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Authors
Tartaglia, Maria Carmela
Rosen, Howard J
Miller, Bruce L

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Neuroimaging in Dementia

Maria Carmela Tartaglia, Howard J. Rosen, and Bruce L. Miller

University of California, San Francisco Memory and Aging Center, 350 Parnassus Avenue, Suite 905, San Francisco, California 94143

Summary: Dementia is a common illness with an incidence that is rising as the aged population increases. There are a number of neurodegenerative diseases that cause dementia, including Alzheimer's disease, dementia with Lewy bodies, and frontotemporal dementia, which is subdivided into the behavioral variant, the semantic variant, and nonfluent variant. Numerous other neurodegenerative illnesses have an associated dementia, including corticobasal degeneration, Creutzfeldt–Jakob disease, Huntington's disease, progressive supranuclear palsy, multiple system atrophy, Parkinson's disease dementia, and amyotrophic lateral sclerosis. Vascular dementia and AIDS dementia are secondary dementias. Diagnostic criteria have relied on a constellation of symptoms, but the definite diagnosis remains a pathologic one. As treatments become available and target specific molecular abnormalities, differentiating amongst the various primary dementias early on becomes essential. The role of imaging in dementia has traditionally been directed at ruling out treatable and reversible etiologies and not to use imaging to better understand the pathophysiology of the different dementias. Different brain imaging techniques allow the examination of the structure, biochemistry, metabolic state, and functional capacity of the brain. All of the major neurodegenerative disorders have relatively specific imaging findings that can be identified. New imaging techniques carry the hope of revolutionizing the diagnosis of neurodegenerative disease so as to obtain a complete molecular, structural, and metabolic characterization, which could be used to improve diagnosis and to stage each patient and follow disease progression and response to treatment. Structural and functional imaging modalities contribute to the diagnosis and understanding of the different dementias.
Key Words: Dementia, MRI, PET, Alzheimer's disease, frontotemporal dementia.

INTRODUCTION

Brain imaging is routinely performed in the evaluation of dementias, and the most recent American Academy of Neurology Practice Parameter recommends the use of structural imaging, i.e., computed tomography (CT) or magnetic resonance imaging (MRI), to assist in the diagnosis of dementia and to specifically rule out reversible, treatable causes [1]. As the clinical approach to dementia moves toward the diagnosis of specific neurodegenerative diseases and their underlying molecular pathology, the role of brain imaging will become more prominent. With the development of treatments targeted at specific molecular pathologies, such as β-amyloid in patients with Alzheimer's disease (AD), tau in various taupathies, such as corticobasal syndrome and progressive supranuclear palsy, and TDP-43 in TDP-43 proteinopathies, such as the semantic variant of frontotemporal dementia (FTD), imaging will be needed to obtain accurate etiologic diagnoses. Accurate diagnosis will help physicians avoid exposing patients to potentially dangerous medications and will facilitate better measurement of the response to treatment. Moreover, as neurodegenerative diseases are associated with the development of pathologic changes long before the development of functional impairment, neuroimaging has a potential role in the diagnosis of early—even presymptomatic—stage of dementing disorders. A variety of imaging techniques are available for evaluating the structural, biochemical, and functional changes of the brain in neurodegenerative diseases. The goal of this review is to provide a broad overview of the various methods used to image neurodegenerative disease and to speculate on future directions.

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Address correspondence and reprint requests to: Maria Carmela Tartaglia, UCSF Memory and Aging Center, 350 Parnassus Avenue, Suite 905, San Francisco CA 94143. E-mail: ctartaglia@memory.ucsf.edu.

STRUCTURAL & FUNCTIONAL IMAGING

CT & structural MRI/T1–weighted imaging

Structural scans lend themselves well to assessing volumetric changes that occur in neurodegenerative disease with decreases in gyral and increases in sulcal

size. These changes probably develop secondary to decreases in synaptic density, neuronal loss, and cell shrinkage. Every neurodegenerative disease has a predilection for specific brain systems or networks, with each associated with tissue loss in particular brain regions.

CT imaging is commonly used in acute settings and/or in clinical settings where MRI is not available or contraindicated in order to rule out alternative pathologies. Although CT scanning is still regularly used for diagnostic assessments and for studies of brain-behavior correlation, MRI is currently the modality of choice for assessing many types of abnormalities seen in neurodegenerative syndromes.

The medial temporal lobes, especially the hippocampus and entorhinal cortex (ERC), are among the earliest sites of pathologic involvement in AD [2], and studies have repeatedly shown decreased hippocampal and ERC volumes in patients with AD compared with age-matched controls [3] (FIG. 1). Other severely affected areas include the lateral parietal and posterior superior temporal regions and medial posterior portion of the cingulate gyrus [4], but atrophy is also evident in the frontal, temporal, and occipital lobes [5], in keeping with the diffuse nature of AD (FIG. 1).

MRI has been used to study patients with mild cognitive impairment (MCI), who are at high risk for progression to AD, with a conversion rate to dementia of ~12–15% per year. MRI studies in MCI have shown that hippocampal volumes and cortical volumes in the parietal and lateral temporal regions are able to predict the likelihood of progression [6]. Longitudinal studies have demonstrated greater atrophy rates in ERC [7], and in the temporal lobe as a whole [8], in MCI patients than in controls.

Although regional volume loss occurs in both MCI and AD, the utility of using structural imaging for diagnosis remains unclear because in most volumetric studies of MCI and even AD, at least some overlap exists between patients and controls. As a result, imaging measures correctly identify between 80 and 100% of AD patients but a much smaller proportion of MCI patients, and this approach has significant limitations for assessing MCI-progressors from non-progressors [9].

