Neuroimaging in Neurodegenerative Dementias

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Abstract

Keywords ► neurodegeneration
► neuroimaging
► dementia
► magnetic resonance imaging (MRI)
► functional magnetic resonance imaging (fMRI)
► functional connectivity magnetic resonance imaging (fcMRI)
► diffusion tensor imaging (DTI)
► [18F] fluorodeoxyglucose positron emission tomography (FDG-PET)
► amyloid positron emission tomography
► dopamine transporter (DAT) imaging
► Alzheimer’s disease
► dementia with Lewy bodies
► frontotemporal dementia

Neurodegenerative dementias are characterized by insidious onset and gradual progression of cognitive dysfunction, initially relatively focal with respect to cognitive domains and brain regions involved. Neuroimaging techniques have contributed enormously to both our understanding of large-scale network specificity in neurodegenerative syndromes and our ability to make clinical diagnoses of syndromes such as Alzheimer’s disease (AD), dementia with Lewy bodies (DLB), posterior cortical atrophy (PCA), logopenic primary progressive aphasia (PPA), agrammatic PPA, semantic dementia (SD), behavioral variant frontotemporal dementia (bvFTD), corticobasal syndrome (CBS), and progressive supranuclear palsy syndrome (PSPS). More importantly, rapid advances in imaging and computational techniques promise to improve our ability to make pathologic diagnoses of AD, DLB, and frontotemporal lobar degeneration (FTLD) pathologies in vivo at an early stage of illness. Neuroimaging is thus integral to the development and application of disease modifying therapies for neurodegenerative illnesses.
Rapid advances in our understanding of neurodegenerative dementias in recent years have translated into a change in the clinical approach to a patient presenting with changes in cognition. Whereas previous practice frequently entailed “excluding treatable causes” and lumping the remaining cases together as presenile dementia, senile dementia, or possibly Alzheimer’s disease or multiinfarct dementia, dementia specialists in the present day actively endeavor to predict a patient’s underlying neuropathology utilizing history, examination, and biomarker data. Advances in neuroimaging techniques, particularly magnetic resonance imaging (MRI), have contributed immensely not only to our understanding of clinical/pathologic relationships in the research setting, but also to our ability to arrive at clinical diagnoses in daily practice.

Most neurodegenerative dementias are characterized by a clinical course of insidious onset and gradual progression of symptoms over months to years. Thought previously to engender global cognitive dysfunction even in the early stages of illness,1 neurodegenerative processes are now recognized to produce focal cognitive dysfunction initially, corresponding to a circumscribed initial distribution of pathology. Localization of cognitive dysfunction via history and examination and localization of neuronal dysfunction and/or neurodegeneration with neuroimaging thus empower clinicians to distinguish between unique clinical syndromes with characteristic early anatomic signatures (∼Table 1).

Converging evidence from cellular and systems-level neuroscience suggests that the anatomic signatures of neurodegenerative processes correspond to large-scale networks in the brain. This concept has been articulated as the network degeneration hypothesis, summarized in ∼Fig. 1 and by Pievani and colleagues.2 Neuroimaging techniques have played a central role in exploring this hypothesis. Functional connectivity MRI (fcMRI), examining interregional correlations in neuronal activity with blood-oxygen-level-dependent (BOLD) signal, has revolutionized our understanding of large-scale functional brain networks.3,4 Supporting a relationship between large-scale networks and neurodegeneration, studies have demonstrated correspondence between distributions of pathology and network anatomy, for example, overlap between the distribution of fibrillar amyloid-β protein (Aβ) as revealed by [11C] Pittsburgh Compound-B (PiB) positron emission tomography (PET) and the default network, a set of brain regions including the medial frontal cortex, posterior cingulate, precuneus, lateral parietal cortex, and medial temporal cortex.5 Employing resting state fcMRI

