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Regional Differences in White Matter Breakdown Between Frontotemporal Dementia and Early-Onset Alzheimer's Disease¹

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Abstract

Background—White matter abnormalities have been associated with both behavioral variant frontotemporal dementia (bvFTD) and Alzheimer's disease (AD).

Objective—Using MRI diffusion tensor imaging (DTI) measures, we compared white matter integrity between patients with bvFTD and those with early-onset AD and correlated these biomarkers with behavioral symptoms involving emotional blunting.

Methods—We studied 8 bvFTD and 12 AD patients as well as 12 demographically-matched healthy controls (NCs). Using four DTI metrics (fractional anisotropy, axial diffusivity, radial diffusivity, and mean diffusivity), we assessed the frontal lobes (FWM) and genu of the corpus callosum (GWM), which are vulnerable late-myelinating regions, and a contrasting early-myelinating region (splenium of the corpus callosum). The Scale of Emotional Blunting Scale (SEB) was used to assess emotional functioning of the study participants.

Results—Compared to AD patients and NCs, the bvFTD subjects exhibited significantly worse FWM and GWM integrity on all four DTI metrics sensitive to myelin and axonal integrity. In contrast, AD patients showed a numerical trend toward worse splenium of the corpus callosum integrity than bvFTD and NC groups. Significant associations between SEB ratings and GWM DTI measures were demonstrated in the combined bvFTD and AD sample. When examined separately, these relationships remained robust for the bvFTD group but not the AD group.

Conclusions—The regional DTI alterations suggest that FTD and AD are each associated with a characteristic distribution of white matter degradation. White matter breakdown in late-myelinating regions was associated with symptoms of emotional blunting, particularly within the bvFTD group.

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Keywords

Alzheimer's disease; behavioral variant; diffusion tensor imaging; early onset; frontotemporal dementia; magnetic resonance imaging; myelin; white matter

Introduction

Behavioral variant frontotemporal dementia (bvFTD) is a neurodegenerative disease characterized by profound changes in personality and behavior. It is one of the most common dementias affecting a younger population with age at onset typically in the fifties [1]. Neuroanatomically, bvFTD is characterized by marked atrophy of the frontal lobes, particularly in the ventromedial and orbitofrontal cortex [2, 3]. In recent years, an increasing number of studies have demonstrated white matter abnormalities associated with bvFTD. Pathological investigations have documented moderate frontal white matter gliosis with demyelination [4, 5]. Structural magnetic resonance imaging (MRI) studies have shown white matter atrophy in bvFTD [6–9], and studies using diffusion tensor imaging (DTI) markers have reported reduced white matter integrity in this population [10–13]. The convergence of evidence suggests that white matter degeneration may be a direct consequence and a major pathological feature of bvFTD, consistent with histopathological evidence of tau deposition in white matter of bvFTD patients [14].

There is also substantial theoretical and empirical evidence that myelin breakdown may be a direct contributing factor to the pathology of Alzheimer's disease (AD) [15–19] [20], and a number of neuroimaging studies have detected white matter breakdown in both AD and mild cognitive impairment [21–25]. A recent meta-analysis of studies of DTI in patients with AD revealed decreased fractional anisotropy (FA) values in all regions studied except parietal white matter and internal capsule [26].

The heterogeneity in chronology of brain development may underlie the regionally specific pattern of white matter breakdown associated with aging and neurodegeneration [20, 27–31]. Regions that myelinate later in brain development such as the frontal lobes, the temporal lobes, and the genu of the corpus callosum (which connects the prefrontal cortices of the left and right hemispheres) are comprised of smaller axons and the myelin sheaths have fewer myelin lamellae [32]. Therefore, these regions tend to be more vulnerable to breakdown by a variety of brain insults including aging and degenerative brain disorders such as bvFTD and AD [28, 33, 34]. Fiber-tracking analysis of DTI data has also shown that the most prominent age-related deterioration of the white matter is observed in association fibers that connect the regions last to complete myelination in the course of development [27, 35]. In contrast, the splenium of the corpus callosum contains primarily sensory (visual) axons that tend to be fully and heavily myelinated in early childhood [36–38] and are more resistant to the degradation in integrity, even in early stages of neurodegeneration.