Differentiating the different causes of dementia can prove challenging. Structural imaging can be useful in more advanced cases, especially in illnesses with focal degeneration. In FTD, a disorder that encompasses a heterogeneous group of patients sharing focal degeneration within the anterior frontal, temporal, and insular regions, MRI has revealed unique patterns of brain atrophy. FTD is a clinical term that includes these patients, while frontotemporal lobar degeneration refers to the pathologic change in this clinical group of focal degenerative disorders. In patients with the behavioral variant of FTD (bvFTD), frontal lobe volumes are reduced compared with those of both AD patients and age-matched controls. The target sites in FTD are the ventromedial frontal cortex, the posterior orbital frontal regions, the insula, and the anterior cingulate cortex, which differentiates this illness from AD as these areas are relatively spared in the latter disease, and atrophy in the frontal lobes is often in the lateral frontal lobe [10] (FIG. 2). The target regions atrophied in bvFTD are the frontal components of the brain's emotional processing systems, so that their involvement in FTD explains the unique behavioral symptoms seen in that disorder. Patients with the semantic variant of FTD have relative preservation of frontal lobe volumes but marked loss of volumes in the temporal lobes, in particular the neocortex in the temporal pole (FIG. 2) as well as atrophy in the amygdala, which is a critical structure for emotional processing [11, 12].

The clinical utility of these patterns of regional atrophy has been demonstrated in a study wherein frontal lobe volumes correctly classified 93% of patients with FTD compared with controls [13].

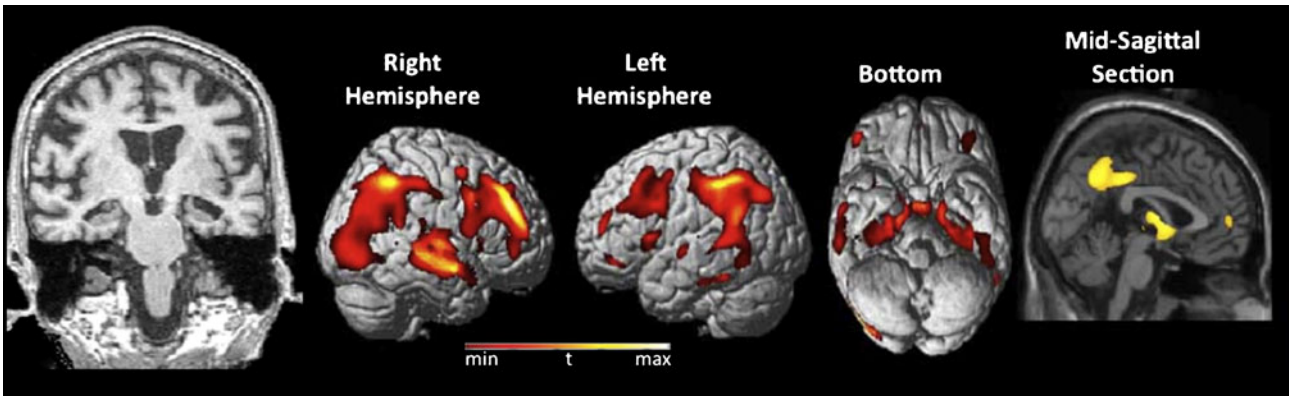

FIG. 1. Coronal magnetic resonance imaging through the brain of patient with Alzheimer's disease (AD). Notice the enlarged temporal horns due to hippocampal atrophy. Voxel-based morphometry analysis showing volume loss in AD compared with the controls in the hippocampus, entorhinal cortex, parietal and lateral posterior superior temporal regions, and medial posterior portion of the cingulate gyrus. (High resolution version of this image is available in the electronic supplementary material.)