### Table 1 Neurodegenerative Dementia Clinical Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Pathologies</th>
<th>Key Clinical Features</th>
<th>Anatomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amnestic AD</td>
<td>AD ± LB</td>
<td>↓ Episodic memory</td>
<td>Medial temporal, temporoparietal</td>
</tr>
<tr>
<td>Posterior cortical atrophy</td>
<td>AD &gt;&gt;&gt; tau, others</td>
<td>Visuospatial, somatospatial dysfunction</td>
<td>Parietal, occipital</td>
</tr>
<tr>
<td>Logopenic PPA</td>
<td>AD &gt; TDP, tau</td>
<td>↓ Word retrieval, sentence repetition</td>
<td>Left temporoparietal</td>
</tr>
<tr>
<td>Dysexecutive AD</td>
<td>N/A</td>
<td>↓ Complex attention, EF</td>
<td>Frontal, temporoparietal</td>
</tr>
<tr>
<td>DLB/PDD</td>
<td>LB ± AD</td>
<td>↓ EF, VF; park., VH, fluctuations</td>
<td>Midbrain, hypothalamus, SI</td>
</tr>
<tr>
<td>bvFTD</td>
<td>TDP ~ tau &gt;&gt;&gt; FUS</td>
<td>Disinhibition, apathy, ↓ empathy, perseveration, Δ diet, ↓ EF</td>
<td>Frontal, temporal, insula, anterior cingulate</td>
</tr>
<tr>
<td>Agrammatic PPA</td>
<td>tau &gt; TDP, AD</td>
<td>Agrammatism ± AOSb</td>
<td>Left posterior frontal, insula</td>
</tr>
<tr>
<td>Semantic dementia</td>
<td>TDP &gt; tau, AD</td>
<td>↓ Confrontation naming, single word comprehension</td>
<td>Left anterior temporal</td>
</tr>
<tr>
<td>PSPS</td>
<td>tau &gt;&gt; others</td>
<td>Subcortical dementia, axial park., falls, ↓ supranuclear gaze</td>
<td>Symmetrical posterior frontal, brainstem</td>
</tr>
<tr>
<td>Corticobasal syndrome</td>
<td>tau &gt; TDP, AD</td>
<td>Asymmetrical parkinsonism, cortical signs</td>
<td>Asymmetrical frontal ± parietalc</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>PrPsc</td>
<td>RPD, myoclonus, ↓ pyramidal, extrapyramidal, cerebellar, VF</td>
<td>Cortex, striatum, thalamus</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; PPA, primary progressive aphasia; DLB, dementia with Lewy bodies; PDD, Parkinson’s disease dementia; bvFTD, behavioral variant frontotemporal dementia; PSPS, progressive supranuclear palsy syndrome; LB, Lewy body; tau, frontotemporal lobar degeneration (FTLD-) tau; TDP, FTLD-TAR DNA-binding protein 43 (TDP); FUS, FTLD-RNA-binding protein FUS; PrPsc, prion; EF, executive function; VF, visual function; park., parkinsonism; VH, visual hallucinations; AOS, apraxia of speech; RPD, rapidly progressive dementia; SI, substantia innominata.

aThe syndrome has not been explicitly defined; no clinical/pathologic correlations available.
bApraxia of speech is predictive of FTLD-tau pathology.
cFocal frontal atrophy is predictive of FTLD-tau pathology.
Key concepts:
- Neurodegenerative syndromes are associated with abnormal functioning in specific large scale functional brain networks.
- In some conditions the patterns and/or progressions of pathological changes (e.g., misfolded proteins, atrophy) appear to occur in the distribution of abnormally functioning large scale networks.
- Hypothesized mechanisms responsible for network degeneration include: (1) transneuronal spread of pathological agents; (2) nodal stress related to heavy network traffic; (3) trophic failure due to disrupted network connectivity, and (4) shared vulnerability within regions of a network due to a shared susceptibility factor (e.g., gene or protein expression signature).*

Issues and unanswered questions:
- The distribution of misfolded proteins does not always correlate with the distribution of neurodegeneration, suggesting variable roles for misfolded proteins in disease pathogenesis.
- Clinical syndromes can occur due to more than one type of underlying pathology, suggesting that different pathological processes can target the same large scale networks.
- The dividing line between clinical syndromes (e.g., PD and DLB, CBS and PSP, others) is not always clear. Multiple, overlapping clinical syndromes frequently occur in the same individual.
- Any given neuropathology can target different networks in different individuals, giving rise to different clinical syndromes. The factors responsible for variability of distribution are unknown.
- Multiple types of misfolded protein inclusions frequently occur in the same individual, and also frequently coexist with vascular pathology. The factors responsible are not well understood.
- In some instances, such as dementia in the population of individuals over 90, clinical symptoms and deterioration are not as tightly coupled with presence and severity of misfolded protein inclusions.

Alzheimer’s Disease
AD represents the most common cause of both late-onset dementia (LOD) and early-onset dementia (EOD),* accounting for ~50–70% of LOD and 20–40% of EOD diagnosed clinically.15,16 The pathologic defining features of AD include extracellular $\beta$-senile plaques (in particular, a subset called neuritic plaques) and intracellular neurofibrillary tangles (NFTs) containing the microtubule-associated protein tau.17 The average lifetime risk of developing AD is ~10–12%; although the presence of a first-degree relative with AD approximately doubles this risk,18 familial autosomal dominant disease due to mutations in the genes presenilin-1 ($PSEN1$, chromosome 14), presenilin-2 ($PSEN2$, chromosome 1), or amyloid precursor protein ($APP$, chromosome 21) account for less than 2% of all cases of AD.19 AD usually presents with an insidious onset of difficulty remembering autobiographic events (progressing from recent to remote) and frequently accompanied to a lesser extent by problems with language (usually word-finding), executive functions, and visuospatial functions. Approximately one-third of early-onset cases present atypically with dysfunction in a cognitive domain other than episodic memory,20,21 consistent with neuropathologic research reporting a younger mean age of onset for individuals with an atypical distribution of tau pathology affecting the neocortex and sparing the medial temporal lobes (“hippocampal sparing AD”).22 The most common extreme nonamnestic

*The distinction between late-onset and early-onset dementia in the literature has frequently been made arbitrarily on the basis of whether symptoms are first noted prior to age 65 versus at age 65 or greater.
Table 2 Imaging Biomarkers of Neurodegenerative Syndromes and Pathology

