. Currently, the knowledge on the relationship between atrophy regions which is valuable for the diagnosis of FTLD and microscopic dispersion is still limited. As compared to morphological changes, the change in diffusion tensor may reflect earlier white matter damage in FTLD.

Impaired integrity of white matter in bvFTD patients

In the present study, TBSS with FWE (family wise error) correction was employed for analysis, and results showed FA in bvFTD patients reduced significantly, and reduced FA was widely distributed in the white matter including important regions such as frontal lobe, temporal lobe and corpus callosum. Comparison of MD between bvFTD patients and HC indicated that MD in bvFTD patients increased markedly as compared to HC and increased MD was mainly found in the frontal lobe, temporal lobe and corpus callosum. The regions with increased MD showed similar distribution to those with reduced FA. In respect of anatomy, uncinate fascicle connects with frontal lobe and amygdale, mainly the motor speech area and orbital gyrus in the frontal lobe and orbital gyrus in the temporal lobe; superior longitudinal fasciculus is the longest tract of the connection fibers and it originates from the prefrontal cortex and ends at the temporal lobe. It also crosses the frontal lobe, parietal lobe, occipital lobe and temporal lobe where it receives fibers from these lobes and projects fibers to these lobes; fasciculus frontooccipitalis origi-

nates from the frontal lobe, is distributed in deep superior longitudinal fasciculus and lateral caudate nucleus close to the central lateral ventricle and ends in the occipital lobe and temporal lobe in a fan form. The damage to these important connection fibers suggests the extensive white matter injury in bvFTD patients as compared to healthy controls, which was consistent with recent findings [10, 19, 20, 24].

Although it is generally accepted that bvFTD patients usually present damages to the anterior temporal lobe and frontal lobe, the lateral parietal and central cortex is also significantly involved at late stage of bvFTD. Arcuate fascicle is an important structure bridging the anterior and posterior language area. There is evidence showing that arcuate fascicle is also damaged in bvFTD patients, suggesting that arcuate fascicle injury may be also related to the abnormal behaviors. The FA of anterior superior longitudinal fasciculus in the left hemosphere increased, this region connects with inferior frontal gyrus and thus may receive the projecting fibers from the arcuate fascicle. Whether this type of white matter damage is unique in bvFTD patients and the characteristics of white matter damage in other diseases such as AD and MCI early stage of AD are still unclear. If the white matter damage is different between AD patients and bvFTD patients, it is helpful for the differential diagnosis of bvFTD.

Difference in the white matter integrity between bvFTD patients and AD patients

Our results showed the FA in bvFTD patients after FWE correction was comparable to matched AD patients, but it tended to be different before correction at $P<0.01$. Analysis of MD showed significant difference between two groups. After FWE correction, the MD in bvFTD patients was significantly higher than in AD patients at $P<0.01$. Following matching with template, the tracts with increased MD were similar to those with reduced FA in the distribution and included left cingulate gyrus, left superior longitudinal fasciculus which was in accordance with recent findings. Zhang et al. [20] found the FA of frontal and temporal lobes (including anterior corpus callosum, bilateral anterior and descending cingulate gyrus and uncinategyrus) reduced in bvFTD patients. Studies on the basis of voxel-by-voxel analysis showed the FA reduced at extensive regions including frontal, temporal and parietal lobes, but occipital white matter was not involved. However, AD patients showed FA reduction in bilateral descending cingulate gyrus, left posterior and anterior cingulate gyrus and left uncinategyrus. The FA reduction in the frontal lobe of bvFTD patients is more obvious, and the reduction in FA of any brain region in AD patients is still lower than that in bvFTD patients, suggesting that the white matter damage in bvFTD patients is more severe than in AD patients although the severity of dementia is similar. In addition, the white matter integrity in AD patients is near to normal. These findings indicate that, among patients with similar MMSE scores and severity of cognition impairment, bvFTD patients tend to present more obvious white matter injury. If the sample size is large enough, there might be significant difference in FA between them. The white matter integrity is affected by multiple factors including cerebrovascular diseases and age. In the present study, cerebrovascular diseases were excluded, and included patients were relatively young. Structural imaging examinations failed to show cerebrovascular diseases which may be unlikely to bias our results.

