European Journal of Neurology 2012, 19: 1487–1511 doi:10.1111/j.1468-1331.2012.03859.x

EFNS GUIDELINES/CME ARTICLE

EFNS task force: the use of neuroimaging in the diagnosis of dementia

M. Filippi[a], F. Agosta[a], F. Barkhof[b], B. Dubois[c], N. C. Fox[d], G. B. Frisoni[e], C. R. Jack[f], P. Johannsen[g], B. L. Miller[h], P. J. Nestor[i], P. Scheltens[j], S. Sorbi[k], S. Teipel[l], P. M. Thompson[m] and L.-O. Wahlund[n]

[a]*Neuroimaging Research Unit, Division of Neuroscience, Institute of Experimental Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy;* [b]*Department of Radiology, VU University Medical Center, Amsterdam, The Netherlands;* [c]*Centre de Recherche de l'Institut du Cerveau et de la Moelle Epinière, Université Pierre et Marie Curie, Paris, France;* [d]*Dementia Research Centre, Institute of Neurology, University College London, London, UK;* [e]*IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli di Brescia, Brescia, Italy;* [f]*Department of Radiology, Mayo Clinic and Foundation, Rochester, MN, USA;* [g]*Memory Clinic, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark;* [h]*Memory and Aging Center, University of California, San Francisco, CA, USA;* [i]*Department of Clinical Neuroscience, University of Cambridge, Cambridge, UK;* [j]*Department of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands;* [k]*Department of Neurological and Psychiatric Sciences, Azienda Ospedaliero-Universitaria di Careggi, Florence, Italy;* [l]*Department of Psychiatry, University of Rostock, and German Center for Neuro-degenerative Diseases (DZNE), Rostock, Germany;* [m]*Department of Neurology, David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA, USA; and* [n]*Division of Clinical Geriatrics, Department of Neurobiology, Karolinska Institute, Stockholm, Sweden*

Keywords:
Alzheimer's disease, amyloid imaging, dementia, diagnosis, guidelines, magnetic resonance imaging, positron emission tomography, single photon emission computed tomography

Received 2 July 2012
Accepted 18 July 2012

Background and purpose: The European Federation of the Neurological Societies (EFNS) guidelines on the use of neuroimaging in the diagnosis and management of dementia are designed to revise and expand previous EFNS recommendations for the diagnosis and management of patients with Alzheimer's disease (AD) and to provide an overview of the evidence for the use of neuroimaging techniques in non-AD dementias, as well as general recommendations that apply to all types of dementia in clinical practice.

Methods: The task force working group reviewed evidence from original research articles, meta-analyses and systematic reviews, published before April 2012. The evidence was classified, and consensus recommendations were given and graded according to the EFNS guidance regulations.

Results: Structural imaging, which should be performed at least once in the diagnostic work-up of patients with cognitive impairment, serves to exclude other potentially treatable diseases, to recognize vascular lesions and to identify specific findings to help distinguish different forms of neurodegenerative types of dementia. Although typical cases of dementia may not benefit from routine functional imaging, these tools are recommended in those cases where diagnosis remains in doubt after clinical and structural imaging work-up and in particular clinical settings. Amyloid imaging is likely to find clinical utility in several fields, including the stratification of patients with mild cognitive impairment into those with and without underlying AD and the evaluation of atypical AD presentations.

Conclusions: A number of recommendations and good practice points are made to improve the diagnosis of AD and other dementias.

Background

Although a detailed clinical assessment remains the basis of the evaluation of a patient with suspected dementia, current European [1,2], UK [3] and US [4] guidelines recommend that 'structural imaging should be used in the assessment of people with suspected dementia to exclude other cerebral pathologies and to

Correspondence: Prof. M. Filippi, Neuroimaging Research Unit, Division of Neuroscience, Institute of Experimental Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Via Olgettina, 60, 20132 Milan, Italy (tel.: 39 02 26433033; fax: 39 02 26435972; e-mail: m.filippi@hsr.it).

This is a Continuing Medical Education article, and can be found with corresponding questions on the Internet at http://www.efns.org/EFNS Continuing-Medical-Education-online.301.0.html. Certificates for correctly answering the questions will be issued by the EFNS.