<table>
<thead>
<tr>
<th>Neuropathology</th>
<th>Presymptomatic</th>
<th>Mild Cognitive Impairment</th>
<th>Dementia</th>
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<tbody>
<tr>
<td>Clinically significant cognitive impairment</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Loss of function in usual activities</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Structural MRI - visual inspection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td>±</td>
<td>D</td>
</tr>
<tr>
<td>FDG-PET&lt;sup&gt;b&lt;/sup&gt;</td>
<td>G</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Quantitative loss of volume or cortical thickness&lt;sup&gt;b&lt;/sup&gt;</td>
<td>G</td>
<td>±</td>
<td>G</td>
</tr>
<tr>
<td>Amyloid PET&lt;sup&gt;c&lt;/sup&gt;</td>
<td>G</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Task fMRI</td>
<td>G</td>
<td>G</td>
<td>G</td>
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<tr>
<td>Resting state fcMRI</td>
<td>G</td>
<td>G</td>
<td>G</td>
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<tr>
<td>Diffusion tensor imaging</td>
<td>G</td>
<td>G</td>
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</tbody>
</table>

Abbreviations: <sup>▼</sup>, Reliable changes detected in individuals; ±, changes inconsistently detected in individuals; G, effects detected in groups; effects in individuals not yet established reliably; X, changes not detected in individuals or groups; MRI, magnetic resonance imaging; FDG-PET, [18F] fluorodeoxyglucose positron emission tomography; fMRI, functional MRI; fcMRI, functional connectivity MRI.<br/><br/><sup>a</sup>Modalities in clinical use.<br/><br/><sup>b</sup>Some automated medial temporal lobe volumetric protocols in clinical use.<br/><br/><sup>c</sup>Recently approved by the Food and Drug Administration for clinical use.<br/><br/><sup>d</sup>Combined use of multiple modalities may increase predictive value for individual subjects.

Phenotypes of AD are a visual variant (PCA), a language variant (logopenic PPA), and a frontal/dysexecutive variant.

**Structural Imaging in Alzheimer’s Disease**

Structural imaging with computed tomography (CT) and MRI represents the most widely used imaging techniques to assist in the diagnosis of AD. High-resolution T1-weighted sequences such as magnetization prepared rapid gradient echo (MP-RAGE) and spoiled gradient echo (SPGR) MRI sequences allow for more exquisite detection of brain atrophy and also lend themselves to quantitative morphometric techniques for measuring volume and cortical thickness. The medial temporal lobes (primarily hippocampus and entorhinal cortex) are typically the first location to demonstrate atrophy, and remain the most severely affected region as illness progresses.<sup>23</sup> Atrophy spreads to paralimbic and association neocortices, in particular temporal and parietal association cortex, with relative sparing of primary sensory and motor cortices until late in the course of illness (<sup>→</sup>Fig. 2). Newer research criteria for the clinical diagnosis of AD have incorporated atrophy as a feature to potentially assist in making an earlier diagnosis and in increasing diagnostic confidence. For example, Dubois and colleagues<sup>24</sup> proposed criteria allowing for a diagnosis of probable AD in individuals with cognitive dysfunction limited to episodic memory provided one obtains certain specified biomarkers of AD, one of which is medial temporal atrophy (MTA) utilizing qualitative ratings.<sup>b</sup> The MTA scale represents one well-validated method toward this end, delineating five levels of atrophy (MTA 0 through 4) based on manual inspection of coronal T1-weighted images.<sup>25</sup> The National Institute on Aging-Alzheimer’s Association (NIA-AA) workgroups introduced diagnostic constructs including “probable AD dementia with evidence of the AD pathophysiological process,” “possible AD dementia with evidence of the AD pathophysiological process,” and “MCI due to AD,” incorporating atrophy in medial, basal, and lateral temporal lobe and medial parietal cortex on MRI as evidence of downstream neuronal degeneration or injury characteristic of AD.<sup>c</sup>

Quantitative structural imaging techniques provide a greater degree of sensitivity, specificity, and reproducibility in both cross-sectional and longitudinal formats than qualitative techniques, and are thus preferred for use in clinical treatment trials.<sup>23,26,27</sup> Methods applied to single subject data have included manual, semiautomated, and automated tracings of the hippocampus or entorhinal cortex,<sup>28,29</sup> longitudinal quantification of global brain volume over time,<sup>30</sup> and the use of support vector machine algorithms to extract information on the pattern and severity of atrophy from a subject’s three-dimensional (3-D) MRI dataset and to compare it with information from large databases of scanned controls and subjects with AD.<sup>31–34</sup> Quantitative measurements of hippocampal volumes in subjects with amnestic MCI have not only revealed associations between smaller hippocampal volumes and/or more rapid hippocampal atrophy and progression to a clinical diagnosis of dementia due to AD,<sup>35–37</sup> but also an association between subregional hippocampal atrophy and progression from cognitively normal status to amnestic MCI.<sup>38</sup>

<sup>b</sup>Additional specified biomarkers include quantitative volumetry of regions of interest, cerebrospinal fluid (CSF), PET, and presence of an autosomal dominant gene mutation causing AD within the immediate family.

