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Distinct MRI Atrophy Patterns in Autopsy-Proven Alzheimer's Disease and Frontotemporal Lobar Degeneration

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Abstract

To better define the anatomic distinctions between Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD), we retrospectively applied voxel-based morphometry to the earliest magnetic resonance imaging scans of autopsy-proven AD (N=11), FTLD (N=18), and controls (N=40). Compared with controls, AD patients showed gray matter reductions in posterior temporoparietal and occipital cortex; FTLD patients showed atrophy in medial prefrontal and medial temporal cortex, insula, hippocampus, and amygdala; and patients with both disorders showed atrophy in dorsolateral and orbital prefrontal cortex and lateral temporal cortex ($P_{\text{FWE-corr}} < .05$). Compared with FTLD, AD patients had decreased gray matter in posterior parietal and occipital cortex, whereas FTLD patients had selective atrophy in anterior cingulate, frontal insula, subcallosal gyrus, and striatum ($P < .001$, uncorrected). These findings suggest that AD and FTLD are anatomically distinct, with degeneration of a posterior parietal network in AD and degeneration of a paralimbic fronto-insular-striatal network in FTLD.

Keywords

Alzheimer's disease; frontotemporal lobar degeneration; autopsy; magnetic resonance imaging; voxel-based morphometry

Introduction

Alzheimer's disease (AD) and frontotemporal dementia (FTD) are the leading causes of early-onset dementia.[1,2] FTD describes a group of clinical syndromes, including 1 behavioral variant (bvFTD) and 2 language variants (semantic dementia [SD] and progressive nonfluent aphasia [PNFA]).[3] FTD can also be associated with motor neuron disease (FTD-MND).[4] FTD, clinically defined, most often reflects underlying frontotemporal lobar degeneration (FTLD)

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histopathology,[5] yet 15% to 30% of patients diagnosed with FTD antemortem show AD at autopsy.[6-8] The goal of this study was to identify magnetic resonance atrophy patterns that help distinguish pathologically proven FTLD and AD. For clarity, we use the term FTD to describe patients defined on clinical grounds and reserve the term FTLD to refer to the group of related histopathologies commonly associated with FTD.

Structural imaging studies have identified signature atrophy patterns in AD and FTD. Compared with controls, patients with AD show greatest volume loss in hippocampus, medial temporal, and posterior temporoparietal cortices, whereas patients with FTD show atrophy throughout the frontal and anterior temporal lobes that varies depending on the specific FTD syndrome.[9-16] Although these atrophy patterns are some-what distinct, there is considerable anatomic overlap between the 2 disorders. Volume loss in dorsolateral prefrontal cortex is common in AD (particularly in early-onset cases),[10-12,17-21] whereas hippocampal, medial temporal, and even parietal atrophy can occur in FTD.[19,21-25] Not surprisingly, visual assessment of medial temporal or frontal atrophy on magnetic resonance imaging (MRI) does not reliably discriminate between AD and FTD.[26]

Previous imaging studies that directly compared brain structure in AD and FTD have generally found greater frontal and anterior temporal atrophy in FTD and greater parietal atrophy in AD, with significant overlap in medial temporal structures.[13,19,21,22,24,27-30] These studies have a number of limitations. First, the majority of studies were based on region-of-interest analysis and, thus, did not explore potential differences across the whole brain.[22,24,27-30] Frontal lobe volumes were often measured as a single variable,[31,32] preventing detection of subregion-specific atrophy. Furthermore, most studies directly comparing AD and FTD stratified patients based on clinical rather than pathological diagnosis. Such studies are limited by potential circularity, because clinical syndromes that are influenced by anatomical focality are used to define regional differences between the 2 disorders. To our knowledge, no study to date has directly compared structural changes across the whole brain in pathologically proven AD and FTLD.

In this study, we used voxel-based morphometry (VBM)[33] to compare whole-brain atrophy patterns in autopsy-confirmed AD and FTLD. A better understanding of the anatomic distinctions between AD and FTLD could improve the diagnostic utility of MRI and focus the search for regional vulnerability mechanisms in each disease. A priori, we hypothesized that atrophy in a frontal paralimbic network, including anterior cingulate, frontal insula, and subcallosal gyrus, would discriminate FTLD from AD. Atrophy in these regions is common across clinical and pathologic FTD subtypes,[9,15,34] and the failure of social and emotional functions mediated by this network[35-37] leads to mal-adaptive behaviors that discriminate FTD from AD.[38-41] Furthermore, we hypothesized that atrophy in posterior parietal cortex would discriminate AD from FTLD. This region shows early functional and structural changes in AD[12,42,43] and mediates cognitive functions (eg, spatial navigation and visual construction) that are selectively impaired in AD compared with FTD.[44-46]

Methods

Patient Selection

We searched the University of California San Francisco Memory & Aging Center (UCSF MAC) database for all patients who underwent autopsy and met pathologic criteria for AD (NIA-Reagan)[47] or FTLD (McKhann).[5] Because our specific hypotheses about anatomic distinctions between the 2 disorders apply to FTLD pathologies that predominantly affect the frontal and anterior temporal cortex, we did not include patients with a pathologic diagnosis of corticobasal degeneration (CBD) (which often leads to asymmetric parietal as well as frontal atrophy) or progressive supranuclear palsy (PSP) (predominantly brainstem and subcortical

atrophy).[48,49] In all the cases, patients or their surrogate decision makers provided a declaration of intent to undergo autopsy antemortem and next-of-kin provided consent to proceed with autopsy at the time of death.