MRI measures derived from DTI are a popular method for investigating white matter microstructural changes. DTI measures the rate of diffusion motion of water molecules on a microscopic spatial scale in a multiplicity of directions. Different DTI parameters, such as FA, radial diffusivity (RD), axial diffusivity (AxD), and mean diffusivity (MD), are sensitive to different aspects of white matter microstructure. Restriction in RD is believed to be primarily caused by axonal and myelin membranes making RD potentially sensitive to myelination, while AxD seems to be most sensitive to axonal size and extra-axonal space [39–41]. FA is a composite measure involving both AxD and RD and was developed as a way to capture the directionality of diffusion [42].

In the current study, we compared DTI biomarkers of white matter integrity between bvFTD and AD patients with the following objectives: 1) examine patterns in myelin breakdown to elucidate regional differences in vulnerability to neurodegeneration associated with each disorder; 2) investigate different DTI metrics to uncover the specific biological aspects of white matter that are affected by bvFTD and AD; and 3) examine the relationship between white matter degeneration and socioemotional functioning in these populations. We chose a region of interest (ROI) approach in order to minimize the potential pitfalls associated with whole brain DTI analyses such as non-linear susceptibility-and eddy current-induced anatomic distortions [43, 44]. We hypothesize that patients with bvFTD will demonstrate significantly greater white matter breakdown compared to AD in the late-myelinating regions of frontal white matter (FWM) and genu of the corpus callosum (GWM) but not in the splenium of the corpus callosum (SWM), an early-myelinating association area. Finally, white matter breakdown in late-myelinating regions will be associated with expression of emotional and behavioral symptoms.

Material and Methods

Participants

A total of 23 patients (11 with bvFTD and 12 with early-onset AD), ranging in age from 45 to 76, were recruited from Neurological Clinics at the University of California at Los Angeles (UCLA) Medical Center. The diagnosis of bvFTD was based on International Consensus Criteria for probable bvFTD [1], which include disinhibition, apathy, loss of empathy, compulsive-like behaviors, dietary changes, and disproportionate executive dysfunction on neurocognitive testing. The diagnosis of AD was determined by the National Institute of Communicable Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for clinically probable AD [45], with the additional requirement of age of symptom onset prior to age 65. Individuals with major medical illnesses (except hypertension or diabetes) or psychiatric illnesses not due to the dementia process were excluded from the study. MRI from two bvFTD participants could not be analyzed due to motion artifact on the images. One additional bvFTD subject was excluded from analysis because she was a statistical outlier by Grubbs' test [46] at $p < 0.05$ (more than 3 SD below the mean of the other subjects) on most of the GWM measures (FA, RD, and MD) as well as two FWM measures (RD and MD). The final clinical sample is comprised of 8 bvFTD and 12 AD subjects.

Twelve age-, gender-, and education-matched healthy adult volunteers with normal cognition (NC), aged 49 to 76, were recruited from the community and hospital staff to participate in a study of healthy aging. Subjects were excluded if they had a history of neurological disorder, psychiatric illness (including drug or alcohol abuse), or head injury resulting in loss of consciousness for more than 10 minutes. The participants were independently functioning, and they did not demonstrate gross neurological abnormalities on clinical interview and brief neurological examination. They had no complaints or evidence of neurocognitive impairment, and their mean Mini-Mental State Examination (MMSE; [47]) score was 29.2 (sd = 0.60, range 28–30).

All subjects received written and oral information about the study and signed written informed consents approved by the local institutional review board prior to study participation.

MRI protocol

All subjects were scanned using the same 1.5 Tesla Siemens MRI instrument and all scans used the same imaging protocol. Details of the protocol have been previously published [41]

and will only be summarized here. DTI acquisition used a single-shot multisection spin-echo echo-planar pulse sequence (TR/TE = 5900/104 ms; flip angle = 90°; averages = 2). It was obtained in the axial plane with a 128 × 128 matrix size, 24 cm FOV, 3.0 mm slice thickness, 35 slices with no interslice gap, and a readout bandwidth of 1630 Hz/pixel. For each slice, diffusion gradients were applied along 12 independent orientations with $b = 800$ s/mm² after the acquisition of non-diffusion sensitized reference images, with $b = 0$ s/mm² (b0 images). Images representing b0, FA, and the three diffusion tensor eigenvalues (E1, E2, E3) were created by post-processing the tensor data on the MRI instrument computer. These images were transferred to a Macintosh imaging workstation and interpolated to 512 × 512 pixels per slice, prior to image analysis.

