Alzheimer’s Disease And Frontotemporal Dementia Exhibit Distinct Atrophy–Behavior Correlates: A Computer-Assisted Imaging Study

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Rationale and Objectives. The purpose of this study was to test the hypothesis that distinct patterns of gray matter atrophy are responsible for unique interruptions of the naming process in Alzheimer’s disease (AD) and frontotemporal dementia (FTD).

Materials and Methods. Voxel-based morphometry (VBM) was performed to characterize at the voxel level the neuroanatomic changes that occur in AD and FTD based on high-resolution T1-weighted three-dimensional (3D) spoiled-gradient echo images of patients (AD, n = 12; FTD, n = 29) and healthy control subjects (n = 12). The cortical atrophy measurements were correlated with performance on behavioral measures of naming and related processes to identify brain regions that may contribute to this language function.

Results. Both AD and FTD have significant naming difficulty, and this difficulty in naming correlates with a measure of lexical retrieval in both patient groups as well. However, only FTD patients showed a correlation with semantic memory. Areas of cortical atrophy common to AD and FTD were found in the anterior temporal, posterolateral temporal, and dorsolateral prefrontal regions of the left hemisphere. Correlation with naming in both AD and FTD was seen in the left anterior temporal cortex, suggesting that this area may play a role in the lexical retrieval component of naming. We also observed several unique areas of cortical atrophy in temporal and frontal cortices of these patients. Right anterior temporal and left posterolateral temporal regions of atrophy correlated with naming difficulty in FTD, suggesting that these areas may contribute to the semantic memory component of naming. Cortical areas correlating with naming that are not atrophic may represent regions that play an optional role in naming.

Conclusion. VBM provides an important first step in analyzing brain–behavior relations in vivo in patients with neurodegenerative diseases. More refined analyses of brain morphology via high-dimensional normalization methods that are capable of modeling local as well as global variability in neuroanatomical structure promise to be even more informative.

Key Words. Alzheimer’s disease; frontotemporal dementia; naming; cortical atrophy; high-dimensional normalization.

Neurodegenerative diseases such as Alzheimer’s disease (AD) and frontotemporal dementia (FTD) are distinguishable clinically on the basis of careful neurologic and neuropsychological examinations. These assessments have been extrapolated from observations at autopsy to suggest unique brain–behavior relationships in an attempt to explain clinical differences between these neurodegenerative diseases. The finding of significant hippocampal atrophy at autopsy in AD, for example, is said to explain the profound memory deficit seen during life in these patients. Observations such as these must be tempered by the fact
that many years often intervene between the time when a reliable cognitive examination can be performed and when regional atrophy of the brain can be assessed directly. Recent innovations in neuroimaging now provide such sufficiently detailed and reliable neuroanatomic data that we can identify distinct patterns of regional cortical atrophy in these neurodegenerative diseases during life and can relate these patterns of atrophy to different neurocognitive profiles observed during an examination performed within minutes of the imaging study.

MRI studies suggest partially distinct patterns of cortical atrophy in AD and FTD. Areas of atrophy seen in both AD and FTD appear to include the hippocampus as well as temporal neocortex and frontal neocortex. However, atrophy in these areas does not appear to involve identical neuroanatomic distributions (1–6). Direct comparisons of atrophy in AD and FTD such as these have been rare. Nevertheless, this work does suggest distinct patterns of atrophy in AD and FTD that can be helpful in diagnosis. While AD patients have severe hippocampal atrophy, for example, some studies show that the subgroup of FTD patients with semantic dementia (SD) have significantly greater atrophy in anterior and ventral temporal distributions (2,4).