We identified a total of 74 patients who had undergone autopsy between May 1999 and January 2007, 36 with AD and 38 with FTLD. Of these, 44 patients (20 AD and 24 FTLD) had a high-resolution MRI at our center during life. In the AD group, 3 patients were excluded because they did not meet NIA-Reagan criteria for high-likelihood AD, 3 were excluded because of mixed pathology (2 AD/PSP, 1 AD/CBD), 2 were excluded because of extensive white matter abnormalities on MRI (that confound image processing for VBM), and 1 patient was excluded because his autopsy tissue and report could not be reviewed. Patients with high-likelihood AD and comorbid Lewy bodies were included because of the high prevalence of Lewy bodies in pathologically confirmed AD, estimated at up to 60% when using modern immunohistochemistry.[50] In the FTLD group, 4 patients were excluded because of MRI motion artifact, 1 patient was excluded because of the presence of a right caudate infarct on imaging, and 1 patient was excluded because he was not considered demented at the time of death (this patient had amyotrophic lateral sclerosis but did not meet clinical research criteria for FTD). The final cohort consisted of 11 AD and 18 FTLD patients (Table 1). Thirteen autopsies were performed at the University of Pennsylvania, 12 at UCSF, 1 autopsy was shared by UCSF and the University of Pennsylvania, and 1 autopsy each was performed at the University of California at Irvine, Stanford University, and the University of Southern California.

All the patients had undergone at least 1 clinical evaluation at the MAC, which included a history and physical examination by a neurologist, a structured caregiver interview administered by a nurse, and a previously described battery of neuropsychologic tests.[46] Patients' functional statuses were measured using the Clinical Dementia Rating Scale (CDR).[51] Forty imaging controls were selected based on age matching from a pool of cognitively normal volunteers followed at the MAC. None of the controls had a history of neurologic or psychiatric illness. All the controls underwent a comprehensive clinical evaluation similar to the patient evaluations. None of the controls underwent autopsy.

Clinical diagnoses (including "normal control") were determined at a multidisciplinary conference. Standard research criteria were used for the diagnosis of AD (NINCDS-ADRDA)[52]; the FTD clinical syndromes bvFTD, SD, and PNFA (Neary)[3]; and dementia with Lewy bodies (DLB) (McKeith).[50,53] Clinical diagnosis at patients' first evaluation was blinded to imaging findings. In all the patients followed longitudinally, the diagnosis closest to the date of the MRI is presented, and longitudinal changes in diagnosis are also noted (Table 1). Onset of symptoms was determined retrospectively based on the estimated date of the first symptom, as identified by patients or caregivers and documented in medical records.

Patients and controls were well matched for age and education, although male gender was more common in FTLD than in AD or controls (Table 2). AD and FTLD patients were well matched for disease duration, time from MRI to autopsy, and dementia severity as measured by the Mini-Mental State Exam[54] and the CDR total and sum of box scores.

Image Acquisition and Analysis

MRI scans were performed on a 1.5-T Magnetom VISION system (Siemens Inc, Iselin, NJ) using a previously published protocol.[9] In patients with multiple MRIs, only the earliest MRI was included in the analysis. VBM[33] was performed using a previously described protocol[55] that includes creation of a study-specific template and custom tissue class prior probability maps.[56-58] This optimized protocol yields more biologically plausible results in neurodegenerative disease than the original VBM methods.[59] Gray matter voxel values were

multiplied by the Jacobian determinants derived from spatial normalization to preserve the original volumes. Images were smoothed using a 12-mm full-width at half-maximum isotropic Gaussian kernel. Total intracranial volume (sum of gray matter, white matter, and CSF volumes derived from image segmentation) was entered into the design matrix as a global correction factor, and age and sex were entered as nuisance variables. Comparisons were made using the following contrasts: (1) AD < normal controls (NC), (2) FTLD < NC, (3) AD < FTLD, (4) FTLD < AD, (5) NC < AD, and (6) NC < FTLD. To identify regions of gray matter loss that occur in both AD and FTLD compared with controls, we tested the conjunction null hypothesis when combining the contrasts AD < NC and FTLD < NC (conjunction analysis).[60] To allow broad visualization of the data, results were displayed on the study-specific template as t-maps thresholded at $P < .001$ (uncorrected for multiple comparisons). Voxels were considered significant at $P < .05$ after family-wise error (FWE) correction for multiple comparisons. All image processing and analyses were implemented in the SPM2 software package (http://www.fil.ion.ucl.ac.uk/spm).

Neuropathology

Twenty-six of 29 autopsies were performed at the University of Pennsylvania or at UCSF using a previously published protocol.[6] Autopsy reports from outside institutions were reviewed by a neurologist (GDR) to ensure adherence to a comparable protocol. At a minimum, all autopsies were required to include tissue sampling in regions relevant to the differential diagnosis of dementia based on published consensus criteria,[5,47,50] tissue staining with hematoxylin/eosin and thioflavin S or Bielschowsky silver staining, and immunohistochemistry using antibodies against Aβ, tau or hyperphosphorylated tau, α-synuclein, and ubiquitin. The pathologic diagnosis of AD was based on high likelihood by NIA-Reagan criteria[47] and FTLD on the diagnostic algorithm of the McKhann work group.[5] FTLD cases were divided into 3 subtypes based on distinct patterns of intracellular inclusions on immunohistochemical staining: (1) tau-positive inclusions with or without Pick bodies (FTLD-T); (2) tau-negative, ubiquitin-positive inclusions (FTLD-U, with or without associated motor neuron disease, designated FTLD-MND); and (3) tau-negative, ubiquitin-negative inclusions (dementia lacking distinctive histology, FTLD-DLDH).[5]

Statistical Analysis

Group differences in continuous variables were examined using 1-way analysis of variance (ANOVA) and Tukey's post hoc contrasts (for comparisons involving 3 groups) or 2-tailed independent sample *t*-tests (for comparisons involving 2 groups). Dichotomous variables were analyzed using χ^2 tests. Statistical analyses were implemented in SPSS 12.0 for Windows software (SPSS Inc, Chicago, IL).

The study was approved by the UCSF and University of Pennsylvania committees on human research.