Image analysis

For analysis of the DTI, the FWM, GWM, and SWM ROIs were first placed on the b0 images to define their anatomic location and avoid partial voluming with cerebrospinal fluid (CSF) or gray matter structures. For all three ROIs, two contiguous slices were chosen for analysis. To sample the FWM, a circular 92.5 mm² ROI of white matter was placed manually by the rater in the middle of the frontal lobe where the largest area of white matter was available and anterior to the cingulate gyrus without impinging on frontal pole cortex, followed by manually editing any regions that were not “normal appearing” white matter. For the two corpus callosum regions (GWM and SWM), a standard rectangular ROI template was first positioned on the midline, and then the caudal (anterior) and rostral (posterior) borders were manually edited to exclude non-corpus callosum tissue such as gray matter and CSF. Lateral borders were defined by the dimensions of the rectangular template that was 14 mm wide in order to minimize the influence of crossing fibers by assessing the central portion of the structures where fibers run in parallel. For the GWM, two slices were chosen on which the angle formed by the left and right sides of the genu appears the most horizontal. This places the ROI consistently in the middle of the genu, which contains primarily fibers connecting prefrontal cortices. For the SWM ROI, the second and third lowest slices on which the fibers of the splenium connected in the midline were chosen. This results in a sample primarily in the lower half of this structure, which contains predominantly primary large sensory (visual) fibers [48].

The ROIs were then copied and pasted onto the three eigenvalue maps (E1, E2, and E3) without further change, and the mean eigenvalue from each of the 3 ROIs was recorded. The individual DTI metrics (FA, AxD, RD, and MD) were computed from the three diffusion tensor eigenvalues.

Emotional blunting

The Scale of Emotional Blunting (SEB; [49]) is an observer rating scale with 16 items, with each item assessed on a three-point scale (0 = “condition absent,” 1 = “slightly present or doubtful,” 2 = “clearly present”). Characteristic items included “absent, shallow, incongruous mood,” “expressionless face,” “unvarying monotone voice,” and “indifference/lack of affection for family, friends.” The sum score of all 16 SEB items was used as the index of emotional blunting.

Data analysis

All statistical analyses were performed using SAS v8.1 (SAS Institute Inc., Cary, NC). Demographic characteristics and global cognitive scores were first compared among bvFTD, AD, and NC groups using one-way analysis of variance (ANOVA) and chi-square tests for continuous and categorical variables, respectively. Tukey tests were conducted for *post-hoc* analysis of any significant group differences. ANOVAs were also performed to compare DTI metrics among the study groups; significant group differences were followed by *post-*

hoc Tukey tests. For the DTI diffusivity measures (AxD, RD, and MD), higher values indicate poorer integrity and greater breakdown. Because scores on the SEB were not normal distributed, Spearman rank-order correlation analyses were conducted to examine the association between DTI and SEB. All *p*-values were assessed as significant at the unadjusted level of 0.05.

Results

Demographic characteristics

The demographic characteristics of the subjects are summarized in Table 1. The groups did not differ by age, education, or gender distribution; therefore, demographic variables were not considered further in subsequent analyses. The bvFTD and AD groups also did not differ significantly on age at onset and indicators of disease severity including MMSE and the Global Score of the Clinical Dementia Rating Scale [50].

Group comparisons on DTI metrics

The means and standard deviations for the DTI measures for all three regions are presented in Table 2. ANOVA tests revealed significant group differences across all DTI parameters in the late-myelinating regions of FWM and GWM ($p < 0.008$). *Post-hoc* Tukey tests showed that the bvFTD group had significantly more white matter breakdown than the AD and the NC groups in these regions. In contrast, the three groups did not differ significantly in SWM across the four DTI metrics. Interestingly, unlike in the FWM and GWM, where the bvFTD demonstrated significantly greater white matter breakdown relative to AD, the reverse pattern was observed in SWM with the AD group having higher diffusivity values than bvFTD, on average, in this region. Furthermore, the AD and NC groups did not differ significantly from each other on any of the DTI measures, even though the numerical trend was in the expected direction with AD patients having worse white matter integrity.

