In the past, neuroimaging for the study of neurodegenerative diseases was mostly concerned with ruling out other, particularly easier to treat, disorders. For instance, in a patient with a progressive cognitive impairment MRI was used to rule out a frontal or a temporal menigioma. Currently, however, advanced MRI techniques are used to support the diagnosis of a neurodegenerative disorder and sort out which is the most likely underlying disease. MRI allows particularly not only for the quantification of volume loss and the detection of white matter changes, but also for the changes in synaptic function that precede and accompany the clinical expression of neurodegenerative diseases.

We will discuss the findings afforded by these techniques in the presymptomatic and symptomatic stages of the most common neurodegenerative disorder, Alzheimer disease and then briefly discuss the fronto-temporal dementias.

**Atrophy**

In familial autosomal dominant AD, as caused by mutations in the presenilin and amyloid precursor protein genes, genotyping allows for the determination, with a high degree of certainty, of who will develop the disease (1). Serial MRIs performed in presymptomatic individuals have suggested that atrophy in some regions, particularly the precuneus and medial temporal areas, may start as early as four years before the onset of cognitive impairment (2). This finding has only been determined with automated methods and not by all investigators (1, 3). One group has even reported increased cortical thickness in presymptomatic individuals (4). Another genetically at-risk group, cognitively intact apolipoprotein (APO) ε4 homozygotes, have been reported to have an increased rate of cortical thinning (5) or, for apolipoprotein ε4 carriers, preferential atrophy of the some hippocampal subregions (6-8). In cognitively normal elderly, cortical thinning in precuneus and medial temporal areas has been found to correlate with subsequent cognitive decline (9) or with amyloid deposition (10, 11), again, suggesting that atrophy may antedate the onset of cognitive decline (Fig 1). Cortical thinning associated with other AD-related changes, such as abeta deposition (10) or increased hippocampal activation during episodic memory tasks (12) has been also been explored as a marker of early AD changes in cognitively normal older individuals. Regional atrophy correlates with regional abeta deposition, particularly in posterior cingulate cortex, in presymptomatic people or those with subjective cognitive complaints, but not in MCI or AD, suggesting that the damaging effect of abeta occurs in the presymptomatic or very mildly symptomatic stages, when abeta-reducing therapies should be applied (11, 13).

In patients with MCI, thinning of the temporal cortex and precuneus are predictors of worsening to AD, particularly when combined with neuropsychological, PET and CSF markers (14-17). Although atrophy can be appreciated visually (18, 19), automated methods are more precise and facilitate longitudinal follow-up (20-22). The accuracy of software that classifies clinically-appropriate cases has been compared favorably with the accuracy of trained readers (23). MRI end-points compared across healthy individuals and those in various stages of the AD continuum have included hippocampal volume, tensor-based morphometry, cortical thickness and a novel technique based on manifold learning (14, 17). The best results are usually achieved combining all features, in one longitudinal clinical study yielding 67% sensitivity and 69% specificity to separate stable MCI from MCI worsening to AD, 86% and 82% to separate healthy controls from MCI worsening to AD, and 93% sensitivity and 85% specificity to separate healthy controls from AD (14). In another longitudinal study with a 3-year follow-up (16), the combination of greater learning impairment and increased medial temporal atrophy was associated with the highest risk: 85% of patients with both risk factors converted to AD within 3 years, vs 5% of those.
with neither. Medial temporal atrophy was associated with the shortest median dementia-free period (16). In autopsy series, containing more advanced AD, medial temporal atrophy, even judged with a visual scale (19), has shown a sensitivity of 91% and specificity of 94% for autopsy confirmed AD (24). Regional atrophy correlates with tangle density and therefore with Braak neurofibrillary tangle stage, rather than with amyloid plaque deposition (24-26). Atrophy typically extends from limbic structures to neocortex at a rate of 2-5% per year (27). Association cortex is preferentially involved, while paracentral cortex is spared (27).