Results

Clinicopathologic Correlations

Pathologic and clinical diagnoses are presented in Table 1. Four patients in the AD group had comorbid neocortical Lewy bodies, whereas 2 patients showed neurofibrillary degeneration of brainstem nuclei. Ten of 18 FTLD patients had FTLD-U, at times associated with FTLD-MND. While this study was in progress, the TAR DNA-binding protein TDP-43 was found to be the ubiquitinated protein associated with FTLD-U and FTLD-MND inclusions.[61] Eight of 10 FTLD-U/FTLD-MND cases included in this study were assessed with TDP-43 immunohistochemistry and all 8 cases showed TDP-43 immunoreactive intraneuronal

inclusions. Six of 7 FTLD-T patients had Pick's disease, whereas 1 patient had a nonspecific tauopathy.

Two patients with a pathologic diagnosis of AD had a clinical diagnosis of bvFTD. One patient from the AD group had a clinical diagnosis of DLB and was found to have neocortical Lewy bodies. Another patient with a clinical diagnosis of mixed AD/DLB had neurofibrillary degeneration of brainstem nuclei, but no Lewy bodies on autopsy.

The majority of FTLD patients had bvFTD or FTD-MND clinically. All patients with a clinical diagnosis of MND had tau-negative, ubiquitin immunoreactive pathology. Three of 6 also met pathologic criteria for FTLD-MND (the spinal cord was not available for examination in the 3 patients who did not meet criteria). One patient with clinical MND had a diagnosis of "AD versus PNFA" at the time of his first MRI. The clinical diagnosis was changed to FTD-MND at a sub-sequent visit 16 months later. In contrast, 1 patient with FTLD-MND pathology had a diagnosis of PNFA-MND at first MRI, which was changed to "PNFA-MND versus AD-MND" at a later clinical evaluation. All 6 patients with Pick's disease presented clinically as bvFTD, as did the patient with DLDH. Three of 4 SD patients had FTLD-U whereas the other had a non-specific tauopathy.

Voxel-Based Morphometry

AD <NC—Compared with controls, AD patients showed diffusely decreased cortical gray matter, most pronounced in posterior temporoparietal regions ($P < .001$, uncorrected for multiple comparisons; Figure 1A). Significant voxels were found bilaterally in inferior frontal, right superior frontal, and right posterior orbital gyrus; bilateral precentral gyrus; bilateral angular and supramarginal gyri; bilateral middle temporal gyrus and right superior temporal sulcus; bilateral middle occipital gyrus; and bilateral caudate head ($P_{FWE\text{-}corr} < .05$, Table 3). Posterior cingulate, precuneus, medial temporal cortex, hippocampus, and amygdala were atrophic bilaterally at $P < .001$ uncorrected, but did not survive multiple comparisons correction.

FTLD < NC—Compared with controls, FTLD patients demonstrated gray matter loss predominantly in the frontal and anterior temporal lobes, though atrophy did extend to posterior temporal and parietal cortex, particularly on the right ($P < .001$, uncorrected; Figure 1B). Following multiple comparisons correction, significant voxels were found bilaterally in dorsolateral prefrontal cortex, anterior cingulate, orbital frontal cortex, frontal poles, sub-callosal gyrus, and frontal insula; left precentral gyrus; bilateral fusiform and parahippocampal gyri and right inferior temporal gyrus; bilateral hippocampus and amygdala; bilateral caudate head and left putamen ($P_{FWE\text{-}corr} < .05$, Table 3).

Conjunction of (AD < NC) and (FTLD < NC).—Conjunction analysis revealed common regions of decreased gray matter in both AD and FTLD compared with controls in bilateral dorsolateral and orbital prefrontal cortex; bilateral angular and supramarginal gyri; throughout the temporal lobes; and in bilateral hippocampus, amygdala, and striatum ($P < .001$, uncorrected; Figure 1C). Following multiple comparisons correction, significant voxels were found in left middle frontal gyrus, right posterior orbital gyrus, and bilateral inferior frontal gyrus; right posterior superior temporal sulcus; and bilateral head of the caudate ($P_{FWE\text{-}corr} < .05$, Table 3).

AD < FTLD—Compared with FTLD patients, AD patients had decreased gray matter in the right precentral gyrus, left superior parietal lobule and supramarginal gyrus and bilateral angular gyrus, bilateral middle occipital gyrus and left intraoccipital sulcus ($P < .001$,

uncorrected; Figure 2A, Table 4). None of these regions survived multiple comparisons correction.

FTLD < AD—Compared with AD patients, FTLD patients showed gray matter loss in left superior and inferior frontal gyrus, right frontal pole, and bilateral anterior cingulate; posterior orbital and subcallosal gyrus; anterior insula and striatum ($P < .001$, uncorrected; Figure 2A and B, Table 4). Only bilateral striatum was significant after multiple comparisons correction ($P_{FWE\text{-}corr} < .05$).

Other contrasts—The contrasts NC < FTLD and NC < AD did not yield significant results (at $P < .001$, uncorrected).

Discussion

In this study, we used VBM to compare gray matter loss in patients with pathology-proven AD and FTLD with cognitively normal controls and with each other. In general, our findings were consistent with previous imaging studies (largely based on clinical diagnosis)[9-14,16,24,28,38,62-64] and with the known gross and microscopic pathologic distribution of disease in AD[47,65] and FTLD.[66,67] We found that lateral parietal and occipital cortices are more atrophic in AD than in FTLD, whereas atrophy in a distinctive set of frontal paralimbic cortices (anterior cingulate, anterior insula, subcallosal gyrus) and the striatum differentiates FTLD from AD (Figure 2). In contrast, gray matter loss in dorsolateral prefrontal cortex and the medial temporal lobes (including hippocampus and amygdala) is found in both AD and FTLD compared with controls and does not help discriminate between the 2 disorders (Figure 1).