Correlation with behavioral variables

Seven bvFTD and 9 AD participants in our sample had SEB data. Spearman's rank-order correlations were performed and significant associations were observed between SEB ratings and GWM DTI measures including FA ($r = -0.661$, $p = 0.005$), AxD ($r = 0.648$, $p = 0.007$), RD ($r = 0.661$, $p = 0.005$), and MD ($r = 0.763$, $p = 0.0006$), indicating that worse white matter integrity was associated with more symptoms of emotional blunting. These relationships are graphically displayed on Fig. 1. Examination of the two clinical groups separately showed that these relationships were largely driven by the bvFTD group as the correlations between DTI diffusivity measures and SEB remained robust ($r > 0.70$, $p < 0.08$), but the AD group generally demonstrated low SEB ratings. The correlations between SEB and SWM DTI metrics were not statistically significant in our sample ($r < 0.40$, $p > 0.13$).

Discussion

Our data demonstrate that patients with bvFTD have significantly greater white matter breakdown in late-myelinating regions of FWM and GWM compared to AD and NC groups across all the DTI metrics. This finding was regionally specific as there were no significant group differences on DTI markers in the early-myelinating region of SWM. The regional differences in white matter breakdown reflect the anatomical specificity of the diseases as the frontal lobe and association areas are affected early in bvFTD but not in the early-onset form of AD. Even though white matter damage in bvFTD and AD has gathered increasing attention in recent years, we are aware of only one other paper that directly compared white matter integrity between these two disease groups [11]. Paralleling our own findings, they

demonstrated that bvFTD had significantly lower FA values than AD in the anterior corpus callosum with a trend toward lower FA in bilateral uncinate fibers. In contrast, their AD group showed no significant regional FA reduction relative to bvFTD patients [11].

Even though the group differences in SWM DTI values were not statistically significant, numerically, the AD group had higher diffusivity values indicating greater white matter breakdown than the bvFTD group in this region. It is interesting to note that this pattern is opposite to that seen in the late-myelinating regions. This finding is in agreement with other studies as Zhang and colleagues [11] also reported a trend toward lower FA value in the posterior corpus callosum for AD compared to NC. It is possible that the brain slices that were sampled for our ROI analysis may include fibers connecting parietal cortices, which would be more vulnerable in AD.

Emotional blunting, which refers to loss of emotional warmth, sympathy, or empathy, is a characteristic feature of bvFTD [1]. The positive correlation we observed between ratings of emotional blunting and DTI metrics in the GWM was largely driven by the bvFTD group, suggesting that as hypothesized, white matter deficits may play an important role in the behavioral symptoms observed in bvFTD. Other studies have also reported correlations between empathic concern and white matter microstructure in tracts providing communicative pathways within the limbic system [51]. The symptoms manifested by patients with bvFTD, including behavioral disinhibition and emotional blunting, may result from disruption of the circuitry containing late-myelinating, high-workload fibers [52].

The human brain is exceptionally myelinated compared to other species [53–55]. Myelination, and the maintenance and repair of this highly vulnerable tissue, is responsible for the exquisitely synchronized timing of action potentials that underlie neuronal network oscillations necessary for optimal human cognitive and behavioral functioning. Circuits in regions that myelinate later in the developmental process, such as the frontal and temporal regions, have fewer oligodendrocytes supporting greater number of axons compared to regions that become myelinated earlier (primary sensorimotor regions and SWM). Oligodendrocytes in the cortical association areas have particularly high metabolic demands, which make these axons more susceptible to pathological processes resulting in the behavioral deficits seen in bvFTD [52].

Another primary objective of our study was to compare different types of white matter and myelin, through examination of different DTI parameters, in order to illuminate the aspects of white matter microstructure that may be differentially compromised in bvFTD. Our previous work on multi-modal examination of white matter integrity across the lifespan highlighted the discrete biological processes of white matter tracked by the specific DTI metrics [41]. In the current study, greater deficit in white matter integrity was observed across all DTI measures in the bvFTD suggesting that the degenerative process results in myelin breakdown, as indicated by increased RD, and possible loss of entire axons resulting in increased extra-axonal interstitial space, which is reflected by higher AxD [41]. Like adult myelination, the neurons most susceptible to degeneration in bvFTD and AD extend axons that myelinate later in life and have smaller diameter [18, 28, 33]. The increased susceptibility of this subset of axons to breakdown [28, 33, 56–58] may be the mechanism underlying the progression of bvFTD and AD pathology. It is possible that examination of more specific tracts and different DTI eigenvalues earlier in the disease process may reveal greater disease-specific pattern of breakdown.