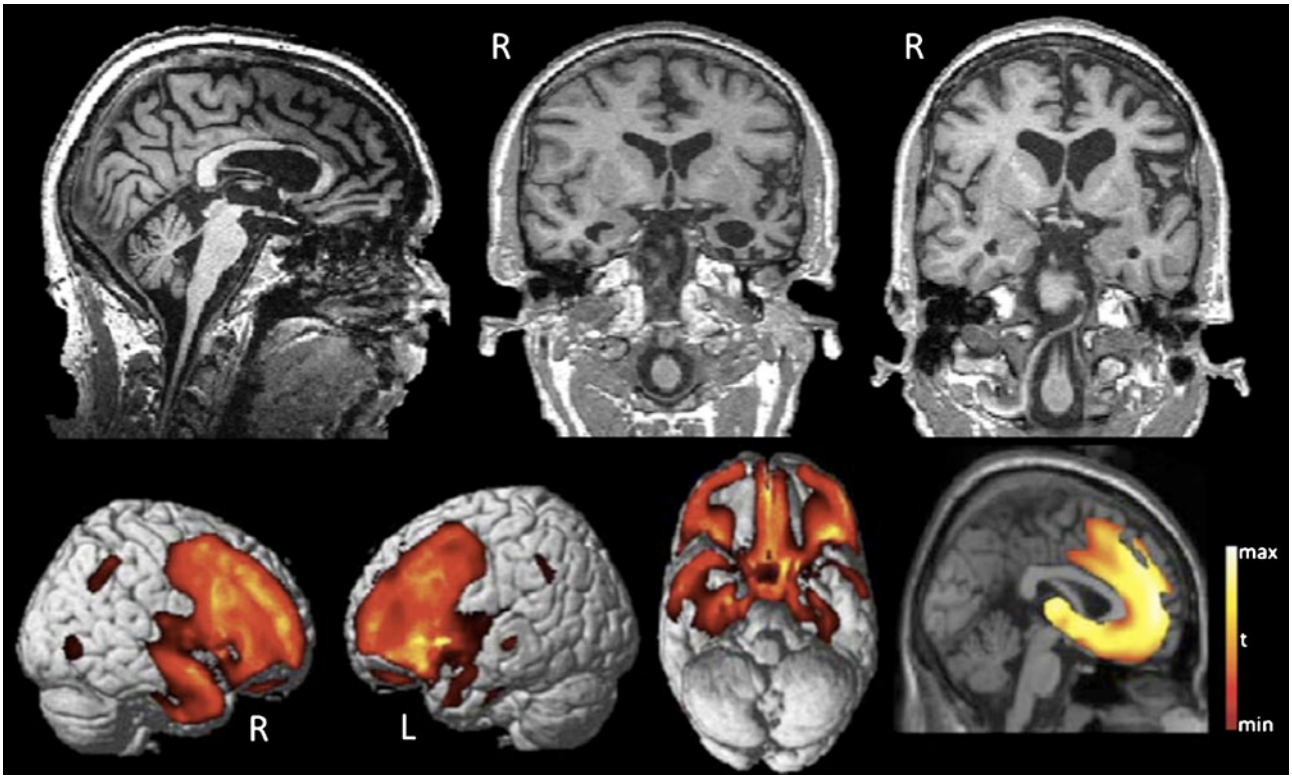

FIG. 2. Top row: Sagittal view of a patient with the behavioral variant of frontotemporal dementia (bvFTD); note the anterior atrophy with relative sparing of the parietal and occipital regions. The anterior corpus callosum is also thinned compared to posterior. Coronal view of patient with semantic dementia showing significant left temporal atrophy. Coronal view of patient with nonfluent variant of FTD showing significant left insular atrophy. Bottom row: VBM study showing that in patients with bvFTD, frontal lobe volumes are reduced compared with age-matched controls. There is volume loss in the ventromedial frontal cortex, the posterior orbital frontal regions, the insula, and the anterior cingulate cortex. (High resolution version of this image is available in the electronic supplementary material.)

Volumetric studies aimed at gaining an understanding of brain–behavior relationships have demonstrated relationships between focal changes in brain volume and cognitive or behavioral changes in dementia. Several studies have found correlations between hippocampal volumes and episodic memory performance in AD, consistent with the long-established role for this structure in memory consolidation [14, 15]. Studies on focal degeneration in non-AD dementias, particularly FTD, have yielded findings that help identify the anatomical basis of language and word access [16] and increase our understanding of facial expressions of emotion [12] and empathy [17].

Parkinsonian dementias cause damage in different networks within the brain and are also associated with specific patterns of regional volume loss. Characteristic of progressive supranuclear palsy—although not diagnostic of this condition— are third ventricle dilatation and midbrain atrophy with shortening of the anteroposterior length of the midbrain. This contrasts with corticobasal syndrome, for which frontally predominant atrophy is more typical [18].

Dementia with Lewy bodies (DLB) is associated with diffuse atrophy, and no established pattern is characteristic on structural MR images. Some forms of spinocerebellar atrophy are associated with cognitive impairment and display both cerebellar and cerebral atrophy along with caudate and putamen atrophy in some variants [19].

High-field MRI

Although 3T and 4T MRI provide good structural data, the resolution remains limited because of the signal-to-noise ratio. The hippocampus and its subfields cannot be well visualized using most clinical or research scanners, which are 1.5 or 3T. The introduction of 7T MRI, currently only used in research, holds promise for better visualization of the macrostructures of subcortical structures, including the hippocampus and basal ganglia. The higher field strength will likely also improve spectral acquisition and functional MRI (fMRI).

The authors of a recent study [20] using 7T MRI reported selective thinning of the CA1 apical neuropil layer relative to the CA1 cell body layer in subjects with mild AD (FIG. 3), with the thickness of the CA1–stratum lacunosum–moleculare (SRLM) being a better indicator than overall hippocampal volume for distinguishing subjects with AD from normal controls. Postmortem studies have shown that the CA1 apical neuropil is an early target of AD pathology [21]. Neurofibrillary tangles appear in the entorhinal cortex first, but the perforant pathway axons project from the entorhinal cortex to the

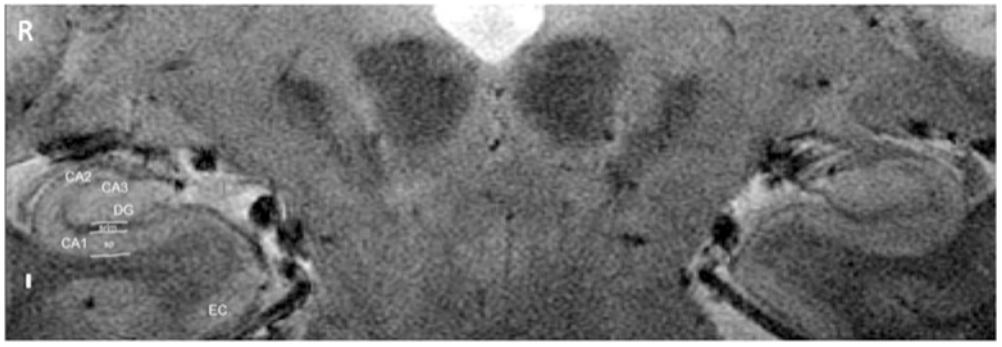

FIG. 3. Cross-section through the hippocampus at the level of the red nucleus in a normal control, obtained using a 7T gradient-recalled echo sequence. DG = Dentate gyrus, CA1–3 = cornus ammonis subfields 1–3, sp = stratum pyramidale, srlm = stratum radiatum/stratum lacunosum-moleculare, EC = entorhinal cortex. Scale bar 1 mm. Image has been reproduced courtesy of Dr. Geoffrey A. Kerchner. (High resolution version of this image is available in the electronic supplementary material.)

outer molecular layer of the dentate gyrus and the distal apical dendrites of CA1 neurons in the stratum lacunosum-moleculare [22, 23]. These two neuropil areas of the hippocampus are among the next sites for tau pathology to appear, but as clinical signs of AD become more pronounced, the varicose, tau-filled CA1 dendrites in the stratum lacunosum-moleculare disappear, possibly corresponding to the thinning of the CA1–SRLM observed *in vivo* in this study and in prior postmortem studies [24, 25].