The majority of cortical areas specifically affected in FTLD (Figure 2) lie at transition zones between primitive allocortex and granular neocortex[68] and are robustly interconnected with each other and with subcortical regions prominently affected in FTLD, including the striatum and amygdala.[69] Converging evidence from lesion, functional neuroimaging, and neurophysiological studies has demonstrated the importance of this anterior paralimbic circuit in mediating emotional and social function, decision making related to reward-punishment contingencies, and autonomic-interoceptive processing.[35,37,69-73]

The unifying function of the network may be to grade the social, emotional, or motivational salience of internal and external stimuli to guide adaptive, context-specific behavior.[37] Failure of the FTLD paralimbic system can result in a host of maladaptive behaviors, many of which discriminate FTLD from AD, including disinhibition, apathy, obsessive-compulsive behaviors, failure to infer the mental state of others, and loss of empathy, satiety, disgust, and pain.[39-41,74] Cognitive tasks that engage the anterior paralimbic system are impaired in FTLD[75] and help distinguish FTLD and AD.[76] This network is further characterized by the presence of von Economo neurons, a group of large, bipolar projection neurons found only in great apes, humans, and selected whales and localized almost exclusively to anterior cingulate and frontal insular cortex.[77,78] von Economo neurons are selectively lost in FTLD compared with both AD and controls, providing a possible clue to the biological substrate of FTLD-selective regional vulnerability.[79]

Gray matter loss in posterior association cortices, including superior and inferior parietal lobules and visual association cortex, was greater in AD than in FTLD (Figure 2A). In AD, β-amyloid deposition, tissue hypometabolism, and cortical atrophy all converge in heteromodal parietal association cortex.[80] Metabolic and structural changes in posterior parietal cortex are apparent in early AD and even in presymptomatic apolipoprotein E4 carriers.[81] These regions are engaged in episodic memory retrieval[82] as well as in spatial and visual construction tasks that discriminate AD from FTLD.[45,46] Parietal association cortices are tightly inter-connected

with the medial temporal lobes,[83] and this connectivity is disrupted in AD.[84] Our inability to detect selective atrophy of medial parietal cortex (including posterior cingulate and precuneus), a critical component of the AD network, may reflect a lack of power because of the limited number of AD cases.

Atrophy in visual association cortex in AD compared with FTD has been previously reported[19] and may, in part, reflect the relatively young ages of our AD patients (mean age 64.5 years, 7/11 patients younger than 65 years at the time of MRI). Cortical atrophy in early-onset AD (symptom onset before 65 years) is more diffuse than in late-onset AD and can involve visual association areas.[85] Although the patients in our study were not all prospectively evaluated for the posterior cortical atrophy (PCA) syndrome, which is associated with greater occipital atrophy than "typical" AD,[86] review of medical records revealed that 1 patient was clinically diagnosed with PCA (Table 1) and 2 patients had early or disproportionate visuospatial or visual perceptual deficits consistent with PCA.

Our finding of selective precentral gyrus atrophy in AD is surprising, because structural, functional, and pathologic changes in AD typically spare primary motor and sensory cortex.[85,87,88] However, atrophy and pathologic involvement of primary motor cortex in AD have been previously reported,[89,90] and the robust significance of this finding in the AD < NC contrast (Table 3) makes it less likely to be spurious. Motor symptoms and signs are also more common in early-onset AD.[91,92] Although a different set of results may have been expected had we compared atrophy in FTLD with late-onset AD (which shows greater hippocampal atrophy and less cortical atrophy compared with early-onset AD),[85] age-matched patient groups provide more clinically applicable findings, because FTLD enters the differential diagnosis most commonly in patients with early-onset dementia.[1,2]

In addition to searching for patterns of atrophy that discriminate between AD and FTLD, we also sought to find regional atrophy common to both disorders. A conjunction analysis revealed that atrophy in dorsolateral prefrontal cortex occurs in both AD and FTLD compared with controls (Figure 1C), consistent with reports that executive dysfunction is found in both disorders and does not reliably distinguish between them.[45,46] Furthermore, hippocampus and amygdala atrophy was seen in both diseases (at $P < .001$ uncorrected, these regions survived multiple comparisons correction only in the FTLD < NC contrast), consistent with previous reports of medial temporal atrophy in both AD and FTD.[22,24] Striatal atrophy was found when comparing both patient groups with controls, as well as in the FTLD < AD contrast. Although the validity of VBM findings in periventricular regions remains a concern because of the imperfect registration of anatomic structures near large image gradients,[59,93] our group has recently validated striatal VBM findings using manual region-of-interest tracing.[34]

Our study has a number of limitations. First, the retrospective study design introduces potential bias. For one, neuropathologists were not blinded to clinical data, including neuroimaging findings, at the time of autopsy. However, the application of a standardized pathologic evaluation that takes into account a broad differential diagnosis for degenerative dementia decreases the chance that clinical data may have biased the autopsy diagnosis. Any potential bias related to imaging analysis is mitigated by our use of VBM, which is an automated, objective, and unbiased tool for comparing gray matter volumes. It is also worth noting that all clinical diagnoses presented in this study were made prospectively while the patients were alive, and the initial clinical diagnosis (Table 1) was blinded to imaging results. Further studies are necessary to determine whether our group-level, retrospective findings can be applied to prospectively predict underlying pathology in individual patients.

As with many imaging studies based on autopsy-proven diagnosis, small group sizes limited our power to detect significant differences in gray matter volume, especially in the direct patient

group comparisons. For this reason, few of the voxels in the direct contrasts between AD and FTLD survived FWE correction for multiple comparisons (Table 4). However, the patterns of atrophy detected in these contrasts at an uncorrected threshold ($P < .001$) matched well with our a priori hypotheses as outlined in the Introduction. Furthermore, the FWE criteria were originally designed for functional imaging studies and may be overly stringent for VBM.[94] For these reasons, we believe that the head-to-head AD versus FTLD findings reported here are meaningful and valid though most did not meet our most stringent statistical criterion.