This study has several limitations. The sample size is relatively small; therefore, the present findings will need to be replicated in a larger, independent sample. The twelve-direction DTI metrics used are approximations of their absolute values, and the DTI sequence employed in

the present study has relatively low-resolution with thick slices. While this is a limitation for automated, tract-based techniques, these scans were appropriate for the ROI-based analyses performed in this study, and the short acquisition time reduces burden on this difficult patient population. The patient groups were diagnosed clinically based on current consensus criteria [1, 45] without CSF biological markers or autopsy control; therefore, the definitive diagnosis or the underlying histopathology of the patients studied remains uncertain. In a cross-sectional study, interpretations of differences between clinical groups as “changes” or “increases/decreases” must be made with caution [59] and prospective studies are needed to better define degenerative changes. Finally, the present study sample is comprised on mostly Caucasian participants; therefore, the results may not generalize to other ethnic groups.

In summary, the regional DTI alterations suggest that bvFTD and AD are each associated with a characteristic distribution of white matter degradation. Results also suggest greater vulnerability of white matter in bvFTD than in early-onset AD and NCs. The advent of *in vivo* neuroimaging methods, especially pertaining to the ability to more specifically assess white matter microstructural changes, has yielded increasing evidence that myelin and axonal integrity is prominently involved in the pathophysiology of bvFTD. However, interpretation of DTI indices with respect to pathology can be ambiguous and more validation studies on the underlying causes of DTI changes, including multimodal imaging to interrogate different tissues and cortical and subcortical white matter, are necessary to improve diagnostic and prognostic criteria for distinguishing between bvFTD and AD.

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Fig. 1. Correlations between DTI metrics (FA, AxD, RD, and MD) and Scale of Emotional Blunting scores for bvFTD and AD subjects.

Table 1
Demographic and clinical characteristics for bvFTD, AD, and NC groups

Demographic variables	BvFTD (n=8) Mean (s.d.)	AD (n=12) Mean (s.d.)	NC (n=12) Mean (s.d.)	F or χ^2	p
Age, y	61.6 (10.1)	56.7 (3.9)	61.2 (8.7)	1.35	0.275
Education, y	15.5 (2.9)	15.4 (2.2)	16.3 (2.1)	0.44	0.648
Gender (m/f)	4 m/4f	5 m/7f	5 m/7f	0.17	0.919
% white	100%	92%	92%	0.71	0.701
Clinical variables				t	p
Age at onset	57.6 (9.7)	51.0 (4.0)		1.82	0.104
MMSE	24.0 (3.8)	22.0 (3.7)		1.08	0.295
CDR Global Score	1.07 (.45)	0.86 (.23)		1.30	0.213

MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating Scale.

Table 2
Comparisons of DTI metrics among behavioral variant frontotemporal dementia (bvFTD), Alzheimer's disease (AD), and normal control (NC) groups for three white matter regions

DTI Metrics/White Matter Regions	bvFTD (n=8) Mean (s.d.)	AD (n=12) Mean (s.d.)	NC (n=12) Mean (s.d.)	F _{2,29}	p
FA					
FWM	0.337 (0.041)	0.426 (0.029)	0.427 (0.048)	15.06	<0.0001
GWM	0.680 (0.070)	0.799 (0.044)	0.768 (0.036)	14.79	<0.0001
SWM	0.832 (0.029)	0.830 (0.035)	0.823 (0.025)	0.23	0.794
AxD					
FWM	1.306 (0.085)	1.213 (0.072)	1.185 (0.066)	6.94	0.003
GWM	1.953 (0.082)	1.837 (0.101)	1.786 (0.129)	5.72	0.008
SWM	1.780 (0.145)	1.831 (0.098)	1.749 (0.141)	1.26	0.298
RD					
FWM	0.788 (0.075)	0.637 (0.053)	0.612 (0.062)	21.23	<0.0001
GWM	0.572 (0.144)	0.332 (0.069)	0.376 (0.069)	17.25	<0.0001
SWM	0.264 (0.033)	0.285 (0.060)	0.280 (0.028)	0.57	0.574
MD					
FWM	0.961 (0.074)	0.829 (0.056)	0.803 (0.055)	17.79	<0.0001
GWM	1.033 (0.117)	0.834 (0.056)	0.846 (0.078)	16.36	<0.0001
SWM	0.770 (0.047)	0.800 (0.046)	0.770 (0.049)	1.60	0.220

AxD, axial diffusivity; DTI, diffusion tensor imaging; FWM, frontal white matter; GWM, genu of the corpus callosum; MD, mean diffusivity; RD, radial diffusivity; SWM, splenium of the corpus callosum.