Deformation-Based Morphometry Reveals Brain Atrophy in Frontotemporal Dementia

Valerie A. Cardenas, PhD; Adam L. Boxer, MD, PhD; Linda L. Chao, PhD; Maria L. Gorno-Tempini, MD, PhD; Bruce L. Miller, MD; Michael W. Weiner, MD; Colin Studholme, PhD

**Objective:** To compare deformation-based maps of local anatomical size between subjects with frontotemporal dementia (FTD) and healthy subjects to identify regions of the brain involved in FTD.

**Design:** Structural magnetic resonance images were obtained from 22 subjects with FTD and 22 cognitively normal, age-matched controls. We applied deformation-based morphometry and compared anatomy between groups using an analysis of covariance model that included a categorical variable denoting group membership and covaried for head size.

**Setting:** University of California, San Francisco, Memory and Aging Center, and the San Francisco Veterans Affairs Medical Center.

**Patients:** Twenty-two subjects with FTD and 22 cognitively normal, age-matched controls.

**Interventions:** Neurological, neuropsychological, and functional evaluations and magnetic resonance imaging.

**Main Outcome Measure:** Deformation maps of local anatomical size.

**Results:** Patients with FTD showed extensive, significant atrophy of the frontal lobes, affecting both gray matter and white matter. Atrophy of similar magnitude but less significance was observed in the anterior temporal lobes. The subcortical and midbrain regions, particularly the thalamus, pons, and superior and inferior colliculi, showed strongly significant atrophy of smaller magnitude.

**Conclusions:** We confirmed frontal and anterior temporal gray matter atrophy in FTD. The observed white matter loss, thalamic involvement, and midbrain atrophy are consistent with pathological findings in late-stage FTD. Dysfunction of ventral-frontal-brainstem circuitry may underlie some of the unique clinical features of FTD.

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Frontotemporal dementia (FTD) is a clinical subtype of frontotemporal lobar degeneration defined by deficits in social and personal conduct. Postmortem studies have suggested that brain atrophy in FTD begins in the frontal lobe, extending into the anterior temporal lobes, basal ganglia, and the thalamus. White matter (WM), including the corpus callosum, is prominently affected.¹

In vivo magnetic resonance imaging (MRI) structural analyses have compared patients with FTD with controls using conventional measures of gray matter (GM), WM, or cerebrospinal fluid volumes obtained from computer segmentation and volumes of manually delineated regions of interest, such as the hippocampus. Using such measurements, atrophy of the frontal and temporal lobes² and corpus callosum³ has been demonstrated in FTD. Hippocampal atrophy is present in FTD as compared with controls, but it is not as severe as in Alzheimer disease.⁴

Unlike region of interest methods, voxelwise structural image analysis assesses anatomical variation without prior hypotheses about the location and extent of the anatomical variation. Early techniques, such as voxel-based morphometry, provided regional indications of GM loss in the frontal and temporal regions.⁵ Because voxel-based morphometry relies on the automated segmentation of images into GM, WM, and cerebrospinal fluid, regions of abnormal WM (prevalent in older populations) may be incorrectly classified as GM by automatic segmentation. In addition, automatic segmentation of subcortical structures can be problematic because of the mixing of GM and WM in these structures. For these

Author Affiliations: Magnetic Resonance Unit, San Francisco Veterans Affairs Medical Center (Drs Cardenas, Chao, Weiner, and Studholme), and Departments of Radiology (Drs Cardenas, Chao, Weiner, and Studholme) and Psychiatry (Dr Chao) and the Memory and Aging Center, Department of Neurology (Drs Boxer, Gorno-Tempini, and Miller), University of California, San Francisco.
reasons, voxel-based morphometry is suboptimal for investigating WM loss or determining subcortical involvement in FTD.

Improvements in image alignment allow purely deformation-based morphometry (DBM) to be used to provide more direct quantitative maps of anatomical variation. By avoiding the need for image segmentation and using robust registration methods, DBM may be more suitable for investigating anatomical variation of WM and subcortical structures.