Selective atrophy of this sort also has important implications for understanding the basis for the distinct clinical profiles of patients with AD and FTD. For example, naming is a complex task that involves interpreting a stimulus such as a visual line drawing, identifying the concept corresponding to the stimulus in semantic memory, and then retrieving and articulating the phonemic sequence that corresponds to the stimulus. Patients with AD (7–11) and FTD (12–14) both have significant naming difficulty. However, comparative behavioral studies suggest that naming difficulty may be caused by interruption of different components of the naming process in these patient groups (15). The finding of different patterns of gray matter atrophy in AD and FTD suggests the possibility that distinct areas of atrophy are responsible for unique interruptions of the naming process in AD and FTD.

In this study, we examine this hypothesis by quantifying the atrophy in gray matter using computational techniques that are capable of detecting subtle regional differences in brain volume and shape on MRI data. These gray matter measurements are then correlated with performance on behavioral measures of naming and related processes to identify brain regions that may contribute to this language function. Specifically, voxel-based morphometry (VBM) (16) is applied to characterize at the voxel level the neuroanatomic changes that occur in AD and FTD. In VBM, image registration techniques that can determine with varying levels of precision the anatomical correspondence between different brains depicted in the images to be registered, are used to reshape or normalize the brain volumes from different subject populations into spatial alignment with a template brain. The template brain establishes a reference coordinate system with which anatomical localization can be made. Residual shape differences between the template and normalized subject brains are assumed to reflect the relative differences that are present among the original brain shapes of the subjects. These differences can be examined on a voxel-wise basis via standard statistical tests and implemented with methods ordinarily applied in functional neuroimaging analysis (16). The result is a 3D map spanning the space of the template brain, where the value at each voxel corresponds to the outcome of the specified statistical test. The statistical parametric maps in our VBM analysis test population differences in brain gray matter and thus depict at the voxel level the extent to which the gray matter in one group differs from the other. This is in contrast with label-based approaches, where changes are measured over anatomical regions of interest (ROIs) defined by the operator. VBM has several advantages over ROI-based morphometry: removal of operator bias in ROI definition (local bias); quantification of subtle features easily missed by operator inspection; and assessment of global structural changes in the brain, unrestricted by some a priori selection of specific ROIs (global bias) (16–18). These favorable aspects of VBM, combined with the availability of automated software for its implementation, have established the approach as one of the leading methods in the field (19). Nevertheless some issues arise in the application of VBM, and these primarily concern the degree to which differences in brain shape are correctly modeled and removed in the normalization step. Poor normalizations may yield inconclusive results or, worse, incorrect conclusions. Paradoxically, perfect normalizations provide no information whatsoever about structure because population differences are completely removed in the process. The latter deficiency, however, can be addressed by modulating the value of each voxel in the normalized gray matter map with the volumetric change induced in the voxel so that the ensemble of voxels composing the brain would be geometrically transformed into a new configuration reshaped to match the appearance of the template brain. In this way, the absolute amount of gray matter is preserved and can subsequently be compared in the mod-
ulated version of VBM (20). Ideally, one would strive to establish as accurately as possible the anatomical correspondences between the subject and template brains to ensure that the same structures are under examination in the analysis. Modulated VBM capitalizes on the sophistication of certain normalization techniques that are capable of resolving highly detailed differences in brain shape (21–25). In particular, the precision of the modulation depends directly on the accuracy of the computed shape transformations. To examine the potential of these techniques for modeling local anatomical variability, we conducted a preliminary assessment of the normalization accuracy that can be achieved in studies of patients afflicted with a neurodegenerative disease.

**MATERIALS AND METHODS**

**Subjects**

We studied 41 patients recently diagnosed with a neurodegenerative condition in the Department of Neurology at the University of Pennsylvania. Initial clinical diagnosis was established by an experienced neurologist (MG) based on published criteria. Subsequently, a consensus committee confirmed the presence of specific criteria based on an independent review of the semi-structured history, mental status examination, and neurologic examination by at least two trained reviewers. If the reviewers disagreed in their diagnosis, consensus was established through open discussion by the entire committee. These patients and their legal representatives participated in an informed consent procedure approved by the Institutional Review Board at the University of Pennsylvania.