<sup>c</sup>The NIA-AA criteria distinguish between biomarkers of β-amyloid deposition (PET or CSF) and biomarkers of downstream neuronal injury or degradation (CSF tau, structural MRI, FDG-PET), requiring both for “high likelihood” biomarker evidence and one for “intermediate likelihood” biomarker evidence.
Additional insights into the neuroanatomy of AD have been obtained via quantitative structural imaging methods such as VBM, cortical thickness mapping, and tensor-based morphometry applied to groups of subjects with AD compared with healthy controls or other conditions.\(^{39}\) VBM represents a widely used technique for investigating topographic differences in gray matter and/or white matter volumes across the entire brain between groups of subjects.\(^{40}\) Studies in AD have consistently demonstrated volumetric reductions in the medial and inferior temporal lobes, posterior cingulate, precuneus, anterior cingulate, and temporo-parietal association cortex relative to control subjects and subjects with nonprogressive mild memory impairment.\(^{41-43}\)

Measurement of cortical thickness using automated or semiautomated algorithms\(^{44}\) provides an advantage of capturing a physical property of the brain that can be measured in an individual person in vivo or postmortem, with thinning of the cortex corresponding to pathologic observations including cellular shrinkage, neuropil loss, and reduction of intracortical myelin.\(^{39,45}\) A consistent pattern of cortical thinning in AD comprises the medial and inferior temporal lobes; inferior and anterior temporal association cortices; superior, inferior, and medial parietal association cortices; along with superior and inferior frontal association regions.\(^{46-48}\) Dickerson and colleagues have demonstrated high reliability of the "cortical signature of AD," a set of regions with thinning across patient samples and scanner platforms that also predicts progression to AD dementia in subjects with MCI\(^{49}\) and older individuals without cognitive impairment.\(^{50}\)

Importantly, structural neuroimaging measures of atrophy appear to correlate well with the magnitude and distribution of NFT pathology. Consistent with the aforementioned relationships between hippocampal atrophy and clinical progression to amnestic MCI and AD, hippocampal volumes measured antemortem in demented and nondemented subjects have been shown to correlate well with postmortem Braak NFT scores.\(^{51}\) Similarly, the magnitude and pattern of gray matter volume loss across the cerebrum as determined by VBM corresponds with the severity and pattern of NFT pathology as determined by NFT counts at Braak stages III and IV and Braak stage itself at stages V and VI.\(^{52}\) Employing a support vector machine algorithm, Vemuri and colleagues likewise obtained excellent correlation between structural MRI changes in single subjects antemortem (as reflected in the Structural Abnormality Index (STAND) score) and postmortem Braak NFT scores.\(^{53}\)

**Functional and Molecular Imaging in Alzheimer’s Disease**

MRI, PET, and single-photon emission computed tomography (SPECT) offer tools for investigating changes in the functioning and/or molecular composition of brain tissues, particularly valuable because such changes may precede atrophy detectable by structural imaging methods. [\(^{18}\)F] Fluorodeoxyglucose positron emission tomography (FDG-PET) and brain perfusion SPECT are currently in widespread clinical use for diagnosis of and discrimination between different types of neurodegenerative dementia. AD typically produces a
characteristic pattern of hypometabolism or hypoperfusion in bilateral temporoparietal and posterior cingulate/precuneus cortex with later involvement of the frontal lobes and sparing of primary sensorimotor cortices. FDG-PET offers higher sensitivity and spatial resolution than does SPECT.\(^5\) Images may be analyzed qualitatively, with volume-of-interest techniques, or with voxel-based analyses in stereotactic space.\(^5\) Studies investigating the use of qualitative criteria to classify PET scans as reflective or not reflective of AD in groups of subjects evaluated for possible memory impairment with eventual pathologically confirmed diagnoses suggest a diagnostic sensitivity of 84–94% and specificity of 74–78%.\(^5,6\) Ongoing efforts to optimize and standardize methodologies for acquiring, analyzing, and interpreting FDG-PET data will further increase its value as a biomarker in the clinical setting and in treatment trials for AD.\(^5\)

Amyloid PET imaging with agents such as PiB and \([^{18}\text{F}]\text{florbetapir (AV-45)}\) has revolutionized the practice of predicting AD pathology in vivo. Amyloid PET agents detect β-sheet rich fibrillar deposits of Aβ as typically present in compact/cored plaques, to varying degrees in diffuse plaques, and in cerebrovascular amyloid.\(^5\) Preliminary studies correlating in vivo PiB or florbetapir PET results with postmortem pathology suggest a high diagnostic PET for detecting probable or definite pathologic AD by CERAD (Consortium to Establish a Registry for Alzheimer’s Disease\(^6\)) criteria and/or intermediate or high likelihood of pathologic AD by NIA/Reagan Institute (National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer’s Disease\(^6\)) criteria, and a high specificity for amyloid deposition.\(^6,5\) The United States Food and Drug Administration’s recent approval of florbetapir PET for clinical use stands to increase clinicians’ diagnostic accuracy for AD (as confirmed pathologically), particularly in less-specialized settings, if used appropriately.\(^5\) Although amyloid imaging appears promising as a tool for predicting progression of MCI to AD dementia\(^6\) and even for detecting AD in its early presymptomatic stages,\(^5\) continued research is required to identify and actualize its full clinical utility.