In this study, our goal was to compare deformation-based maps of local anatomical size between subjects with FTD and healthy subjects to identify regions of the brain involved in FTD. We hypothesized that subjects with FTD would show atrophy in frontal and temporal GM and WM and subcortical structures, including the basal ganglia and thalamus.

METHODS

PARTICIPANTS

All subjects underwent neurological, neuropsychological, and functional evaluations at the University of California, San Francisco, Memory and Aging Center. Cognitively normal (CN) controls (mean ± SD age, 63 ± 7 years; n = 22; 7 women) had cognitive test scores within the normal age and education-adjusted range. All subjects with FTD (mean ± SD age, 63 ± 6 years; n = 22; 7 women; mean ± SD 6.6 ± 3.7 years since disease onset) met Neary's criteria for FTD. In addition, 3 subjects with FTD also met El Escorial criteria for possible or probable amyotrophic lateral sclerosis. Diagnoses were blinded to neuroimaging results to avoid confounding future neuroimaging analyses. Pathological verification of diagnosis was obtained in 5 subjects (2, Pick disease; 2, FTD-ubiquitin; 1, FTD–motor neuron disease). The Clinical Dementia Rating (CDR) scaled and sum of boxes scores were 0 for both measures for CN controls and 1 for the CDR and 2 for the sum of boxes.

MAGNETIC RESONANCE IMAGING

The MRI data were acquired at the San Francisco Veterans Affairs Medical Center on a clinical 1.5-T MRI scanner (Vision; Siemens Medical Systems, Iselin, NJ). Coronal T1-weighted images were acquired using a magnetization-prepared rapid-acquisition gradient-echo sequence (repetition time, 9 milliseconds; inversion time, 300 milliseconds; echo time, 4 milliseconds; 1 × 1 mm2 in-plane resolution; 1.5-mm slabs); images were acquired orthogonal to the long axis of the hippocampus.

FULLY AUTOMATED DBM

A B-Spline free-form deformation algorithm driven by normalized mutual information was used to register individual scans to a 72-year-old female reference atlas, chosen to retain the finest anatomical structures for accurate registration. The Jacobian determinant of this transformation at each point, giving the pattern of volume change required to force the individual anatomy to conform to the reference, was mapped and smoothed using an intensity-consistent filtering approach. These voxel maps of relative local anatomical size of each individual were then analyzed using statistical parametric mapping. Using a general linear model, we compared the FTD and CN groups with a categorical variable coding group membership and head size (defined as the average Jacobian determinant within the intracranial vault delineated on the reference anatomy) included as a covariate, as shown in the equation, where \( |f(x)| \) is the Jacobian evaluated at voxel \( x \), and \( a(x), b(x) \), and the intercept \( c(x) \) are estimated at each voxel. Because statistics were computed independently at each voxel, we calculated the corrected \( P < .05 \) peak threshold using permutation testing, where we permuted the group membership 1000 times and recalculated the voxel statistics to build the null distribution, and also the method of Bonferroni (using all voxels within the average brain). We used FMRISstat to identify in FTD clusters of contracting or expanding voxels, where both magnitude (all voxels within the cluster must be significant at \( P < .001 \) uncorrected) and spatial extent (larger clusters are less likely to be false positives) were jointly used to assess corrected significance.

RESULTS

DEFORMATION-BASED MORPHOMETRY

Figure 1 shows regions where patients with FTD demonstrate brain volume reductions compared with CN controls. Regions where patients with FTD show significant (\( P < .01 \) uncorrected, or \( T = 2.70 \)) atrophy are overlaid on the average spatially normalized MRI. The threshold at \( P = .05 \) corrected for multiple comparisons using permutation testing is \( T = 5.0 \) and the corrected threshold using the method of Bonferroni is \( T = 6.62 \); these 2 thresholds are marked on the Figure 1 color bar (as PT \( P = .05 \) and BF [Bonferroni over brain voxels] \( P = .05 \), respectively). Figure 1 reveals many voxels where patients with FTD show significant atrophy relative to CN controls even after correction for multiple comparisons, including a large region of the pons and midbrain, the right superior and inferior colliculus, thalamus, left superior frontal GM, anterior frontal WM, and a ventromedial frontal WM region. At lower significance, patients with FTD showed extensive atrophy of frontal and anterior temporal WM and GM.