Among the participants, 12 patients were given the diagnosis of AD, based on NINCDS-ADRDA criteria (26). Briefly, this included a prominent anterograde memory deficit, associated with circumlocutory speech, a visual constructional impairment, and/or an executive limitation.

Another 29 patients were given the diagnosis of FTD, according to published criteria (27,28). This included 15 patients with primary progressive aphasia (including both semantic dementia and progressive nonfluent aphasia), and 14 patients with a disorder of social and executive functioning.

The initial clinical diagnosis of a neurodegenerative disease was consistent with the results of serum studies, structural imaging studies such as MRI or CT, studies of cerebrospinal fluid (when available), and functional neuroimaging studies such as SPECT or PET (these studies were not available to the consensus committee). Exclusion criteria included the presence of other neurologic conditions such as stroke or hydrocephalus, primary psychiatric disorders such as depression or psychosis, or a systemic illness that might interfere with cognitive functioning. Many of these patients were taking a fixed dosage of an acetylcholinesterase inhibitor (eg, donepezil, rivastigmine, or galantamine). Some of these patients may have been medicated with a low dosage of a nonselective antidepressant (eg, serotonin-specific reuptake inhibitors such as sertraline) or an atypical neuroleptic agent (eg, quetiapine) as well, as indicated clinically, but none of the patients showed any evidence of sedation suggesting overmedication. Table 1 summarizes the demographic and clinical features of these patients. The patient groups were matched in age, education, duration of disease, and Mini Mental State Examination (MMSE) score (29).

Confrontation naming in these patients was compared with cohorts of 25 healthy older control subjects who were age- and education-matched to each group of patients. The performance of each patient was converted to a z-score based on each group’s matched control subjects, and we compared these normalized z-scores statistically across the patient groups in the Results section below. It should be noted that the subgroups of control subjects did not differ statistically in their naming performance. The patients were participating in a longitudinal protocol: For the purpose of the present study, we selected the naming performance dataset closest in time to the MRI (naming data were obtained typically on the same day as the MRI). Imaging data in these patients were compared with 12 healthy control subjects who were matched for age.

**Table 1**

| Clinical and Demographic Features, and Performance on Measures of Naming and Related Processes |
|---|---|
| Alzheimer’s disease (n = 12) | Frontotemporal dementia (n = 29) |
| Age (years) | 70.8 (±8.5) | 65.1 (±12.1) |
| Education (years) | 16.0 (±3.0) | 15.1 (±2.2) |
| Duration (months) | 51.1 (±18.4) | 41.3 (±31.8) |
| MMSE (max = 30) | 21.3 (±6.5) | 20.5 (±6.5) |
| Naming (z-score) | -3.03 (±2.37) | -3.94 (±3.12) |
| Visual (z-score) | -0.26 (±1.30) | -0.96 (±1.82) |
| Semantic (z-score) | -1.28 (±1.58) | -0.27 (±0.61) |
| Retrieval (z-score) | -3.19 (±0.66) | -3.22 (±1.04) |

Values given as Mean (±SD)
(mean [±SD] = 68.5 [±9.4] years) and education (mean [±SD] = 15.4 [±1.8] years).

**Cognitive Materials and Procedure**

We administered several measures to assess confrontation naming and the processes thought to contribute to naming:

*Confrontation naming.*—To assess confrontation naming, we used an abbreviated version of the Boston Naming Test thought to be representative of the full protocol (30,31). Each subject was asked to name each test stimulus (n = 15). Patients were given as much time as they needed to respond. All visual stimuli were black-and-white line drawings, and they were equally divided among high-frequency, mid-frequency and low-frequency items.

*Visual–spatial functioning.*—To assess visual–spatial functioning (31), patients were asked to copy four geometric designs that were graded in their perceptual complexity. Performance was evaluated on an 11-point scale. One patient in each group did not complete this test.