Figure 1. Neurobiological changes in the various stages in the development of AD, illustrated by specific neuroimaging techniques. A taller area in red indicates a greater degree of the neurobiological disorder (abeta deposition, impaired synaptic function or atrophy and decreased white matter anisotropy). Amyloid PET: \(^{11}C\)-PIB positron emission tomography (PET); FDG PET: \(^{18}F\) fluoro-deoxy-glucose PET; fMRI: functional MRI; SPECT: single photon emission computed tomography; MR-DTI: diffusion tensor imaging performed with functional MRI.

**White-Matter Anisotropy Loss**

White matter abnormalities in the fornix (28) or in fronto-occipital and inferior temporal fasciculi, the splenium of the corpus callosum, subcallosal white matter and the cingulum bundle (29) have been found with the use of diffusion tensor imaging (DTI) in healthy at-risk for AD individuals, either with autosomal dominant mutations (4, 28) or carrying the APO ε4 allele (29). In affected areas, DTI shows decreased functional anisotropy (28) or increased mean diffusivity (4). However, higher anisotropy can be found in white matter volumes where a disrupted tract, such as the superior longitudinal fasciculus, crosses an intact one, such as the corticospinal tract, effectively increasing volume anisotropy (30). In agreement with the anatomy of cortical atrophy, neocortical white matter changes are more pronounced in late-myelinating fiber pathways, while sparing the corticospinal tract, originating in paracentral cortex (31). White matter abnormalities are also present in MCI and are milder than the changes in AD, which affect to the greatest degree the cingulum bundle, the uncinate fasciculus, the corpus callosum and the superior longitudinal fasciculus (30, 32-36). Changes in the parahippocampal cingulum may separate best MCI
from healthy controls (37). For DTI, discrimination values higher than 90% have been achieved comparing MCI to healthy controls using support vector machine classifiers (38, 39). However, these optimistic outcomes need to be validated in independent samples. The value of DTI to predict worsening from MCI to AD is still to be determined.

**Impaired Synaptic Function**

Impaired synaptic function across the various AD stages can be gauged with techniques measuring the fMRI bold signal, regional metabolism, and regional perfusion. Findings are concordant, but each technique is amenable to different applications. Metabolism has been studied most extensively but the most recent development is the increasing use of resting state fMRI to assess functional connectivity changes.

**BOLD Signal**

*Activation.* The great variety of methods, including different activation paradigms, has yielded disparate results among various groups. For instance, both increased (40-43) and decreased (44, 45) medial temporal lobe activation has been reported in APOE ε4 carriers. Some apparent differences may reflect still unclear underlying biology. For instance, the apparent discrepancy in activation in APOE ε4 carriers may be explained by their failure to experience a decreased in activation with age, as other APOE genotypes do (46). Then, APOE ε4 carriers will be likely to show decreased activation compared to other APOE genotypes in young samples (44, 45), but increased activation in older samples (40-43). Despite the complexity of activation results, a bimodal pattern seems consistent. Medial temporal activation, increased in asymptomatic at-risk subjects (12, 47, 48) (but see (49)), tends to decrease as the AD process worsens and cognition deteriorates (50, 51). Indeed, increased activation in mildly symptomatic, or even asymptomatic, individuals may predict their worsening (50, 51).

*Functional connectivity.* Abnormalities in functional connectivity have been found consistently in the different stages of AD and correspond to abnormal DTI, volumetric and metabolic findings (52, 53). Most of the recent studies have explored resting BOLD, easier and faster to obtain than activation paradigms. This potentially powerful technique depends heavily on careful data recording and analysis; even in the best hands it can yield results that reflect non-biological variables, such as greater movement in the scanner on the part of one of the study groups (54). As with other neuroimaging findings, abnormal connectivity may already be detected in presymptomatic, at-risk individuals, particularly to and from areas, like the posterior cingulate gyrus, precuneus and medial temporal regions, known to be affected early in the disease (55-60). Unlike atrophy, impaired functional connectivity reflects synaptic dysfunction, not neuronal loss. For this reason it tends to be affected in areas with low metabolism (61) and amyloid deposition (57, 61). Different precuneus connectivity patterns have been reported in AD and diffuse Lewy-body dementia (DLB) (62, 63) and across APOE genotypes (60).