Cluster analysis using FMRISstat revealed a single connected cluster of contraction in patients with FTD vs CN controls encompassing all the regions mentioned earlier. Figure 2 shows the T statistic map overlaid on the average spatially normalized MRI, where voxels belonging to this significant cluster of contraction are outlined in red. Negative T values that indicate atrophy in patients with FTD compared with CN controls are in green and blue; positive T values that indicate expansion in patients with FTD relative to CN controls (all located within cerebrospinal fluid) are in yellow and red.

To estimate the magnitude of atrophy in patients with FTD, the brainstem (including midbrain), thalamus, and ventromedial frontal lobe were defined anatomically on the average image, and we then averaged the estimates \( a(x) \) from the equation at all statistically significant voxels \( x (t > 5) \) within each region of interest. We found that tissue volume was reduced by 10% in the brainstem region in patients with FTD compared with CN controls, by 26% in the thalamic region, and by 34% in the ventromedial frontal region. Although no single voxel in the
temporal lobes reached significance after correction for multiple comparisons, the regions of the temporal lobes were part of the significant cluster of contraction. To determine whether the relatively small T statistics in the anterior temporal lobe were due to a small volume difference between groups or due to variability within groups, we averaged the estimates \( a(x) \) from the equation at all voxels \( x \) in the anterior temporal lobe that belonged to the significant cluster of contraction. This showed that tissue volume was reduced by 35% in the anterior temporal region in patients with FTD compared with CN controls, as large a reduction as observed in the frontal lobes.

To validate DBM, we calculated region of interest measures on 22 consecutive subjects (11 with FTD and 11 CN controls), measuring frontal and temporal lobe volumes and brainstem volume (midbrain, pons, and medulla) on a single midsagittal slice. Volumes were then normalized to account for global head size differences and expressed as a percentage of intracranial volume, as shown in the Table. Similar to DBM, we found significant volume differences between patients with FTD and CN controls within the frontal lobe and brainstem and no significant difference within the temporal lobe. The magnitude of the reduction within the frontal and temporal lobes was smaller, probably because these regions of interest included the entire frontal or temporal lobe, whereas our DBM estimates were within only significant subregions.

We used DBM to examine brain structure differences between patients with FTD and CN controls. The major findings of this study are (1) patients with FTD showed significant atrophy in the frontal lobes, affecting both WM and GM, (2) significant atrophy was observed within the thalamus and adjacent WM in FTD, (3) the brainstem, including the midbrain and pontine tegmentum as well as the superior and inferior colliculi, showed significant tissue volume reduction in FTD, and (4) regions of the anterior temporal lobes were atrophied in FTD.

The frontal and anterior temporal GM atrophy observed in FTD is consistent with previous postmortem and voxel-based morphometry studies. The frontal and temporal volumes were comparably reduced, although the reduction in the temporal lobes was not as significant. A quantitative validation showed excellent agreement between our deformation-derived (reference image was the same 72-year-old subject as in this study) and manually delineated temporal volumes, so it is unlikely that this lower significance in the temporal lobe arises because of poor alignment. Instead, we believe that some patients with FTD have much smaller temporal lobes than CN individuals but that in others the FTD disease does not involve or has not progressed to the stage where the temporal lobes are atrophied.
greatly affected. Such an inconsistent spatial pattern
within the FTD group would explain the lowered signifi-
cance of atrophy in the anterior temporal region, and this
interpretation is highly consistent with the considerable
variability in clinical and neuroimaging features ob-
served in FTD. Consistent with other reports, we did
not observe any significant atrophy in parietal or occipi-
tal lobes in the patients with FTD.