*Semantic category membership judgment.*—To assess semantic memory with a relatively simple task that requires little expression and minimal executive resource demands (32), patients were asked to judge the semantic category membership of 48 individually presented stimuli (32), patients were asked to judge the semantic category membership of 48 individually presented stimuli in response to a simple probe (“Is it an X?”). One target category was natural (VEGETABLES) and one manufactured (TOOLS), and in each category half of the stimuli were targets and half foils. Half of each category of stimuli consisted of printed words and half of color photos. Stimuli were presented in a manner blocked by category and material. Patients were given as much time as they needed to complete the task. Two FTD patients did not complete this test.

*Lexical retrieval.*—To assess lexical search and retrieval in a semantic context (33), patients were asked to name as many different words as possible belonging to a familiar semantic category, i.e., ANIMALS. They were given 60 seconds to complete the task. We report the number of unique words meeting the criterion in this time span. Two FTD patients did not complete this test.

The patients were offered rest breaks between tasks as needed during the performance of these measures.

**Imaging Procedure**

All images were acquired with a GE Horizon Echospeed 1.5-T MRI scanner (GE Medical Systems, Milwaukee, WI). Each study began with a rapid sagittal T1-weighted image to determine patient position. Next, high-resolution T1-weighted 3D spoiled-gradient echo images were acquired with a repetition time (TR) of 35 milliseconds, an echo time (TE) of 6 milliseconds, a slice thickness of 1.3 mm, a flip angle of 30°, a matrix size of 128 × 256, and a rectangular field of view giving an in-plane resolution of 0.9 × 0.9 mm².

**Morphometric Procedure**

SPM99 (34) was used to implement the voxel-based morphometric analysis of gray matter atrophy in the patients (16). First, the brain volumes were normalized to Talairach and Tournoux neuroanatomical coordinates (35) by registration to the T1 template (36) of 305 averaged brain volumes in SPM99. The default SPM99 normalization was applied, consisting of a 12-parameter affine registration, followed by 12 iterations of a nonlinear registration using 7 × 8 × 7 basis functions and medium regularization (37). The normalized volumes were then segmented into four tissue types (gray matter, white matter, cerebrospinal fluid, and other). The segmentation algorithm in SPM99 calculates a probability for each voxel of each tissue group in the volume, taking into account a priori information about the tissues and the likelihood of their appearance in different regions of the brain (16). Finally, each gray matter volume was smoothed with a 12-mm full-width half-maximum (FWHM) Gaussian filter to minimize individual gyral variations. These gray matter maps formed the basis of the statistical comparisons with which cortical atrophy patterns were identified in the AD and FTD patients.

A second set of normalizations was performed using a different, very high-dimensional registration method to explore the extent to which brain shape differences can be removed in the patient groups as a first step toward the application of modulated VBM analyses that may reveal additional, more subtle patterns of atrophy in AD and FTD. The method is a spline-based extension of the popular Demons algorithm (24), where, in place of Gaussian filtering, multi-level B-spline approximations are used to interpolate and smooth the correspondence solution (38). As with the original Demons registration, the extended version is designed to be fast, deriving its speed from the uncoupling of the correspondence calculation and shape deformation interpolation procedures, each of which are then amenable to efficient implementation. To capitalize on the method’s capability to model highly localized variation in neuroanatomy, the subject data were normalized by registration to the single-subject T1 template available.
in SPM. Unlike the mean brain template, the single-subject version retains the fine anatomic detail of the cortex.

**Statistical Analysis**

SPM99 was used for all statistical analyses. This included a two-sample t-test routine to compare the gray matter concentrations of each patient group with the control group of 12 healthy seniors. A proportional analysis threshold was used to include only voxels with 40% or more of the grand mean value. Implicit masking was used to ignore zeros, and global calculation was based on the mean voxel value. We set our statistical threshold for the atrophy studies relative to control subjects at a value of $P < 0.001$. The correlation analyses involved a regression of confrontation naming on gray matter atrophy (based on the difference between each patient group and control subjects), and set at a statistical threshold of $P < 0.001$. For all analyses, we accepted only clusters composed of 100 or more adjacent voxels as significant.