MRI of vascular damage

Hyperintensity, or increased (bright) signal, on T2–weighted and fluid-attenuated inversion recovery (FLAIR) images is associated with cerebral pathology characterized by edema and gliosis. T2/FLAIR imaging is very sensitive to ischemic injury due to both small vessel and large vessel disease. Small vessel disease causes incomplete or complete infarcts in the white matter (WM) or in subcortical gray matter nuclei that on FLAIR images appear as hyperintensities (FIG. 4a), whereas complete infarcts present as lacunes (diameter, 2–15 mm), which are hypointense to the brain and isointense to the cerebrospinal fluid [26]. The results of a quantitative MRI study in non-demented elderly subjects suggested that this subcortical injury impacts brain function and correlates with frontal executive impairment [27].

T2/FLAIR imaging, especially T2*-gradient echo images, are also sensitive to microhemorrhages, which appear as hypointense lesions due to the inhomogeneities in the local field caused by the cerebral iron deposition and can be seen in up to 65% of patients diagnosed with vascular dementia [28] (FIG. 4b). Amyloid angiopathy, unlike hypertension-related lesions, is usually associated with microhemorrhages in the cortico–subcortical junctions of the frontomesial, fronto-orbital, and parietal regions [29]. Common neurodegenerative disorders, such as AD and FTD, are usually not associated with major changes on T2/FLAIR scans.

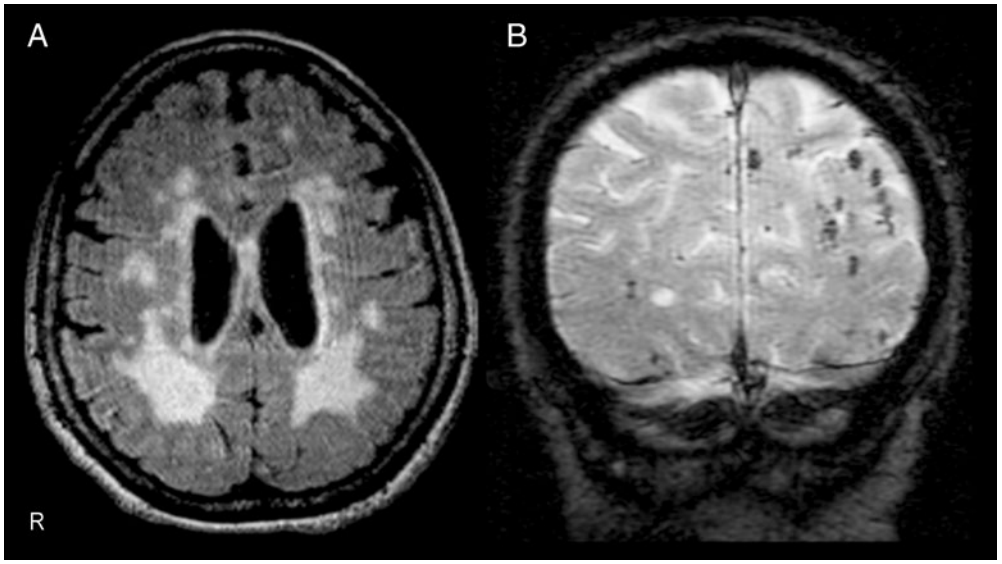

FIG. 4. (A) Axial section through fluid-attentuated inversion recovery image from a patient with vascular dementia, showing multiple patchy areas of high signal in periventricular white matter. (B) Coronal gradient echo MR image showing multiple microhemorrhages. (High resolution version of this image is available in the electronic supplementary material.)

Many rapidly progressive dementias can cause leukoencephalopathy, including progressive multifocal leukoencephalopathy and leukodystrophies, limbic encephalitis, infections and toxic conditions, or mixed gray and WM involvement, such as mitochondrial diseases and intravascular lymphoma [30]. MRI with contrast should be used in the evaluation of most rapidly progressing dementias.

Diffusion-weighted imaging and diffusion-tensor imaging

Diffusion-weighted imaging (DWI) is based on the analysis of the random motion of water molecules in the brain and is an integral part to any assessment of acute stroke victims, as it shows all acute injury extremely well. In most neurodegenerative diseases, DWI images appear to be normal; however, in Creutzfeldt–Jakob disease (CJD), decreased diffusion in the cerebral cortex (called cortical ribboning) with an associated decrease in basal ganglia is a highly sensitive (91%) and specific (95%) diagnostic marker of CJD [31] (FIG. 5). Variant CJD is often associated with high signals in the pulvinar and dorsomedial thalamic region [32].