Research studies utilizing BOLD functional MRI (fMRI) have contributed a great deal to our understanding of AD and other neurodegenerative dementias, and offer additional potential biomarkers for clinical use in treatment trials and beyond. Task fMRI studies employing block or event-related memory paradigms in subjects with AD and healthy older controls have consistently revealed disease-related decreases in activity in MTL structures (hippocampus, parahippocampus), prefrontal regions, superior parietal lobule, precuneus, cingulate, and lingual gyrus (see Schwidt and Black\(^5\) for meta-analysis). In contrast, numerous investigators have reported increases in MTL activity during encoding in subjects with MCI or asymptomatic individuals with genetic or family risk factors who remain able to perform the tasks well (reviewed in Sperling et al\(^5\)). Although this may reflect compensatory mechanisms, longitudinal studies have suggested that increased MTL activity at baseline predicts rapid cognitive decline and decreased MTL function.\(^5\)

Functional connectivity MRI offers advantages of not requiring or having to account for task performance, not requiring additional hardware, and of potentially generating reproducible data across scanner platforms with relatively short acquisition sequences.\(^5\) Studies employing fMRI with either “seed-based” or independent component analysis (ICA) methods have suggested that, relative to controls, groups of subjects with AD have exhibited reduced intrinsic functional connectivity between default network regions,\(^7,8\) a finding that also appears to discriminate between subjects with MCI who progress to dementia and those who do not.\(^7\) Additional research is needed to validate functional MRI techniques for potential use as a biomarker of AD in single subjects.\(^8,5\)

### Atypical Presentations of Alzheimer’s Disease

As described above, AD occasionally presents atypically, with prominent primary dysfunction in language, attention/executive processing, or higher-order visual processing. In such cases, neuroimaging frequently helps to confirm the presence of a neurodegenerative syndrome with a characteristic pattern of atrophy involving specific neocortical regions and sparing the medial temporal lobes (Fig. 2). PCA frequently causes parietal and occipital symptoms such as visual dysfunction in the absence of ocular disease, elements of the syndromes of Bälint and/or Gerstmann,\(^9\) constructional apraxia, visual field defects, and environmental disorientation\(^7\) (see Crutch et al\(^7\) for review). Structural imaging characteristically reveals prominent, relatively symmetric atrophy in the parietal and occipital lobes.\(^7\) Logopenic PPA is characterized by significant word-retrieval difficulties, poor repetition of phrases and sentences, phonologic errors in speech, but preserved grammar, motor output, and repetition and comprehension of single words.\(^7\) Imaging evidence consists of atrophy and/or hypoperfusion or hypometabolism in left posterior perisylvian temporal and parietal cortices.\(^7\) Dysexecutive or “frontal” AD has been less explicitly characterized as a clinical syndrome distinct from frontotemporal dementia (FTD), but appears likely to involve early frontal and temporoparietal atrophy.\(^7,5\)

Imaging studies have suggested that, though clinically distinct, these nonamnestic phenotypes share a common core temporoparieto-frontal network.\(^5\) Not only have voxel-based techniques revealed substantial overlap in patterns of atrophy across groups of patients with PCA, logopenic PPA, and early-onset AD,\(^5\) they have been used to discriminate between groups of patients with pathologically confirmed AD (both amnestic and nonamnestic) and frontotemporal lobar degeneration regardless of clinical diagnosis.\(^5,8\) Similarly, PET studies comparing atypical or early-onset AD with typical

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\(^5\)It is worth noting that a high specificity for amyloid deposition does not translate directly into a high specificity for AD pathology given the presence of cerebral amyloid in conditions other than AD.

Bälint’s syndrome comprises simultagnosia, optic ataxia, and oculomotor apraxia; Gerstmann’s syndrome comprises agraphia, acalculia, left-right confusion, and finger agnosia.
AD have revealed similar patterns of fibrillar amyloid deposition between atypical and typical cases as well as hypometabolism in a core distribution of regions including temporoparietal, posterior cingulate, and precuneus.84,85

**Dementia with Lewy Bodies**

Dementia with Lewy bodies and Parkinson’s disease dementia (PDD) are the second most common type of neurodegenerative dementia behind AD, with estimated prevalences of 0.7% and 0.3%, respectively, in the population of individuals aged 65 and older.86 In addition to dementia, central features of DLB (and frequently PDD) include fluctuations in attention, alertness or cognition, visual hallucinations, and parkinsonism (see McKeith et al87 for consensus clinical criteria). Early changes in cognition frequently involve attention, executive functions, and higher-order visual functions.88,89 Additional commonly encountered features include neuropsychiatric symptoms (depression, anxiety, apathy, and delusions), rapid eye movement (REM) sleep behavior disorder, severe sensitivity to neuroleptic medications, and autonomic dysfunction.