The FTLD group defined for this study included a number of clinical FTD and pathological FTLD sub-types. The majority of patients in our analysis (16/18) presented clinically as either bvFTD or SD (Table 1). Although these disorders are clinically and anatomically distinct, both variants share similar behavioral features,[3,95] and anterior paralimbic atrophy is a common denominator in both disorders.[9] Inclusion of patients with MND may have decreased our sensitivity to detect atrophy, because FTLD patients with MND generally show more restricted gray matter loss than those without MND.[96] Our analysis also included comparable numbers of the FTLD-U (N=10) and FTLD-T (N=7) pathologic subtypes. Significant overlap exists in the clinical presentation and anatomic patterns associated with these histopathologies.[6,7,15,34] Because the clinician is likely to encounter the full spectrum of FTLD-associated clinical and pathological variants, our approach allowed us to identify regions affected across subtypes that may best differentiate FTLD from AD. Antemortem prediction of specific FTLD pathology will be critical for developing and testing disease-specific therapies and represents an important area for future investigation.

In summary, this study found distinct patterns of brain atrophy in AD and FTLD, with greater posterior parietal atrophy in AD and greater FTLD-associated atrophy in an anterior fronto-insular-striatal network. Bedside tasks that selectively engage these networks may be of great utility in differential diagnosis. Further studies are necessary to determine whether these findings can improve diagnostic accuracy when prospectively applied to MRI scans from individual patients. Finally, special attention to the unique anatomic and biologic properties of these networks may yield further clues to the pathogenesis of AD and FTLD.

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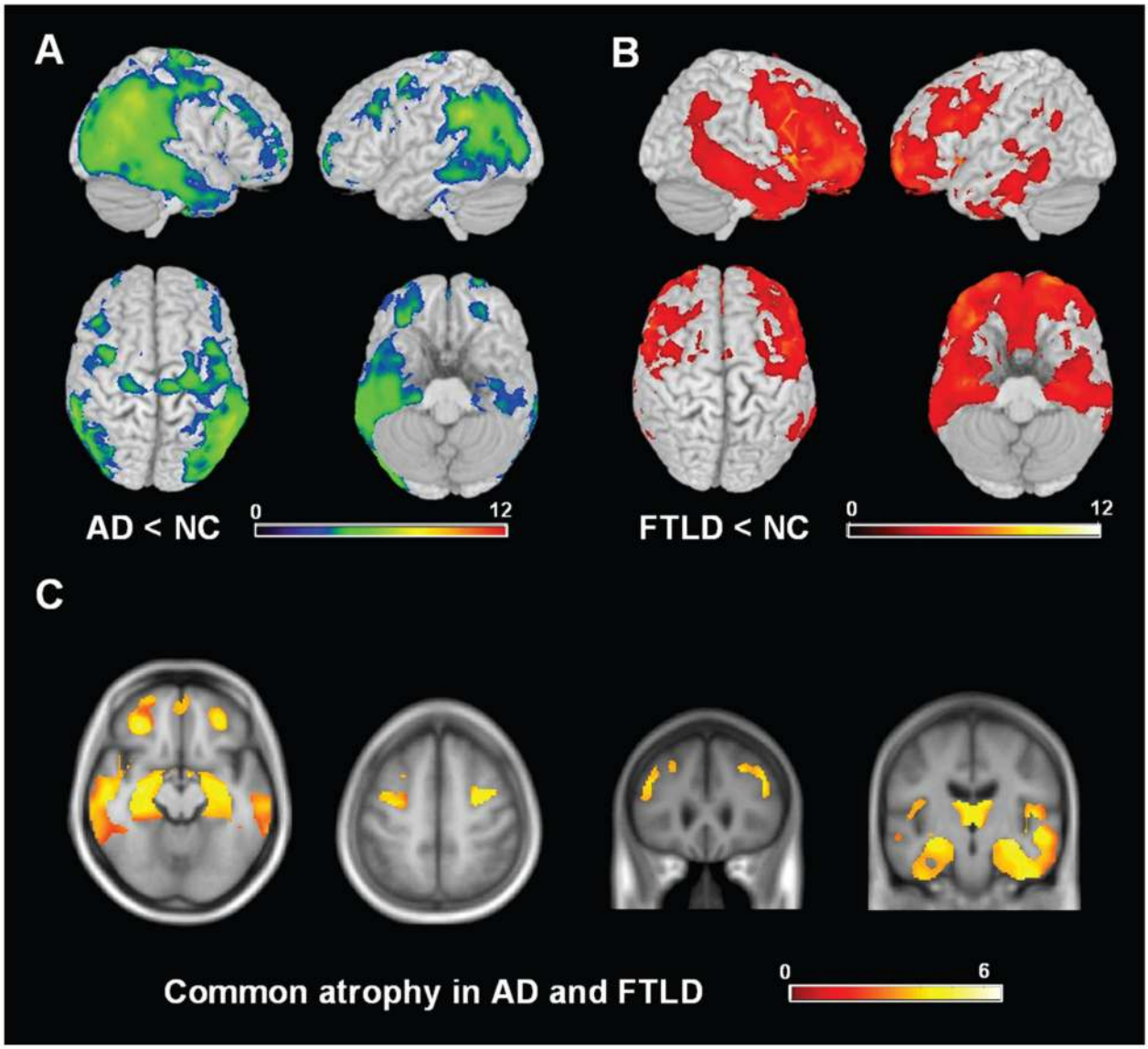

Figure 1.