As compared to bvFTD patients, AD patients did not display significant reduction in FA at any region. In bvFTD patients, the frontal lobe and anterior temporal lobe were damaged, but imaging examinations showed the posterior cortex was damaged in AD patients without significant reduction in FA. This might be ascribed to the different patterns of white matter and grey matter involvements during the progression of AD. Especially in early stage of AD, the grey matter is mainly involved, but in early bvFTD, both are involved, or the injury to white matter is more severe. In addition, the included patients with AD were relatively young, and they might present similar FA reduction with the progression of AD as in bvFTD patients. The clinical significance of change in FA is unclear in AD, and the change in white matter might be secondary to grey matter injury. Generally, Aβ is deposited in neurons of AD patients, and subsequently or almost at the same time tau pathology occurs, resulting in neuron degeneration (including lesions of white matter tracts related to axonal damage). Braak et al. [26] hypothesized that, during the neurodevelopmental, the myelin formation occurred later as compared to the neuron development, thus only a small amount of oligodendrocytes in the cortex provide nutrients to a large amount of

axons. Thus, axons in these regions is susceptible to pathological processes including oxidative stress [26, 27]. Salat et al. [28] found, in the early stage of AD, some patients did not present obvious grey matter atrophy as compared to the hippocampal atrophy, but there was still diffusion change in the white matter around the hippocampus including the FA reduction of ventromedial prefrontal lobe and praecuneus. The structures connecting with the middle temporal lobe are closely related to the memory, indicating that the degradation of white matter around the hippocampus is likely an imaging marker of early AD. Our study did not reveal more severe damage to the white matter around the hippocampus and more obvious reduction in FA. These findings suggest that bvFTD patients may also present damages to the white matter in these regions, which is consistent with the hippocampal atrophy in some bvFTD patients [29, 30].

In present study, only white matter integrity was emphasized in DTI, and MD reduced in the grey matter of regions with brain atrophy. These also indicate the damage to the residual brain cells, and the white matter tracts connecting with these grey matters are also damaged. bvFTD patients presented MD increase in extensive grey matters, and bilateral temporal lobe, frontal lobe and parietal cortex were susceptible to the involvement. At late stage, the middle parietal cortex may be also significantly involved. In the same patient, the regions with MD increase in grey matters were highly consistent with those with brain atrophy. The close spatial relationship between brain atrophy and abnormal diffusion indicates the abnormality in residual tissues. Our study also showed the MD elevation in anterior hemisphere was more obvious in bvFTD patients than in AD patients, suggesting that regional MD increase, especially in the anterior white matters (such as frontal lobe), is helpful for the diagnosis and differential diagnosis of bvFTD with higher sensitivity as compared to FA.

Laterality of white matter damage in bvFTD patients

The distribution of FA in both hemispheres showed its asymmetry. We further analyzed the lateralization effects, and results showed FA was dominant in left hemisphere in HC group, but there was no significant difference in bvFTD patients and in AD patients. The regions with significant difference in FA between bvFTD patients and HC were matched with standard template, and results showed significant difference in left thalamus radiation, left inferior longitudinal fasciculus and left cingulate gyrus, suggesting that the damage is more obvious in left white matter of bvFTD patients, but the clinical significance of this asymmetry is required to be further studied. Whitwell et al. [31] employed VBM to analyze the lateralization effects of dorsolateral cortex of frontal lobe, medial prefrontal lobe and orbitofrontal cortex in 80 patients with bvFTD. Results showed symmetry in 65% of patients, evident left atrophy in 20% of patients and obvious right atrophy in remaining 15% of patients. Liu et al. also investigated the lateralization in AD patients with DTI, and they found the white matter around the right hippocampus displayed significant FA reduction, and FA reduction was also observed in the right front dome and left superior longitudinal fasciculus in AD patients [32]. Most of other studies do not report the lateralization of white matter integrity in AD patients.

There were still limitations in the present study. The sample size of this study was still small. Typical bvFTD usually progresses rapidly, and bvFTD patients are often unable to cooperate with imaging examinations and neuropsychological assessment due to apathy and declined executive function. Thus, patient recruitment is difficult. Some studies on bvFTD with high quality often employ pathological support. In the present study, the diagnosis was not confirmed by pathology, and to assure that patients with early bvFTD were recruited and the diagnosis was reliable was difficult. Thus, when the clinical symptoms were suspicious and imaging examinations were unable confirm the diagnosis, patients were excluded from this study, which is a reason for small sample size.

Conclusions

MRI-DTI shows evident white matter lesions in bvFTD patients, and the injury to white matter at left thalamic radiation, left cingulate gyrus, forceps minor, left fasciculus occipitofrontalis inferior, right inferior longitudinal fasciculus and left uncinate fasciculus deteriorates. Moreover, the asymmetrical damage to the left thalamic radiation, left inferior longitudinal fasciculus and left cingulated is helpful for the early differential diagnosis.

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Disclosure of conflict of interest

None.

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