Lewy bodies, the pathologic hallmark of DLB, consist of filamentous intraneuronal protein inclusions containing the protein α-synuclein distributed throughout the central, peripheral, and autonomic nervous systems.87 To what degree the quantity and distribution of Lewy body pathology correlates with symptom type, severity, and progression in Lewy body disorders remains a matter of debate.90 Synaptic dysfunction and/or cell loss may provide better correlates of clinical dysfunction. Although most patients with DLB have high levels of senile plaques containing Aβ, the level of neocortical NFT pathology is more variable and more directly influences the presence of AD-like versus DLB-like phenotypic manifestations.87,91

**Structural Neuroimaging in Dementia with Lewy Bodies**

Given the pathologic heterogeneity of DLB, it is perhaps not surprising that studies investigating cortical and subcortical atrophy in DLB have yielded inconsistent results (see Taylor and O’Brien92 for review). Structural neuroimaging demonstrating relative sparing of the medial temporal lobes from atrophy supports a clinical diagnosis of DLB rather than AD in the correct context.93,94 Notably, this principle was supported by a recent MRI volumetric study with neuropathologic classification of subject groups revealing increasing antemortem hippocampal and amygdalar volumes with increasing likelihood of DLB pathology and lower volume of the dorsal mesopontine gray matter in the group with high likelihood DLB compared with healthy control subjects and with subjects with AD.95

**Functional and Molecular Imaging in Dementia with Lewy Bodies**

Several types of PET or SPECT studies can be used to support a diagnosis of DLB. Low dopamine transporter (DAT) uptake as measured by [18F]fluorodopa PET or [123I]ioflupane SPECT is useful to distinguish degenerative from nondegenerative causes of parkinsonism.96 A large multicenter study comparing ioflupane SPECT against a gold standard of clinical diagnosis of DLB or non-DLB dementia established longitudinally, suggested diagnostic sensitivity of ~80% and specificity of ~90% for SPECT,97 findings corroborated by a smaller study yielding sensitivity of 88% and specificity of 100% against a pathologic gold standard of DLB versus non-DLB dementia.98 Perhaps of greater clinical utility, ioflupane SPECT is also reliable in confirming cases of clinically possible DLB,99 supporting the inclusion of reduced DAT uptake as a “suggestive feature” of DLB in formal criteria.87

Hypometabolism or hypoperfusion in the occipital and posterior temporoparietal regions on PET or SPECT also occurs frequently, although sensitivities and specificities are debated.92 Kantarcı and colleagues100 demonstrated the value of utilizing multiple imaging biomarkers to distinguish between clinical DLB and AD, achieving an area under the receiver operating characteristic (ROC) curve of 0.98 by combining measures of hippocampal volume, global PiB retention, and occipital metabolism. Additional studies with multiple modes of imaging and pathologic correlation will likely shed additional light on the relationship between amyloid pathology, network function, neurodegeneration, and clinical symptoms in DLB.

**Frontotemporal Lobar Degeneration**

Frontotemporal lobar degeneration (FTLD) comprises several distinct subtypes of pathology that have a predilection to involve the frontal and/or temporal lobes early in the course of illness. The more commonly occurring subtypes of FTLD are those distinguished by tau inclusions (FTLD-tau) and those by inclusions containing TAR DNA-binding protein 43 (FTLD-TDP). FTLD-tau pathologies are further classified into 3R, 4R, or combined 3R/4R subtypes on the basis of the number of microtubule-binding repeats in the tau protein, a consequence of differential mRNA splicing.101 FTLD-TDP can be classified into types A, B, C, and D based upon neuropathologic features.102 The remaining minority of FTLD cases are characterized by inclusions containing RNA-binding protein FUS (FTLD-FUS) or other rare pathologies.

Frontotemporal dementias, the variety of clinical syndromes arising in the setting of FTLD pathology, include bvFTD, agrammatic PPA, SD, FTD with motor neuron disease (FTD-MND), PSPS, and CBS. FTD represents a common cause of early-onset dementia, with an incidence and prevalence similar to that of AD.103 An estimated 25–50% of cases have a family history of dementia; an estimated 10–25% of cases demonstrate a pattern of inheritance suggestive of an autosomal dominant gene mutation.104,105 The most common genes associated with familial autosomal dominant FTD are the tau gene (MAPT; associated with FTLD-tau), the
programalgin gene (GRN; associated with FTLD-TDP), and the chromosome 9 open reading frame 72 gene (C9ORF72; associated with FTLD-TDP), a relatively common cause of both familial FTD and familial amyotrophic lateral sclerosis (ALS) Clinical/pathologic associations vary for different FTD syndromes; for example, PSPS is almost always associated with 4R FTLD-tau pathology, whereas CBS and bvFTD are pathologically more heterogeneous.

**Neuroimaging in Behavioral Variant Frontotemporal Dementia**

Unlike most other neurodegenerative clinical syndromes, bvFTD produces early dramatic changes in personality and behavior often out of proportion to cognitive deficits detectable by standard neuropsychologic measures (see Piguet et al for review). Symptomatic hallmarks, reflected in the most recent consensus clinical diagnostic criteria, include disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviors, hyperorality/change in food preference, and executive dysfunction. Approximately 50% of bvFTD cases demonstrate FTLD-TDP pathology (all subtypes, most commonly type A), ~40% FTLD-tau pathology, and the majority of the remaining cases FTLD-FUS pathology.

In its earliest stages, bvFTD can be difficult to discriminate from developmental or psychiatric conditions that may present in similar fashion, a phenomenon described in the literature on nonprogressive bvFTD “phenocopies.” Atrophy in nodes of the salience network, a paralimbic circuit comprising anterior insular (right > left), medial frontal, orbitofrontal, and temporopolar regions (among others) is reliably associated with progressive, degenerative bvFTD. Kipps and colleagues developed a qualitative visual rating scale for FTD with high inter-rater reliability on the basis of atrophy in the frontal lobes, anterior temporal lobes, and posterior temporal lobes. VBM has been used to demonstrate the pattern and progression of atrophy from very mild bvFTD to moderate to severe disease, as well as to delineate multiple distinct patterns of atrophy via hierarchical agglomerative cluster analysis. Algorithms for pattern-based classification of individual MR images as FTD, AD, or healthy older individuals have yielded promising results.