(A, B) Patterns of gray matter loss in autopsy-proven Alzheimer's disease (AD) (A) and frontotemporal lobar degeneration (FTLD) (B) compared with controls. *T* score maps are rendered on the Montreal Neurological Institute template brain. (C) Conjunction of contrasts shown in (A) and (B). *T* score maps are displayed on axial (from left, z=-15 and 52) and coronal (from left, y=28 and -15) sections of the study-specific template brain in neurologic orientation. All results are presented at a threshold of $P < .001$ uncorrected. To highlight gray matter structures for display purposes, the findings are presented using the segmented gray matter image of the study-specific template as a region of interest.

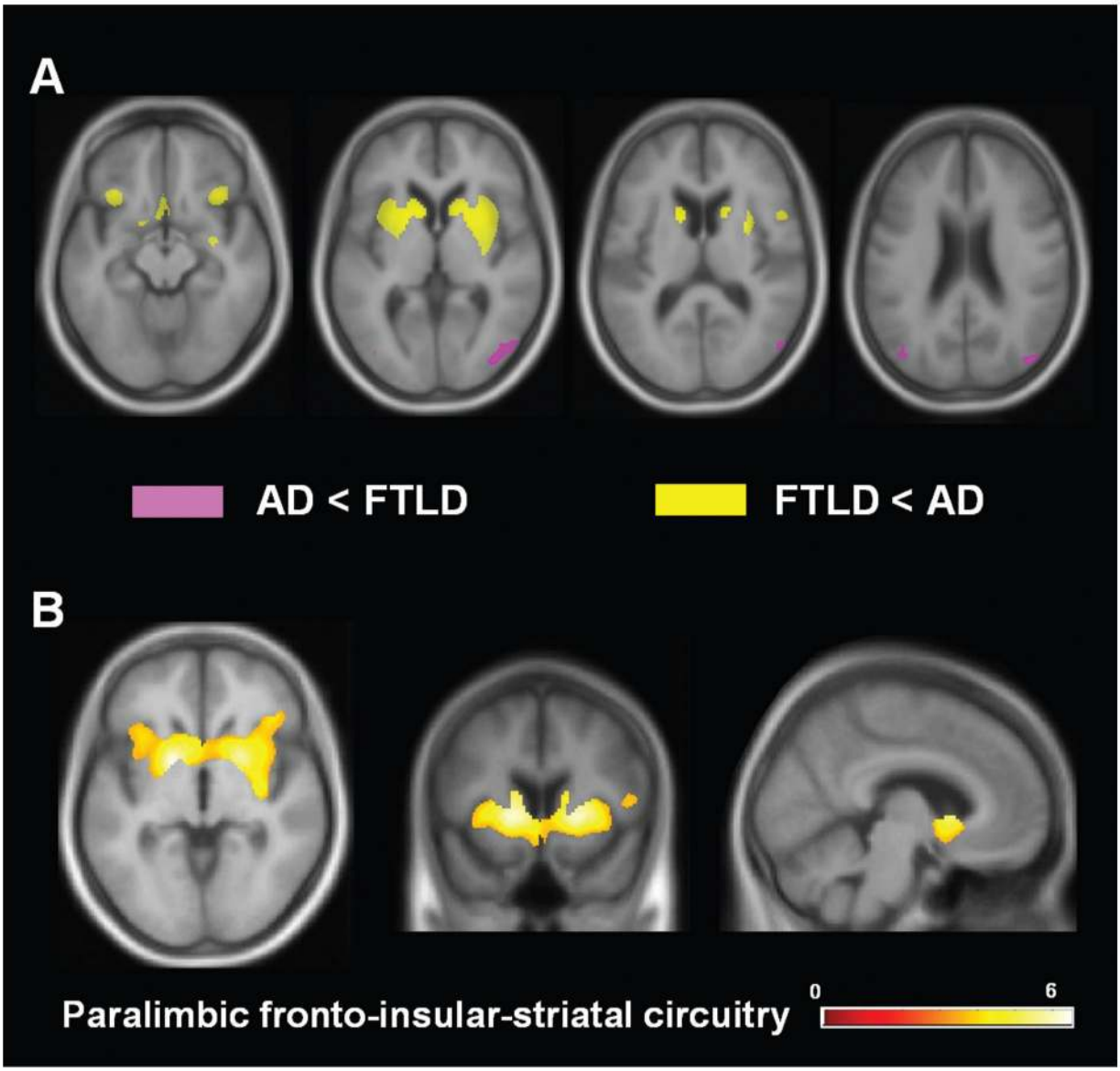

Figure 2.

(A) Direct comparison of atrophy in pathology-proven frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD). Regions of atrophy specific to AD (pink) and FTLD (yellow) are displayed on axial sections (from left, z=-14, 3, 11, and 24) of the study-specific template. (B) The FTLD < AD contrast highlights a fronto-insular-striatal paralimbic network. T score maps are displayed on axial (z=-4), coronal (y=11), and sagittal (x=-6) sections of the study-specific template in neurologic orientation. All results are presented at a threshold of $P < .001$ uncorrected. For display purposes, the data are shown using the segmented gray matter image of the study-specific template as a region of interest.