Diffusion tensor imaging (DTI), is a novel MRI technique that enables the integrity of WM tracts to be better evaluated, revealing injury that may not be apparent with other imaging techniques. DTI, unlike DWI, evaluates the diffusion of water in each of the three main directions (right/left, front/back, up/down) and so allows quantification of the degree of anisotropy and local fiber direction on a voxel-by-voxel basis. Diffusion of water is anisotropic (directionally dependent) in WM fiber tracts because axons and myelin sheaths act as barriers; consequently, in axons, the diffusion of water (diffusivity) is significantly greater along the axis of those fibers, thereby providing a tensor measurement [33]. Fractional anisotropy (FA) is a measure of the degree of anisotropy of a diffusion process and ranges from zero, when diffusion is isotropic (i.e., unrestricted in all directions), to one, when diffusion occurs only along one axis and is fully restricted in the other directions. FA can therefore provide information on the orientation and integrity of fibers. Until recently, the focus of research in neurodegenerative disease was restricted to the gray matter. However, it has become evident that although there is significant gray matter pathology in neurodegenerative diseases (and particularly in AD), WM pathology is also present in AD, specifically in temporal lobe and posterior cerebral WM and the corpus callosum [34]. Reduced FA was recently identified in the portion of the cingulum bundle connecting the hippocampus to the posterior cingulate region in patients with MCI and AD compared with controls [35]. WM tract integrity has also been correlated with measures of episodic memory in AD and MCI [36].

DTI may also be useful for differentiating amongst the different dementias. One recent study reported decreased FA in the parietal lobes of patients with DLB compared to those with AD, which is in keeping with metabolic studies and the prominent visuospatial difficulties often seen in these patients [37]. Another recent study compared AD and FTD and found that patients with FTD had reduced FA in frontal and temporal regions, including the anterior corpus callosum, bilateral anterior, and descending cingulum (Cg) tracts, and in the uncinate (UNC) fasciculus compared to controls, while patients with AD had reduced FA in the parietal, temporal, and frontal regions, including the left anterior and posterior Cg tracts, bilateral descending Cg tracts, and left UNC fasciculus [38]. This study highlights the fact that the WM pathology is focal and that it may play a more important role in the pathophysiology of FTD than in that of AD. Various tracts can be defined using tractography, including the superior longitudinal fasciculus (SLF), UNC, and inferior longitudinal fasciculus (ILF), all of which are common study targets (FIG. 6). The different syndromes in FTD have a predilection for different tracts. In bvFTD, decreased FA was observed in

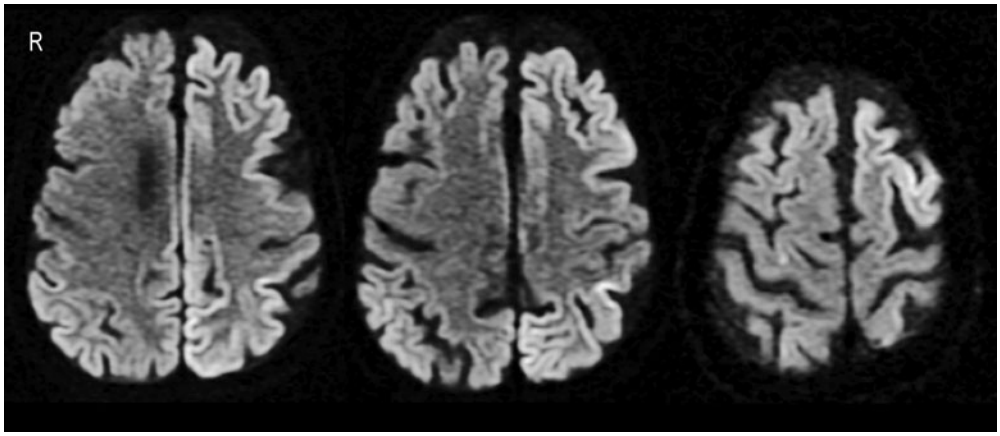

FIG. 5. Axial diffusion-weighted imaging showing cortical ribboning, left more than right, in a patient with Creutzfeldt–Jakob disease. (High resolution version of this image is available in the electronic supplementary material.)

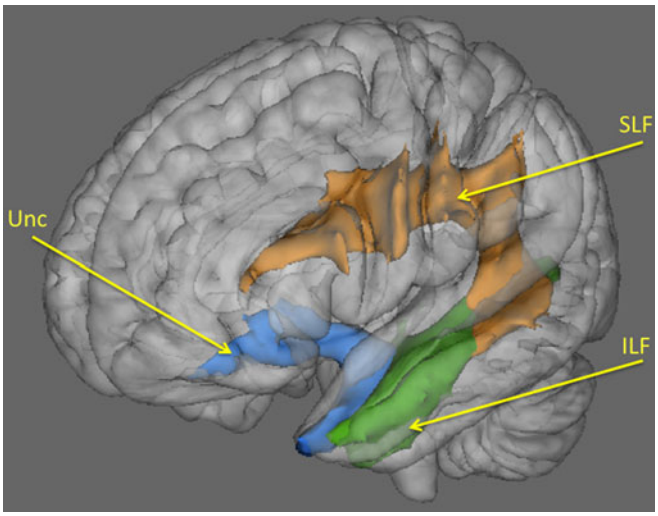

FIG. 6. Diffusion tensor imaging-derived tracts in normal controls. Unc = Uncinate, SLF = superior longitudinal fasciculus, ILF = inferior longitudinal fasciculus. Image has been reproduced courtesy of Dr. Sebastiano Galantucci. (High resolution version of this image is available in the electronic supplementary material.)

bilateral UNC, anterior Cg, anterior SLF, left posterior SLF, and anterior ILF. In the semantic variant, decreased FA was noted in left posterior ILF, UNC, posterior Cg, and left anterior SLF. Progressive nonfluent aphasia showed the most significant alterations in diffusivity in the SLF, with decreased FA in the anterior SLF, left posterior and superior SLF, and right UNC [39]. Studies have also evaluated the contribution of WM injury to the cognitive and behavioral changes observed in the different dementias [40, 41].