**Imaging in the Evaluation of New AD Therapies**

Recent therapeutic trials with anti-abeta antibodies have benefited from the use of imaging to determine the target effect of the medication (64). Although improving or arresting the AD cognitive decline is the main goal of the new therapies, a more immediate need is to know whether abeta-removing therapies indeed remove abeta from the brain of the participants. Results from PIB imaging have been reported for at least two therapeutic trials of abeta-removing antibodies (65, 66). Combined with MRI, abeta-imaging has shown that the antibodies remove abeta from the brain and that in regions where the original
concentration of abeta was higher, focal edema and microhemorrhages are more likely to develop (65) (Fig 2). These findings suggest that abeta is cleared through the vascular system of the brain, promoting increased vascular permeability and arteriolar wall fragility. Abeta deposition in arteriolar walls, causing increased fragility, was one of the neuropathological observations from an earlier trial using an abeta vaccine (67).

**Figure 3.** MRI and \(^{11}\text{C}\) PiB PET scans of an APOE \(\varepsilon4\) heterozygote given bapineuzumab (2.0 mg/kg). The times indicated in the images represent time from bapineuzumab administration. Baseline FLAIR image without evidence of ARIA-E (A). FLAIR sequence obtained at week 6 (C) shows bifrontal parenchymal hyperintensity (arrows; ARIA-E) which resolved by week 19 (D). Additionally, week 19 gradient echo T2*-weighted sequence (F) shows the development of bifrontal microhaemorrhages (ARIA-H; arrows) not present on previous images (not shown). A corresponding week 19 \(^{11}\text{C}\) PiB scan (E) shows reduced \(^{11}\text{C}\) PiB uptake (arrows) compared with that at baseline in regions with ARIA-E and ARIA-H (arrows; B). FLAIR=fluid attenuation inversion recovery. \(^{11}\text{C}\) PiB = \(^{11}\text{C}\) Pittsburgh compound B. ARIA-E = amyloid-related imaging abnormalities thought to be parenchymal vasogenic oedema and sulcal effusions. ARIA-H = amyloid-related imaging abnormalities thought to be a result of microhemorrhages and hemosiderosis. Reproduced from (65), with permission.

**Lobar Dementias (and AD) as Brain Network Disorders**

Clinically, neuropathologically and genetically, the fronto-temporal dementia (FTD) or lobar dementia group comprises a heterogeneous group of disorders (68, 69). It can present with a **frontal-lobe syndrome**, characterized by impulsivity and disinhibition (70), or as a **progressive aphasia**, either
semantic or non-fluent, or as an *apraxic syndrome* (progressive supranuclear palsy and corticobasal degeneration). Atrophy on MRI, decreased metabolism on FDG-PET or decreased perfusion on SPECT tends to be regional and corresponds well to the area preferentially affected by the pathology. Except for rare cases with motor neuron involvement, these disorders tend to affect association cortex, rather than primary motor or sensory cortices. Clinical, imaging and neuropathological findings are summarized in Table 1. The most common clinical variety, frontotemporal dementia, is also the most neuropathologically and genetically heterogeneous (70, 71), as is the more recently characterized hippocampal sclerosis dementia (72). Fronto-temporal abnormalities on FDG-PET / SPECT may antedate the atrophy that eventually becomes obvious on MRI (73, 74). For this reason, PET has been approved for FTD diagnosis by the Centers for Medicare & Medicaid Services (CMS, USA). Amyloid imaging is negative in the frontotemporal dementias (75). Interestingly, neuroimaging has been used to determine and illustrate how neurodegenerative disorders target specific brain networks (76, 77). For instance, AD targets the default network, which is earliest and most predominantly affected in the disorder.