Table 1

Clinical and Pathologic Diagnoses[a]

No.	Age at Death	Clinical Diagnosis	Pathologic Diagnosis	Comments
Alzheimer's disease				
1	62.6	AD possible	High probability AD	Infrequent limbic LBs
2	59.7	AD probable	High probability AD	Infrequent brainstem and limbic LBs
3	75.5	AD probable	High probability AD	Brainstem, limbic, and neocortical LBs
4	90.5	AD probable	High probability AD	Amyloid angiopathy
5	66.3	AD probable	High probability AD	Brainstem, limbic, and neocortical LBs; amyloid angiopathy
6	69.0	AD probable	High probability AD	Brainstem, limbic, and neocortical LBs; possible amyloid angiopathy
7	62.8	AD probable (PCA)	High probability AD	
8	73.2	AD/DLB probable	High probability AD	Neurofibrillary degeneration of brainstem nuclei
9	68.1	DLB probable	High probability AD	Brainstem, limbic, and neocortical LBs
10	61.9	bvFTD	High probability AD	
11	56.8	bvFTD	High probability AD	Neurofibrillary degeneration of brainstem nuclei
Frontotemporal lobar degeneration				
1	56.9	bvFTD	FTLD-DLDH	
2	74.4	bvFTD	Pick's (FTLD-T)	
3	72.1	bvFTD	Pick's (FTLD-T)	
4	68.3	bvFTD	Pick's (FTLD-T)	Moderate neuritic plaques; remote infarct frontal subcortical white matter
5	69.7	bvFTD	Pick's (FTLD-T)	Severe intracranial atherosclerosis with white matter ischemia
6	58.8	bvFTD	Pick's (FTLD-T)	
7	61.6	bvFTD	Pick's (FTLD-T)	
8	78.3	SD	Tauopathy NOS (FTLD-T)	Tau-positive grains and threads, mainly in hippocampus and temporal neocortex
9	53.5	bvFTD	FTLD-U/TDP-43	
10	76.8	SD	FTLD-U	TDP-43 stain not done
11	58.4	SD	FTLD-U/TDP-43	
12	73.5	SD	FTLD-U/TDP-43	
13	77.2	AD-MND vs PNFA-MND[b]	FTLD-U	Spinal cord not available; TDP-43 stain not done
14	63.5	FTD-MND	FTLD-U/TDP-43	Spinal cord not available
15	59.5	FTD-MND	FTLD-U/TDP-43	Spinal cord not available
16	53.3	FTD-MND	FTLD-MND (FTLD-U/TDP-43)	Remote infarcts left temporal pole and left orbital frontal cortex
17	59.3	FTD-MND	FTLD-MND (FTLD-U/TDP-43)	
18	53.1	PNFA-MND[c]	FTLD-MND (FTLD-U/TDP-43)	

Note: AD = Alzheimer's disease; FTLD = frontotemporal lobar degeneration; DLB = dementia with Lewy bodies; bvFTD = behavioral-variant frontotemporal dementia; MND = motor neuron disease; SD = semantic dementia; PNFA = progressive nonfluent aphasia; FTLD-DLDH = FTLD with dementia lacking distinctive histology; FTLD-T = FTLD with tau-positive inclusions; FTLD-U = FTLD with ubiquitin-positive/tau-negative inclusions; FTLD-U/TDP-43 = FTLD with ubiquitin and TDP-43 positive inclusions; FTLD-MND = FTLD that also meets pathologic criteria for motor neuron disease; NOS = not otherwise specified; LBs = Lewy bodies.

[a] Age at death is shown in years. Clinical diagnosis refers to diagnosis at the time of MRI. Clinical diagnosis did not change by autopsy unless otherwise specified.

[b] Diagnosis at autopsy was FTD-MND.

[c] Diagnosis at autopsy was AD-MND versus PNFA-MND.

Table 2

Group Characteristics[a]

	AD (N = 11)	FTLD (N = 18)	NC (N = 40)	P
Gender (M:F)	5:6	15:3	17:23	0.01[b]
Education (years)	16.5 ± 2.9	17.2 ± 2.2	17.4 ± 2.4[c]	NS
Age at MRI (years)	64.5 ± 9.7	62.5 ± 8.7	63.5 ± 5.8	NS
Onset to MRI (years)	6.0 ± 4.6	5.8 ± 4.2	N/A	NS
MRI to death (years)	3.4 ± 2.0	2.5 ± 1.7	N/A	NS
MMSE	19.9 ± 6.9	21.9 ± 8.2[c]	29.7 ± 0.5	< .001[d]
CDR—total	1.2 ± 0.5[c]	1.0 ± 0.6[c]	N/A	NS
CDR—sum of boxes	7.3 ± 2.6[c]	5.7 ± 3.2[c]	N/A	NS

Note: AD = Alzheimer's disease; FTLD = frontotemporal lobar degeneration; NC = normal control; MRI, magnetic resonance imaging; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; N/A = not applicable; NS = not significant ($P > .05$).

[a] Continuous variables are presented as means ± standard deviations.

[b] Individual comparisons significant between FTLD and controls ($P < .001$) and between FTLD and AD ($P < .05$).

[c] Data not available for all subjects.

[d] Post hoc significant between AD and controls ($P < .001$) and between FTLD and controls ($P < .001$).

Table 3

Regions of Gray Matter Loss in AD and FTLD Compared With Cognitively Normal Controls[a]