MR spectroscopy and biochemical information

In vivo proton MR spectroscopy (^{1}H MRS) allows the noninvasive evaluation of brain biochemistry by measuring the levels of specific metabolites, including *N*-acetylaspartate (NAA), choline, creatine, lactate, myoinositol, and glutamate. NAA is thought to be a marker of neuronal integrity, and many studies have reported on NAA content in patients with dementia. NAA is consistently reported as being lower in the parietal gray matter and hippocampus of patients with AD than in cognitively normal elderly subjects [42]. In vascular dementia, the greatest deficits occur in the frontal and parietal cortex [43]. ^{1}H MRS has also been used to look for differences between the non-AD dementias, including FTD [44], prion diseases [45], and Huntington disease [46]. In a ^{1}H MRS study comparing AD and FTD patients, Mihara et al. [44] reported that the NAA/creatine ratio was reduced in the posterior cingulate cortex in both the patients with AD and in those with FTD/Pick's disease, but that the former showed a greater decrease posteriorly, while the patients with the FTD/Pick complex displayed a greater decrease in the frontal region.

Functional activation using MRI

fMRI is based on the principle that increased neuronal activity is associated with a local hemodynamic response involving an increase in both cerebral blood flow and blood volume. The increase in blood flow, however, is greater than is necessary for oxygen delivery to match increased consumption, so the ratio of deoxy-to-oxyhemoglobin is altered. Deoxyhemoglobin is paramagnetic and distorts an applied static magnetic field, and since magnetic field inhomogeneities are found around blood vessels, their magnitude increases with the amount of paramagnetic deoxyhemoglobin [47]. A consequence of this increase in blood flow above that required for the increased tissue demands in response to neuronal activation is that the oxygen extraction fraction decreases. The lower ratio of deoxy-to-oxyhemoglobin in draining blood is associated with a small increase in MRI signal, and this is the basis of blood–oxygen-level-dependent contrast fMRI. A series of brain images are acquired while there is some change in cognitive state, and a spatial 'map' that indirectly reflects neuronal activation changes is generated by statistical analysis of the time series of data. fMRI has been proposed as a surrogate of brain activity related to cognitive processing because increased synaptic activity leads to local increases in blood flow.

An fMRI study of memory showed decreased regional function in the medial temporal lobe in patients with AD [48] and in elderly patients with isolated memory decline. Rombouts et al. [49] studied frontal lobe dysfunction in early FTD and compared it with that in early AD by applying a parametric verbal working memory task (n-back) during fMRI. These researchers found that in FTD, brain activation in the frontal and parietal cortex was significantly decreased. Frontal

regions in patients with FTD showed less of a linear activation increase with working memory load than did these regions in patients with AD. The FTD group displayed a stronger response in the cerebellum, leading the authors to postulate that this might be a compensatory mechanism. A recent study on a visual motion processing task also showed increased temporal lobe activation in DLB patients compared with AD patients [50]. Since the significance of increased activation is still only incompletely understood, the role of fMRI in the diagnosis or monitoring of patients with dementia remains unclear.

Resting state fMRI

Resting-state fMRI examines spatial synchronization of intrinsic fluctuations in blood–oxygen-level-dependent signals arising from neuronal and synaptic activity that is observed independent of overt cognitive information processing. Resting-state fMRI has been used to elucidate coherent large-scale brain networks subserving vision, audition, language, and attention, and a frontal opercular network that has been related to stimulus salience [51–53]. One of the resting-state networks, referred to as the default mode network, involves a set of regions that routinely decrease their activity during attention-demanding tasks [54, 55]. The default mode network, which includes the posterior cingulate, inferior parietal, inferolateral temporal, ventral anterior cingulate, and hippocampal regions, has received considerable attention in AD and has been shown to have decreased activity in AD and MCI. In FTD, a 'salience' network that includes the dorsal anterior cingulate and orbital/frontoinsular regions and tracks with emotional measures, was altered [52]. Resting-state data provide a means of evaluating and following patients who may be too impaired to perform cognitive tasks, and so will likely become increasingly more routine in both research and clinical settings [56].

GLUCOSE METABOLISM AND BRAIN PERFUSION

Positron emission tomography and single-photon emission computed tomography

Functional imaging provides insight into the operational aspects of the brain, and since it appears that brain pathology in dementia begins long before there is clinical evidence of disease (with ongoing compensation maintaining adequate cognitive function in the face of pathologic change), functional imaging is attractive for the early detection of dementia. The ideal test would allow for disease to be detected in the presymptomatic stage, and thus for treatment, if available, to be initiated before there is evidence of damage.

Single-photon emission computed tomography (SPECT), positron emission tomography (PET), and fMRI are becoming increasingly relevant to the study of dementia. The most commonly used techniques are SPECT and PET. In both techniques, various chemical compounds can be used to measure a variety of physiologic parameters in the brain. PET is most often used with [^{18}F] fluorodeoxyglucose (FDG) to measure brain energy metabolism, while SPECT is most commonly used to study cerebral perfusion with compounds such as 99mTc-hexamethylpropyleneamine oxime. These techniques can reveal metabolic abnormalities in the structurally normal brain. The FDG–PET scans of AD patients demonstrate reduced glucose metabolism in the parietal and superior/posterior temporal regions (FIG. 7). Very early metabolic deficits occur in AD and MCI in the medial portion of the parietal cortex, in the posterior cingulate or retrosplenial region [57]. Frontal lobe hypoperfusion is often also reported in AD patients, but usually in conjunction with temporoparietal abnormalities.