**RESULTS**

**Behavioral Analyses of Naming Performance**

Mean confrontation naming accuracy is summarized in Table 1. As can be seen, the average naming deficit in each patient group differed significantly from older control subjects’ performance, as judged by a criterion of $z < -1.96$ [$P < .05$]. However, an analysis of variance (ANOVA) did not reveal a difference in naming accuracy across patient groups. An evaluation of individual patient performance profiles revealed that 7 (58.3%) of the AD patients and 21 (72.4%) of the FTD patients differed significantly from the control subjects.

Table 1 also summarizes the performance of the patient groups on measures of each of the major cognitive components thought to contribute to confrontation naming. Neither of the patient groups differed significantly from older control subjects in their performance on the visual measure or the semantic measure, according to the averaged $z$-scores, although AD patients differed significantly from FTD patients in their semantic memory performance at the $P < .05$ level, according to a $t$-test. Both patient groups differed from control subjects in their lexical retrieval performance at the $P < .05$ level, although there was no difference between the patient groups.

**Cortical Atrophy in AD and FTD**

The anatomic loci of peak gray matter atrophy in patients with AD and FTD, and the extent of the associated clusters, are summarized in Table 2. These findings show partially distinct distributions of atrophy across the patient groups (Fig 1). AD patients showed gray matter atrophy...
in the bilateral temporal, left frontal, and right parietal regions. FTD patients also showed atrophy in the bilateral temporal and frontal brain regions, although the areas of atrophy appear to overlap only partially with the atrophic regions in AD. Patients with AD and FTD thus seemed to show atrophy in the ventral temporal and dorsolateral prefrontal regions of the left hemisphere.

The validity of these results can be visually assessed by examining the mean brain images of the patient groups, obtained by averaging the spatially normalized results across the subjects in each group (Fig 2). Global neuroanatomic variability is successfully removed by the SPM99 normalization, a prerequisite for VBM analysis. In contrast, note the detailed anatomy that is apparent in the corresponding mean images generated from the normalized results obtained with the high-dimensional registration (Fig 3). The uniformly sharper images reflect a more precise alignment of the brain tissue interfaces. To ensure that the registration also produced the correct structural correspondences, the results were verified by examining the alignment of various sulci between the template and normalized subject brain volumes.

**Naming–Atrophy Correlations in AD and FTD**

Patterns of correlation between naming difficulty and cortical atrophy are summarized in Table 3. In AD, naming difficulty correlated with gray matter atrophy in a left anterior superior temporal distribution. This left anterior temporal area overlaps in part with the distribution of atrophy seen in FTD. There was also a significant correlation between naming and atrophy in AD in the left anterior superior cingulate cortex above the body of the corpus callosum.

In FTD, impaired naming correlated with atrophy of the bilateral ventral and anterior temporal regions. The temporal distribution of atrophy and correlation for naming in FTD overlap in part with that seen in AD in anterior portions of the left temporal lobe. However, the naming–atrophy correlation also was more robust in the right anterior temporal cortex in FTD compared with AD. We also found that the correlation for naming extends into the bilateral frontal regions in FTD. These observations are consistent with the hypothesis that the neural basis for impaired naming in FTD differs in part from the source of naming difficulty in AD.
DISCUSSION

We found impaired naming in AD and FTD that was quantitatively equivalent across groups. Lexical retrieval also appeared to contribute to naming difficulty across both patient groups. However, semantic memory was more impaired in FTD than in AD. This suggested that semantic memory may contribute to naming difficulty in FTD.