Visual interpretation of perfusion SPECT or FDG-PET scans has been shown to improve diagnostic accuracy in distinguishing between FTD and AD based on clinical information. Differentiating between a pattern of hypometabolism in frontal association cortex, anterior temporal cortex, and anterior cingulate cortex from a pattern of hypometabolism in posterior cingulate and posterior association cortex improved clinical diagnostic accuracy from 79% to 90% in an FDG-PET study with pathologic confirmation. Visual interpretation of perfusion SPECT improved specificity for a clinical diagnosis of FTD (vs AD) and sensitivity for a diagnosis of AD (vs FTD) from 77% to 84% in a separate study with pathologic confirmation.

Diffusion tensor imaging (DTI) and fcMRI have offered exciting tools for probing the integrity of white matter tracts and functional networks in vivo in bvFTD. Reduced fractional anisotropy (FA), reflecting reduced integrity of white matter, has been detected with DTI in bvFTD versus healthy controls in frontal and temporal tracts including the anterior corpus callosum, anterior and descending cingulum tracts, and the uncinate fasciculus. Reduced FA in the anterior cingulum tracts has been shown to predict executive dysfunction (left tract) and deficits in visuospatial attention and working memory (right tract) in bvFTD. Consistent with these DTI results and with the pattern of regional atrophy in bvFTD, fcMRI studies to date have reported decreases in salience network connectivity.

**Neuroimaging in Semantic Dementia and Agrammatic PPA**

SD and agrammatic PPA usually present with changes in language out of proportion to other cognitive domains. The left temporal variant of SD causes a fluent aphasia with impairments in single-word comprehension and confrontation naming, reduced vocabulary, and frequently associated features including impaired object knowledge, and inability to read or spell orthographically irregular words, with time, behavioral features such as irritability, emotional withdrawal, disinhibition, and behavioral rigidity usually develop. The less frequently encountered right temporal variant frequently presents with changes in emotional and social functioning such as apathy, emotional blunting, loss of exteriorization, in addition to difficulty recognizing people and objects and later on the anomia aphasia similar to that seen in the left temporal variant. A strong majority of SD cases show FTLD-TDP type C pathology, with much fewer cases exhibiting FTLD-tau pathology or AD pathology (reviewed in Grossman). SD very reliably produces asymmetrical atrophy, hypoperfusion, or hypometabolism of the anterior temporal lobes (see Fig. 3).

In contrast to SD, agrammatic PPA causes a nonfluent aphasia with agrammatism, effortful, halting speech, and frequently, impaired comprehension of syntactically complex sentences. Cases can be classified based on whether there is superimposed apraxia of speech, an oral motor speech disorder characterized by difficulty initiating utterances, abnormal rhythm, stress, and intonation, inconsistent articulation errors, effortful trial and error with groping, and self-correction of errors. Although agrammatic PPA can be associated with FTLD-tau, AD, DLB, and FTLD-TDP type A pathology, Josephs and colleagues have demonstrated that the presence of apraxia of speech predicts FTLD-tau pathology. Neuroimaging characteristics of agrammatic PPA include atrophy or hypometabolism in the posterior left frontal/insula region, including inferior frontal gyrus, frontal operculum, insula, premotor and supplementary motor areas (see Fig. 3).

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6 4R tau pathologies include corticobasal degeneration, progressive supranuclear palsy, argyrophilic grain disease, and sporadic multisystem atrophy. Pick’s disease pathology involves 3R tau inclusions. MAPT gene mutations may produce 3R, 4R, or combined 3 + 4R tau inclusions. Tau inclusions in Alzheimer’s disease (not considered a subtype of FTLD) are both 3R and 4R.
Neuroimaging in Progressive Supranuclear Palsy and Corticobasal Syndromes

CBS and PSPS are syndromes characterized by atypical parkinsonism with varying levels of cognitive impairment and dementia, originally recognized in the setting of distinctive 4R tau pathologies, corticobasal degeneration (CBD), and PSP. Clinical features of CBS include asymmetrical apraxia and extrapyramidal symptoms (bradykinesia and rigidity/tremor, dystonia) accompanied by signs of cortical involvement such as alien limb syndrome, cortical sensory loss, hemisensory neglect, myoclonus, and/or impairments in speech and language, visuospatial function, or executive function. PSP comprises core features of severe early postural instability and falls, supranuclear gaze impairment that manifests with decreased saccade velocity or ophthalmoplegia, and an extrapyramidal syndrome with prominent axial rigidity. A majority of patients with PSPS also develop a dementia syndrome with frontal and subcortical features such as disinhibition or impulsivity, apathy, social withdrawal, stimulus bound/imitative/utilization behavior, psychomotor slowing, executive dysfunction, and pseudobulbar affect. As might be predicted by the multiple phenotypes caused by both PSP and CBD pathologies, it is possible to see patients with overlapping features of CBS, PSP, agrammatic PPA, bvFTD, and other syndromes.