EUROPEAN JOURNAL OF NEUROLOGY
THE OFFICIAL JOURNAL OF THE EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

help establish subtype diagnosis'. If the diagnosis is in doubt, functional imaging techniques should also be used to help distinguish different forms of neurodegenerative dementia [2,3]. In general, the tendency is to move away from simply excluding other (brain) diseases, towards finding specific pointers to a diagnosis [5]. This approach is exemplified by the formal incorporation of biomarkers, including those from neuroimaging, in the most recent revisions of the diagnostic criteria for Alzheimer's disease (AD) [6–8]. Two major classes of biomarkers have been identified: biomarkers of *disease state* [i.e. biomarkers of amyloid β (Aβ) accumulation, which are abnormal (increased) tracer retention on amyloid positron emission tomography (PET) imaging and abnormal (low) cerebrospinal fluid (CSF) Aβ42] and biomarkers of *disease stage* [i.e. biomarkers of neuronal injury, which are elevated CSF tau, decreased fluorine-18 (^{18}F)-2-fluoro-2-deoxy-D-glucose (FDG) uptake on PET in the temporoparietal cortex, and atrophy on structural magnetic resonance imaging (MRI) in a specific topographical pattern involving medial, basal, and lateral temporal lobes and medial and lateral parietal cortices]. Regardless of whether clinical criteria for possible AD are fulfilled, when both Aβ and neuronal injury biomarkers are negative, the dementia is unlikely to be attributable to AD pathology [6–8].

Aims of the European Federation of Neurological Societies task force

The purpose of the task force is to revise and expand previous European Federation of Neurological Societies (EFNS) recommendations on the use of structural and functional neuroimaging for the diagnosis and management of patients with AD [2] and to provide an overview of the evidence for the use of these techniques in vascular dementia and other neurodegenerative dementias, as well as providing general recommendations that apply to all types of dementia in clinical practice. Furthermore, in these guidelines, special attention has been given to clarifying the current status and potential future clinical role of PET with new ligands and also the use of non-conventional (advanced) MR techniques in these disorders. Consensus recommendations are given and graded according to the EFNS guidance regulations [9]. Where there was lack of evidence but consensus amongst experts was reached, we have stated our opinion as 'good practice points'.

Search strategy

The evidence for these guidelines has been identified from searches of MEDLINE and references from relevant articles published in peer-reviewed journals before April 2012. Other published meta-analyses, systematic reviews and evidence-based management guidelines in dementia have also been considered, including the practice parameters from the American Academy of Neurology [4], the previous recommendations for the diagnosis and management of AD and other disorders associated with dementia from the EFNS [1,2], and the National Institute for Health and Clinical Excellence guideline [3]. Only articles published in English were reviewed.

Methods for reaching consensus

Consensus was reached by circulating drafts of the manuscript to the task force members and by discussing the classification of evidence and recommendations. All members had the opportunity to comment on the recommendations and approved the final version of this document.

Diagnosis and differential diagnosis: the present approach

Which neuroimaging techniques?

Exclusion of a potentially (surgically) treatable cause of dementia (e.g. tumour or subdural haematoma) and evaluation of the presence and extent of cerebrovascular disease can be ascertained using computed tomography (CT). However, MRI offers benefits over CT for the demonstration of markers of specific diseases, particularly cerebral atrophy patterns [e.g. hippocampal atrophy for AD; very focal temporal and/or frontal atrophy for frontotemporal dementia (FTD) and midbrain atrophy for progressive supranuclear palsy (PSP)] [10–12]. Therefore, MRI should be considered the 'preferred modality to assist with early diagnosis' in a subject with dementia [2,3].

The essential MR sequences that will provide the important minimum set of information required to be addressed in a subject suspected of having dementia are 3D T1-weighted gradient echo; turbo/fast spin echo T2-weighted and fluid attenuated inversion recovery (FLAIR) and T2*-gradient echo [5]. If 3D T1-weighted techniques are unavailable, coronal oblique 2D images can serve as an alternative. A multiplanar reformatting tool can be applied to such images to assess specific brain regions (e.g. to reslice the data on the anterior/posterior commissure line or perpendicularly to the long axis of the hippocampus). Two other MR techniques that are very frequently used in a clinical setting include diffusion-weighted imaging (DWI) and post-contrast 2D T1-weighted spin echo images

[5]. DWI can be useful to identify recent infarcts in patients with vascular dementia, transient global amnesia or in the context of vasculitis and to identify neocortical or striatal abnormalities in patients with Creutzfeldt–Jakob disease (CJD). Post-contrast T1-weighted images are recommended in those patients, typically younger, where there is a suspicion of infectious (e.g. herpes simplex virus encephalitis) or inflammatory disorders (e.g. vasculitis, sarcoid, multiple sclerosis).

Single photon emission computed tomography (SPECT) and PET both rely on the detection of radioactive signals from a labelled compound that selectively binds in the brain. The most commonly used tracer to examine cerebral blood flow (CBF) using SPECT is ^{99m}-Tc-hexamethylpropylene (HMPAO). FDG serves as a marker of cerebral glucose metabolism for PET. SPECT is technically less demanding and more widely available, whilst PET is more sensitive, mainly because of its higher resolution [13–16], but comes at the cost of more complex detector system and tracer production facilities. In general, the magnitude of hypometabolism seen with FDG PET is greater than the amplitude of hypoperfusion seen with CBF SPECT [13]. SPECT and PET images can be analysed for diagnostic purposes by means of visual inspection. However, the visual method greatly depends on the observer's experience and lacks a clear cut-off between normal and pathological findings. To overcome these limitations, FDG PET images can be assessed using software that analyses the pattern of tracer uptake voxel-wise by comparing the subject's scan with a reference data set of normal ageing. T-maps (statistical maps of level of significance based on *t* tests) are created that allow better recognition of the pattern of hypometabolism compared with visual interpretation [17].