In addition to frontal and temporal GM tissue loss,
we observed frontal WM and thalamic atrophy in
patients with FTD compared with CN controls. Tha-
lamic volume loss of up to 37% has previously been
described in neuropathological studies of FTD. In a
proposed scheme for staging pathological disease sever-
ity in FTD, WM and thalamic atrophy are thought to
occur at later stages, only after the frontal and temporal
lobes are severely affected, roughly corresponding to
CDR scores of 3 to 5. Our data suggest that these
changes are measurable in patients with FTD at earlier
stages of disease (mean ± SD CDR score 1.2 ± 0.68). Our
study also may have had greater sensitivity to these
changes because of a more homogeneous clinical
sample (all had FTD) and a smaller interval between
CDR and brain atrophy measurement, as well as the
more quantitative nature of the DBM analysis over
visual atrophy measurements.

Although midbrain atrophy has not previously been
emphasized in imaging studies in FTD, FTD-related
pathological features are frequently found in the sub-
stantia nigra and other brainstem structures, and this
finding supports the known clinical overlap between FTD
and progressive supranuclear palsy (PSP). Neuroimag-
ing and pathological features of PSP show atrophy in the
midbrain, basal ganglia, and other structures. Cases
of clinically diagnosed FTD have been found to have PSP
pathological features at autopsy, and clinically diag-
nosed PSP cases have been described with FTD-
ubiquitin pathological features involving the mid-
brain. Recent evidence suggests that patients with FTD
have measurable saccade abnormalities, which may in part

<table>
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<tr>
<th>Table. Region of Interest Volumes Expressed as a Percentage of Intracranial Volume</th>
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<tr>
<td>Intracranial Volume, Mean ± SD, %</td>
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<tr>
<td>Cognitively Normal Controls</td>
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<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Frontal lobe</td>
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<td>Temporal lobe</td>
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<td>Brainstem midsagittal</td>
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*Expression of scientific notation. Alternatively, 7.65E-05 can be expressed as 7.65 × 10⁻⁵ or 0.0000765.
†Expression of scientific notation. Alternatively, 7.46E-05 can be expressed as 7.46 × 10⁻⁵ or 0.0000746.
reflect damage to the superior colliculus and/or WM tracts that connect it to the frontal lobes and basal ganglia, consistent with our results. Midbrain and thalamic pathologic features may underlie some of the deficits in social function and emotion perception identified in FTD since integrity of this region is likely to be necessary for function of a midbrain-thalamus-amygdala pathway implicated in emotion perception. Finally, there is an extensive literature on midbrain involvement in FTD at a pathology level. For example, in the original study by Knopman et al on dementia lacking distinctive histologic features, the authors noted that 79% of these patients had pathologic features in the midbrain. In previous voxel-based morphometry work from our center, we also found atrophy in the midbrain, and DBM is a better technique for delineating these changes.

These cases were defined on the basis of their clinical features and only a small number have been autopsy confirmed. Because FTD is a pathologically heterogeneous disorder, it will be of particular interest to confirm these results in histopathologically diagnosed FTD and to assess whether subcortical and brainstem atrophy is associated with specific biochemical FTD phenotypes, such as tau protein inclusions, which might further strengthen the link between FTD and PSP.

Taken together, our findings suggest that dysfunction of a frontal-subcortical-brainstem circuit may underlie some of the unique clinical features of FTD and that DBM measures of volume may be useful for exploring these brain-behavior relationships.

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Correspondence: Valerie A. Cardenas, PhD, University of California, San Francisco, Department of Veterans Affairs Medical Center, 4150 Clement St, 114M, San Francisco, CA 94121 (valerie.cardenas-nicolson@ucsf.edu).

Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Cardenas, Boxer, Chao, Gorno-Tempini, and Weiner. Acquisition of data: Gorno-Tempini. Analysis and interpretation of data: Cardenas, Boxer, Chao, Gorno-Tempini, Miller, Weiner, and Studholme. Drafting of the manuscript: Cardenas and Boxer. Critical revision of the manuscript for important intellectual content: Cardenas, Boxer, Chao, Gorno-Tempini, and Weiner. Statistical analysis: Cardenas and Gorno-Tempini. Obtained funding: Miller, Weiner, and Studholme. Administrative, technical, and material support: Cardenas, Boxer, Chao, Weiner, and Studholme. Study supervision: Boxer, Chao, Gorno-Tempini, Weiner, and Studholme.

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