SPECT scans also demonstrate temporoparietal hypoperfusion or hypometabolism in patients with AD, as well as posterior cingulate pathology [58]. The temporoparietal abnormality is usually bilateral but can be asymmetrical. Here also, frontal lobe hypoperfusion is often reported but again in conjunction with temporoparietal abnormalities. The presence of bilateral temporopar-

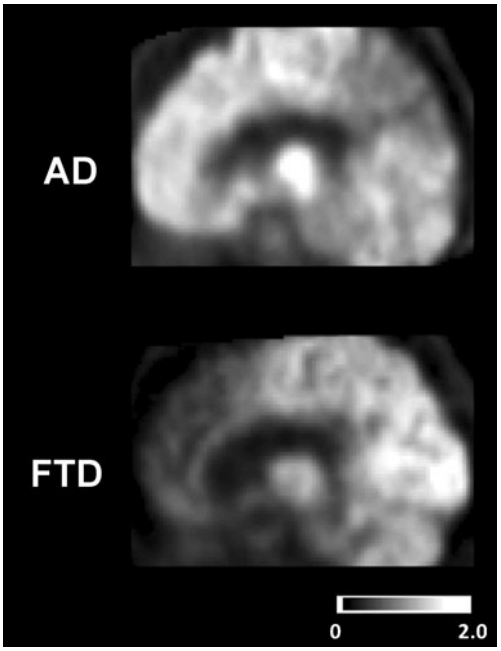

FIG. 7. [^{18}F]Fluorodeoxyglucose–positron emission tomography (PET) scan of AD and FTD patients. Note reduced glucose metabolism in the superior/posterior temporal and parietal regions of the AD scan. In comparison, the FTD scan shows hypometabolism in the frontal and anterior temporal regions, with relative sparing of the posterior brain regions. Image has been reproduced courtesy of Dr. Gil Rabinovici. (High resolution version of this image is available in the electronic supplementary material.)

ietal hypoperfusion or hypometabolism is a useful biomarker for discriminating AD patients from age-matched controls as well as from vascular dementia and FTD patients [59].

FDG–PET has been reported to have a better sensitivity than SPECT but a poorer specificity [60]. In one histopathologically confirmed study, the bilateral temporoparietal hypometabolism evident on FDG–PET scans was 93% sensitive and 63% specific for AD [61]. SPECT alone had a sensitivity of 63% and a specificity of 93% [62].

Since early detection is the goal in neurodegenerative diseases, a stage more amenable to treatments aimed at prevention or delay of progression than those aimed at reversal of neurodegeneration, there is a fervent search for biomarkers of early disease. Johnson et al. [63] assessed the accuracy of SPECT in the temporoparietal region in predicting MCI progression to probable AD. The sensitivity and specificity were 78 and 71%, respectively, for differentiating between the group that progressed and the one that did not. Several studies have also found that FDG–PET distinguished between patients with a progressive course and those with a non-progressive course with a sensitivity of 93% and a specificity of 74% based on the temporoparietal metabolism of the respective patients [64].

The results from a number of studies combining SPECT imaging and genetics indicate that abnormal metabolism is associated with the apolipoprotein E (APOE) gene-ε4 allele in the temporoparietal region [65, 66]. Additional regions related to disturbances in association with APOE-ε4 are the posterior cingulate and prefrontal area [67].

Patterns of metabolic abnormality differ according to dementia subtype. In FTD, hypometabolism is observed in the frontal and anterior temporal regions, with relative sparing of posterior brain regions (FIG. 7). DLB is associated with decreased occipitotemporal metabolism compared with AD, which is consistent with the increased difficulty such patients have with visual processing [68].

AD patients can be discriminated from age-matched controls as well as from patients with vascular dementia and FTD [57], and FDG–PET can increase the diagnostic accuracy beyond clinical features alone for discriminating AD from FTD [69].

Altered regional brain metabolism has been correlated with cognitive and behavioral changes in dementia. A PET study demonstrated a correlation between right–left hemisphere metabolic asymmetry in AD patients with the degree of language *versus* visuospatial impairment [70]. Hippocampal metabolism [71] has been correlated with memory function, and anterior cingulate region metabolism with apathy [72].

PET and SPECT can be used to study neurotransmitter systems using molecules that bind to neurotransmitter receptors or interact with neurotransmitter systems in other ways. In AD, where the cholinergic deficit has been shown *in vitro*, the cholinergic system can be evaluated using a variety of agents that interact with acetylcholine receptors and acetylcholinesterase, a key enzyme whose function decreases in AD [73]. PET imaging has potential as a tool for monitoring treatment, as it has been used to demonstrate significant increases in ^{11}C-nicotine binding sites after 3 months of treatment with rivastigmine, with the increases positively correlated with improvements in the performance of attentional tasks at 12 months [74]. In a PET study with *N*-[^{11}C]methyl-4–piperidyl acetate, which labels acetylcholine systems, and [^{18}F]fluorodopa, a measure of dopamine uptake, cholinergic and dopaminergic function were evaluated in patients with Parkinson's disease (PD) with and without dementia [75]. While [^{18}F]fluorodopa uptake in the striatum was decreased in both groups, cortical *N*-[^{11}C]methyl-4–piperidyl acetate binding was severely decreased in patients with PD with dementia compared with controls, but only moderately decreased in patients with PD alone. The ability to measure each of these neurotransmitter systems could help to guide treatments specific to each system.

Arterial spin labeling

Arterial spin-labeling (ASL) perfusion MRI is another method for assessing brain perfusion and function in dementia [76]. In ASL, the assumption is made that regional metabolism and perfusion are coupled; therefore, when arterial blood water is labeled as an endogenous diffusible tracer for perfusion, it can depict functional deficiencies similarly to FDG–PET and hexamethylpropyleneamine oxime SPECT [77] but is non-invasive and free of exposure to ionizing radiation, intravenous contrast agents, and radioactive isotopes. Results from ASL studies in AD patients have shown regional hypoperfusion in a pattern similar to that seen in PET and SPECT studies [78]. Hypoperfusion in the right inferior parietal lobe extending into the bilateral posterior cingulate gyri, and bilateral middle frontal gyri could be seen in the AD and MCI scans even after accounting for gray matter atrophy. The MCI group showed less hypoperfusion, but the most significant regional hypoperfusion relative to the control group was observed in the inferior right parietal lobe, similar to the region of greatest significance in the AD group [79].