In the present study, an area of cortical atrophy common to AD and FTD was the anterior temporal cortex in the left hemisphere. We found that atrophy in this area correlated with confrontation naming difficulty in both patient groups. This is consistent with previous work showing a correlation between confrontation naming and the left anterior temporal cortex in a combined group of AD and FTD patients (4). Based on the observation that naming difficulty correlated with impaired lexical retrieval in AD and FTD, it is possible to infer that the left anterior temporal region contributes to the lexical retrieval component of naming. Moreover, because of convergent evidence for atrophy and a correlation with naming in the same region, this left anterior temporal region is likely to play a necessary role in naming.

We found a correlation between naming and anterior cingulate gray matter volume in AD, although this area
was not particularly atrophic in AD. We speculate that a correlation in an area that does not have significant atrophy suggests an optional role for this brain region in naming. The anterior cingulate has been associated with selective attention and response selection, components of naming that can be impaired in AD. However, the observation that anterior cingulate atrophy does not progress over time in AD, despite much evidence that naming worsens in AD, suggests that this area may not contribute meaningfully to the naming difficulties of AD patients. Longitudinal work is needed to determine the role of the anterior cingulate in naming. We also observed areas of distinct cortical atrophy in FTD. These patients showed distinct distributions of significant cortical atrophy involving the anterior and ventral portions of the temporal lobe bilaterally, for example, and the inferior portions of the frontal lobe bilaterally. These neuroanatomic distributions of atrophy correspond to previous reports of atrophy in MRI studies of FTD (6,39,40). Our observations also parallel reports of functional defects using SPECT and PET glucose metabolism (41–43) and reports of the distribution of atrophy following direct observations at autopsy (44–47). Correlations of gray matter atrophy with confrontation naming in FTD implicated an extensive area of the left temporal cortex as well as the right anterior temporal cortex. Behavioral studies showed that impaired semantic memory contributed uniquely to the naming deficit seen in FTD. We infer that the left posterolateral temporal and right anterior temporal regions play a role in the semantic component of the naming deficit in FTD.

A previous study of the FTD subgroup with semantic dementia showed that these patients have impaired naming earlier in the course of their disease but develop semantic memory deficits as the disease progresses (14). The investigators associated this behavioral progression with the spread of the disease process from anterior portions of the left temporal lobe to anterior portions of the right temporal lobe. Another possibility suggested by our observations is that the disease involves greater portions of the left hemisphere as the condition progresses, including the left posterolateral temporal region. This left posterolateral temporal area has been associated with semantic memory in correlation and activation neuroimaging studies of AD (48–50) and reports of semantic memory in healthy subjects studied with functional MRI (51,52).

Semantic memory is a complex process that involves multiple subcomponents. Among these is the neural representation of feature knowledge associated with objects, actions, and the like, and the semantic categorization processes that organize these features into coherent concepts. The left posterolateral temporal cortex has been associated with a semantic categorization process in previous work (50,52), and the anterior temporal cortex (albeit in the left hemisphere) has been associated with the representation of features for some categories of knowledge (53). Additional work is needed to establish whether the left posterolateral temporal and right anterior temporal cortices help support two different subcomponents of semantic memory during confrontation naming in FTD. This may require a more refined analysis of brain morphology and thus the conduct of modulated versions of voxel-based morphometry, which entail the use of high-dimensional normalization methods that are capable of modeling local as well as global variability in neuroanatomical structure. Our preliminary results indicate that such methods are effective in removing detailed brain shape differences and should facilitate the examination of more subtle effects in imaging studies of structure–function associations in neurodegenerative diseases such as AD and FTD.

<p>| Table 3  |
| Correlations of Gray Matter Atrophy With Confrontation Naming |</p>
<table>
<thead>
<tr>
<th>Anatomic locus (Brodmann area)</th>
<th>Coordinates</th>
<th># Voxels</th>
<th>Z-score</th>
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<td>1683 3.20</td>
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<td></td>
<td>Left anterior cingulate (24)</td>
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<td>192 3.22</td>
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<td>18934 4.41</td>
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<td></td>
<td>Left prefrontal (6)</td>
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<td>203 3.82</td>
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REFERENCES