**Table 1. Non-amyloid dementias.** (70, 71, 78, 79).Courtesy of Dr. Keith Josephs

<table>
<thead>
<tr>
<th>Dementia Type</th>
<th>Clinical Findings</th>
<th>Atrophy (MRI) ↓ Metabolism (PET) ↓ Perfusion (SPECT)</th>
<th>Motor Neuron Disease</th>
<th>Ubiquitinated bodies (TDP-43)</th>
<th>Tau</th>
<th>Known Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral variant frontotemporal dementia (bvFTD)</td>
<td>Behavioral and personality changes &amp; executive dysfunction</td>
<td>Bilateral frontotemporal atrophy, hypometabolism and hypoperfusion</td>
<td>20%</td>
<td>50%</td>
<td>50%</td>
<td>Progranulin (GRN) and microtubule associated protein tau (MAPT)</td>
</tr>
<tr>
<td>Frontotemporal dementia with motor neuron disease (FTD-MND)</td>
<td>Similar to bvFTD</td>
<td>Frontal &gt; temporal lobe atrophy, hypometabolism and hypoperfusion</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td>C9ORF72 on chromosome 9</td>
</tr>
<tr>
<td>Semantic Dementia (SD)</td>
<td>Anomic aphasia, loss of comprehension, surface dyslexia</td>
<td>Bilateral (L&gt;R) anterior temporal, atrophy hypometabolism and hypoperfusion</td>
<td>&lt;5%</td>
<td>80%</td>
<td>20%</td>
<td>MAPT</td>
</tr>
<tr>
<td>Progressive non-fluent aphasia (PNFA)</td>
<td>Non-fluent speech with agrammatism</td>
<td>Left perisylvian association cortex atrophy, hypometabolism and hypoperfusion</td>
<td>&lt;5%</td>
<td>20%</td>
<td>80%</td>
<td>PGRN &amp; MAPT</td>
</tr>
<tr>
<td>Corticobasal syndrome (CBS)</td>
<td>Apraxia, rigidity</td>
<td>Asymmetric frontoparietal, lenticular &amp; thalamic atrophy, hypometabolism and hypoperfusion</td>
<td>&lt;5%</td>
<td>5%</td>
<td>95%</td>
<td>MAPT H1 haplotype and GRN</td>
</tr>
<tr>
<td>Progressive supranuclear palsy syndrome (PSPS)</td>
<td>Vertical supranuclear palsy, apathy, symmetric parkinsonism</td>
<td>Midbrain atrophy. Mild frontal lobe atrophy, hypometabolism and hypoperfusion</td>
<td>&lt;1%</td>
<td>1%</td>
<td>99%</td>
<td>MAPT H1 haplotype</td>
</tr>
</tbody>
</table>
REFERENCES


5. F. Crivello et al., Effects of ApoE-epsilon4 allele load and age on the rates of grey matter and hippocampal volumes loss in a longitudinal cohort of 1186 healthy elderly persons. *Neuroimage*, (Jan 6, 2010).


36. K. Kantarci et al., Dementia with Lewy bodies and Alzheimer disease: neurodegenerative patterns characterized by DTI. *Neurology* **74**, 1814 (Jun 1, 2010).


46. L. Nichols et al., Hippocampal activation during episodic memory processing in healthy adult Apolipoprotein E ε4 carriers is significantly influenced by age. *Neurology* **74** (Suppl 2), A338 (2010).


54. J. D. Power, K. A. Barnes, A. Z. Snyder, B. L. Schlaggar, S. E. Petersen, Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 59, 2142 (Feb 1, 2012).


56. N. Gour et al., Basal functional connectivity within the anterior temporal network is associated with performance on declarative memory tasks. *Neuroimage* 58, 687 (Sep 15, 2011).


60. Y. I. Sheline et al., APOE4 allele disrupts resting state fMRI connectivity in the absence of amyloid plaques or decreased CSF Abeta42. *J Neurosci* 30, 17035 (Dec 15, 2010).


71. K. A. Josephs et al., Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. *Neurology* 66, 41 (Jan 10, 2006).


73. M. F. Mendez, J. S. Shapira, A. McMurtray, E. Licht, B. L. Miller, Accuracy of the clinical evaluation for frontotemporal dementia. *Arch Neurol* 64, 830 (Jun, 2007).


75. C. C. Rowe et al., Imaging beta-amyloid burden in aging and dementia. *Neurology* 68, 1718 (May 15, 2007).