TARGETING MOLECULAR ABNORMALITIES

Amyloid imaging with PET

Although functional and structural imaging provide invaluable information for the diagnosis and assessment of patients with neurodegenerative disease, the distinct molecular pathologies in the various diseases provide an

opportunity for accurate diagnosis. The recent development of new PET ligands for imaging disease-specific pathology may revolutionize brain imaging in neurodegenerative disease. B-amyloid, a pathological protein that forms plaques in the brains of patients with AD, has been extensively studied, and a number of compounds that can bind amyloid, such as radiolabeled Pittsburgh compound B ([^{11}C]PiB), have been discovered (FIG. 8). In 16 mild AD patients, Klunk et al. [80] demonstrated marked retention of PiB in the frontal, parietal, temporal, and occipital cortices as well as the striatum— but none in controls. These association areas are known to contain large amounts of β-amyloid in AD. The pattern of PiB retention was consistent with the pattern of amyloid plaque deposition seen in postmortem studies—early on, plaque is distributed evenly across neocortical association cortex in AD, but there is little in the mesial temporal lobe areas [2]. In contrast, the distribution of neurofibrillary tangles begins focally in the transentorhinal cortex and progresses through limbic areas to the neocortex. [^{11}C]PiB is not entirely specific, as studies have demonstrated increased retention in up to ~20–30% of cognitively normal older individuals [81]. This increased [^{11}C]PiB retention in cognitively normal individuals is consistent with pathologic studies indicating that up to ~37% of autopsies in patients who were cognitively normal prior to death showed pathology meeting National Institute on Aging–Reagan criteria for a high or intermediate likelihood of AD [82]. Whether or not the healthy controls with PiB-positivity represent an early presymptomatic stage of AD is being actively studied.

Increased[^{11}C]PiB retention has been demonstrated in patients with MCI [83], and several reports have examined [^{11}C]PiB retention in non-AD dementias. A recent study of AD and FTD demonstrated that all patients with AD (7/7) had increased [^{11}C]PiB retention by visual inspection, while most (8/12) patients with FTD and five (5/5) controls had no increase in [^{11}C]PiB retention [84]. The increased [^{11}C]PiB retention in the four patients with FTD may represent AD pathology mimicking the clinical presentation of FTD, or it may represent coexisting pathology. In addition to [^{11}C]PiB, other approaches for imaging specific molecular pathology in neurodegenerative disease are under development, thus far only in AD [57].

The short half-life and need for a cyclotron preclude the use of PiB in many clinical and research settings. The novel agent, [^{18}F]AV-45 or flobetapir F 18, has a longer half-life than PiB. It has been tested in an open-label, multicenter study where it was shown to accumulate in cortical regions expected to be high in β-amyloid deposition (e.g., precuneus and frontal and temporal cortices) in AD patients, while minimal accumulation of the tracer was seen in cortical regions of normal controls. The new tracer could be used to discriminate between AD and normal controls [85]. Its sensitivity has been found to be similar to PiB for fibrillar β-amyloid binding, but less specific. It will hopefully be a useful alternative that can be more widely used.

Currently there is no *in vivo* imaging of tau, TDP-43, or α-synuclein, the other major pathological proteins implicated in the neurodegenerative diseases. The hope lies that in the near future it will be possible to target these proteins and make more accurate diagnoses.

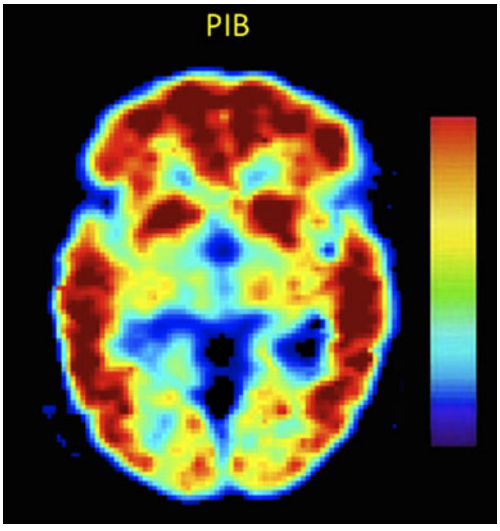

FIG. 8. Results of a Pittsburgh Compound B (PiB) PET scan. PiB reveals amyloid in the brain. Warmer colors (e.g., red) indicate greater concentrations of amyloid deposition, and blue indicates the absence of amyloid on a PiB PET scan. Image has been reproduced courtesy of Dr. Gil Rabinovici. (High resolution version of this image is available in the electronic supplementary material.)

CONCLUSION

As our understanding of neurodegenerative disease progresses and treatments become available, the need for more accurate diagnosis will likely drive neuroimaging towards more ligand- and functional-based technology so that molecular abnormalities and early functional changes can be detected. Treatment of neurodegenerative disease lies in early diagnosis and likely not in the reversal of disease. There are a number of techniques currently available for studying the changes associated with neurodegenerative disease, including WM tract integrity, neurotransmitter function, task-related synaptic activity, and chemical content, but the bulk of imaging research in dementia is still focused on regional abnormalities in glucose metabolism, perfusion, and tissue content. Multimodal assessments for diagnosis and longitudinal follow-up will likely emerge as being critically important factors for the care of patients. The future of brain imaging will likely involve combinations

of imaging techniques to identify the presence of a molecular abnormality, to gauge its impact on the brain structure and function, and to predict and follow the effects of treatment.

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