MRI in CBS characteristically reveals asymmetric atrophy of the perirolandic cortex and basal ganglia, whereas PSPS has been associated consistently with atrophy of the brainstem (particularly midbrain and superior cerebellar peduncle) and frontal white matter with lesser involvement of the frontal cortex. Specific measurement of the areas of the midbrain tegmentum and the pons on midsagittal MRI and computation of the midbrain/pons ratio has been shown to discriminate between patients with a clinical diagnosis of PSP and those with diagnoses of Parkinson’s disease or multiple system atrophy of the Parkinson type. In subjects with CBS focal atrophy of the posterior frontal cortex has been found to predict CBD (FTLD-tau) pathology, more widespread frontotemporal atrophy to predict FTLD-TDP pathology, and more widespread temporoparietal atrophy to predict AD pathology. Similarly, an AD-like pattern of hypoperfusion or hypometabolism with SPECT or PET imaging may predict CBS due to AD versus CBS due to other pathologies.

Imaging and Prediction of Molecular Pathology in FTLD

Quantitative morphometric MRI studies have generated the most robust body of data thus far with respect to delineating the spatial patterns of FTLD subtypes (see Whitwell and Josephs for review). In a large retrospective study employing cluster analysis of pathologic groups, Rohrer and colleagues proposed a neuroanatomic framework for understanding profiles of atrophy, differentiating between pathology associated with relatively symmetric, localized temporal or extratemporal atrophy (FTLD-tau caused by MAPT mutations, CBD, FTLD-FUS), pathology associated with relatively asymmetric, localized temporal atrophy...
(FTLD-TDP type C), and pathology associated with relatively asymmetric, distributed atrophy (Pick’s disease, FTLD-TDP type A caused by GRN mutations). Somewhat consistent with this framework, Whitwell, Josephs, and colleagues identify relatively focal posterior frontal and subcortical atrophy in 4R FTLD-tau (more consistently symmetric in PSP than CBD), relatively focal and symmetrical temporal atrophy in FTLD-tau caused by MAPT mutations, and a broader pattern of frontal, temporal, and paralimbic atrophy in Pick’s disease, with more bilaterality in their sample. They further highlight asymmetrical widely distributed frontotemporoparietal atrophy in FTLD-TDP type A, mild frontal and medial temporal atrophy in FTLD-TDP type B (a subtype strongly associated with FTD-MND), and focal, asymmetrical temporal atrophy in FTLD-TDP type C. FTLD-FUS, associated with a syndrome of very early-onset bvFTD in patients 20–45 years old, characteristically produces severe atrophy of the caudate nucleus. DTI correlates of patterns of white matter involvement in FTLD subtypes have not been as well delineated, but should have value given the distinctive white matter features of different subtypes. A combination of regional differences in both gray matter volume and white matter integrity discriminated between groups of patients with FTLD and AD pathology with 87% sensitivity and 83% specificity, with reduced FA in the corpus callosum characteristic of FTLD versus AD. Similar methods were used to accurately discriminate a group with FTLD-TDP from a group with FTLD-tau with greater reductions in FA in the superior longitudinal fasciculus in the FTLD-tau group corroborated by postmortem pathologic examination. Reduced FA in the left uncinate fasciculus and left inferior occipitofrontal fasciculus has been reported in asymptomatic GRN mutation carriers in a four-generation FTLD pedigree, illustrating the potential value of this technique in early stages of illness.

Diffusion tensor imaging (DTI) has been widely used to study presymptomatic familial FTLD due to mutations in both GRN and MAPT. In contrast to reductions in salience network connectivity detected in symptomatic patients, presymptomatic mutation carriers demonstrated increased connectivity, possibly indicative of compensatory mechanisms. Preclinical MAPT mutation carriers have demonstrated altered default network connectivity (including reduced connectivity in lateral temporal and medial prefrontal cortex and increased connectivity in the medial parietal lobe), changes similar to those seen in a group clinically diagnosed with bvFTD.

Summary and Conclusions

Diagnosis of neurodegenerative dementia is currently predicated on identifying insidious onset and gradual progression characteristic patterns of cognitive dysfunction, involving memory (amnestic AD), language (agrammatic and logopenic PPA, SD), visual processing (PCA, DLB), executive dysfunction (bvFTD, DLB), or social/emotional cognition (bvFTD, SD), with or without parkinsonism or motor neuron disease. Structural and functional neuroimaging techniques have advanced our understanding of how patterns of cognitive dysfunction localize to large-scale networks, which appear to serve as substrates for the pathologic neurodegenerative processes themselves. At present, high-resolution structural MRI, FDG-PET, perfusion SPECT, and DAT imaging are widely used modalities that contribute to clinical diagnosis. Ongoing research developing and refining these techniques and newer techniques such as amyloid PET, fMRI, and DTI promises to improve our ability to establish pathologic diagnoses in vivo in early stages of illness. Imaging biomarkers are likely to be most powerful when used together, with nonimaging biomarkers, and with sophisticated computer algorithms for pattern recognition. Large, multicenter longitudinal studies including the Alzheimer Disease Neuroimaging Initiative and the Dominantly Inherited Alzheimer Network, and biomarker studies in FTLD continue to propel these efforts.

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