Structure	BA	*x*	*y*	*z*	*T*	*P* (FWE-corr)
AD <NC						
L Superior frontal gyrus	6	-24	-9	51	5.86	0.01
R Inferior frontal gyrus	44	38	9	33	5.82	0.01
	44	41	20	29	5.44	0.03
L Inferior frontal gyrus	44	-38	10	27	6.77	0.00
R Posterior orbital gyrus	11	29	37	-11	5.82	0.01
R Precentral gyrus	6	27	-16	75	5.49	0.02
L Precentral gyrus	4	-31	-13	47	5.43	0.03
R Angular gyrus	39	58	-52	40	6.87	0.00
	39	47	-58	44	6.81	0.00
L Angular gyrus	40	-60	-45	33	7.05	0.00
R Supramarginal gyrus	40	43	-31	42	5.68	0.01
L Supramarginal gyrus	40	-54	-49	38	6.57	0.00
R Posterior middle temporal gyrus	37	48	-64	23	7.36	0.00
L Posterior middle temporal gyrus	37	-43	-55	16	6.98	0.00
R Superior temporal sulcus	21/22	55	-24	-7	6.10	0.00
R Middle occipital gyrus	19	42	-82	-3	5.66	0.01
L Middle occipital gyrus	19	-40	-80	1	5.32	0.01
R Caudate head	-	6	11	10	5.94	0.01
L Caudate head	-	-5	7	10	5.32	0.01
FTLD <NC						
L Superior frontal gyrus	10	-25	62	6	7.09	0.00
Cingulate sulcus/superior frontal gyrus (bilateral)	24/32	1	50	24	6.00	0.00
R Middle frontal gyrus	9	25	34	36	6.02	0.00
	46	28	48	20	5.84	0.01
	46	41	51	3	5.96	0.01
L Middle frontal gyrus	46	-26	13	47	5.76	0.01
L Middle frontal gyrus/pole	11	-25	63	0	6.89	0.00
R Inferior frontal gyrus, pars opercularis	44	50	11	18	8.04	0.00
L Inferior frontal gyrus, pars opercularis	44	-42	9	27	7.98	0.00
L Inferior frontal gyrus, pars triangularis	45	-54	26	25	6.29	0.00
L Inferior precentral sulcus	6/44	-52	3	38	6.27	0.00
R Anterior cingulate	24	8	25	20	5.90	0.01
L Anterior cingulate	24	-6	25	19	6.48	0.00
R Frontomarginal gyrus	11	24	74	-5	5.85	0.01
L Frontomarginal/medial orbital gyrus	11	-18	69	-19	5.24	0.05
Subcallosal gyrus (bilateral)	25	0	29	-10	6.06	0.00
R Medial orbital gyrus	11	22	67	-9	6.25	0.00
L Medial orbital gyrus	11	-22	65	-8	7.07	0.00
L Anterior orbital gyrus	11	-22	65	-8	7.07	0.00
L Lateral orbital gyrus	10/11	-39	55	-5	5.75	0.01
R Frontal insula	-	44	9	-5	7.65	0.00
L Frontal insula	-	-44	4	-4	6.29	0.00
R Mid insula	-	47	-4	-3	6.80	0.00
L Precentral gyrus	4	-34	-12	47	5.88	0.01
R Inferior temporal gyrus	20	45	-19	-44	7.01	0.00
R Fusiform gyrus	20	38	-16	-36	5.52	0.01
L Fusiform gyrus	20	-43	-21	-33	5.33	0.01
R Parahippocampal gyrus	36	26	-6	-30	5.89	0.01
L Parahippocampal gyrus	36	-27	-11	-34	5.37	0.01
	35	-36	-20	-41	5.89	0.01
L Isthmus/parahippocampal gyrus	27	-12	-33	-1	6.11	0.00
R Hippocampus	20	32	-20	-14	7.32	0.00

Structure	BA	*x*	*y*	*z*	*T*	*P* (FWE-corr)
L Hippocampus	20	-28	-20	-14	6.38	0.00
R Amygdala	-	20	3	-21	5.85	0.01
L Amygdala	-	-20	1	-20	7.73	0.00
R Caudate head	-	9	16	7	11.00	0.00
L Caudate head	-	-7	13	8	11.63	0.00
L Putamen	-	-18	6	2	10.19	0.00
Conjunction (AD <NC) and (FTLD <NC)						
L Middle frontal gyrus	9	-31	-13	47	5.43	0.03
R Inferior frontal gyrus	44	38	9	33	5.82	0.01
	45	41	20	29	5.44	0.03
L Inferior frontal gyrus	44	-38	10	27	6.77	0.00
R Posterior orbital gyrus	47	29	37	-11	5.82	0.01
R Posterior superior temporal sulcus	21/22	55	-23	-8	6.12	0.00
R Caudate head	-	6	11	10	5.94	0.01
L Caudate head	-	-5	11	8	5.41	0.03

Note: AD = Alzheimer's disease; FTLD = frontotemporal lobar degeneration; NC = normal control; BA = Brodmann area; *T* = *T* score at given voxel; *P* (FWE-corr) = *P* value corrected via familywise error for multiple comparisons.

[a]Coordinates of peak voxels are presented in millimeters in Montreal Neurological Institute stereotactic space.

Table 4

Regions of Gray Matter Loss That Distinguish AD and FTLD[a]

Structure	BA	*x*	*y*	*z*	*T*
AD <FTLD					
R Precentral gyrus	6	27	-16	75	3.54
L Superior parietal lobule	7	-19	-50	46	3.67
L Supramarginal gyrus	40	-49	-58	60	3.77
R Intraparietal sulcus	7	37	-86	47	3.88
R Angular gyrus	39	36	-61	26	4.10
L Angular gyrus	39	-38	-54	28	4.76
L Intraoccipital sulcus	18/19	-26	-94	32	4.01
R Middle occipital gyrus	19	33	-74	17	3.92
	19	37	-76	-2	5.01
L Middle occipital gyrus	19	-39	-79	-2	4.10
FTLD <AD					
L Superior frontal gyrus (pole)	10	9	78	1	3.53
L Inferior frontal gyrus (pars opercularis)	44	54	12	10	3.58
L Anterior cingulate	24	-6	22	26	3.32
R Frontomarginal gyrus	11	18	77	0	4.37
R Posterior orbital gyrus	47	37	25	-9	4.44
L Posterior orbital gyrus	47	-35	22	11	4.14
Subcallosal gyrus (bilateral)	25	0	21	-12	3.41
R Frontal insula	-	33	20	-6	3.79
L Frontal insula	-	-33	20	-5	3.90
R Striatum	-	22	9	0	5.70[b]
L Striatum	-	-17	6	0	6.24[b]

Note: AD = Alzheimer's disease; FTLD = frontotemporal lobar degeneration; BA = Brodmann area; *T* = *T* score at given voxel.

[a] Coordinates of peak voxels are presented in millimeters in Montreal Neurological Institute stereotactic space.

[b] Voxels significant at *P* (FWE-corr) < .05.