Structural MRI findings

Vascular brain diseases

Cerebrovascular disease can be detected by CT and structural MRI. Although both modalities perform relatively well in depicting large-vessel infarcts, MRI is more sensitive to subtle small-vessel vascular changes than CT. T2-weighted and FLAIR sequences are highly sensitive for detecting major strokes as well as small strategic infarcts and small-vessel ischaemic white matter damage. FLAIR performs less well than T2-weighted sequences in detecting thalamic infarcts [18]. Extensive white matter changes visible as diffuse hyperintense abnormalities on T2 and FLAIR, predominantly involving the periventricular and deep white matter, but relatively sparing of the U-fibres, are the imaging correlate of Binswanger's disease [19]. Marked hypointensity on T1-weighted images usually represents tissue destruction in the presence of a complete large-vessel infarct, whereas white matter changes are usually not prominently hypointense on T1-weighted images. Finally, lacunar infarcts are focal complete infarcts of deep small vessels, which are hyperintense on T2-weighted images and markedly hypointense on T1 and FLAIR images [19]. On FLAIR, lacunae are often surrounded by a hyperintense rim.

According to the National Institute for Neurological Disorders and Stroke Association pour la Recherche l'Enseignement en Neurosciences (NINDS-AIREN) international criteria [20], structural brain imaging is an essential element for the diagnosis of vascular dementia, and without it vascular dementia will be 'possible' at best. In addition, the operational radiological definitions for the NINDS-AIREN criteria provided indications on the topography and severity of vascular lesions [21]. Bilateral infarcts in the area of the anterior cerebral artery, infarcts in the area of the posterior cerebral artery, association areas or watershed regions are thought to be causative of large-vessel vascular dementia [21]. Extensive white matter lesions involving at least 25% of the white matter, or multiple basal ganglia, thalamic and frontal white matter lacunar infarcts, or bilateral thalamic lesions, are considered relevant radiological lesions associated with small-vessel vascular dementia [21]. Research criteria to specifically diagnose subcortical ischaemic vascular dementia have also been proposed [19]: the presence of extensive periventricular and deep white matter lesions and lacunar infarcts in the deep grey matter or multiple lacunae in the deep grey matter and at least moderate white matter lesions, in the absence of cortical and/or cortical–subcortical (non-lacunar) territorial infarcts, watershed infarcts, haemorrhages and other specific causes of white matter lesions.

Different methods can be used to measure the extent of white matter changes to diagnose subcortical ischaemic vascular dementia. Visual rating of white matter hyperintensities is relatively easy, and several scales [22–24] are available with good reproducibility. Volumetric studies use semi-automatic techniques that may provide more information on location and size, as well as continuous data, but are time consuming [25]. With the Age-Related White Matter Changes (ARWMC) scale [24], for instance, a score of 3 in at least two regions and a score of 2 in two other regions could be sufficient for a diagnosis of subcortical vascular dementia [25]. A conversion table amongst some of the most popular scales to rate white matter lesions can be found in Frisoni *et al*. [26].

Cerebral microbleeds (or microhaemorrhages) are small, rounded, dot-like lesions of low signal intensity in the brain that can be observed on T2*-weighted images, such as gradient echo [27–29]. Susceptibility-weighted imaging has considerably increased microbleed detection rates compared with gradient echo sequences [30,31]. The sensitivity to detect microbleeds is also dependent on slice thickness and magnetic field strength [32]. Microbleeds in deep brain regions are most likely to be associated with vasculopathy owing to hypertension, whilst their distribution is mostly lobar in specific disorders such as sporadic cerebral amyloid angiopathy (CAA) [33]. Sporadic CAA is the most common cause of lobar intracerebral haemorrhages in the elderly and results from cerebrovascular deposition of β-amyloid protein in the media and adventitia of small- and medium-sized vessels of the superficial layers of the cerebral cortex and leptomeninges, with sparing of the deep grey matter nuclei [34]. According to a set of validated criteria (termed Boston criteria) [35], a diagnosis of probable CAA can be reached in elderly patients with at least two acute or chronic lobar haemorrhagic lesions (including microbleeds), in the absence of other definite cause of intracerebral haemorrhage.

The presence of extensive white matter lesions and multiple bilateral, lacunar infarcts on T2-weighted and FLAIR images is critical for the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), a genetic form of vascular dementia in relatively young people [36]. The most distinctive MRI features suggestive of CADASIL are the presence of T2 hyperintensity of the temporal pole, the U-fibres at the vertex and external capsule or insular region, and multiple microhaemorrhagic foci (basal ganglia, internal capsule, thalamus and pons), which can be seen on gradient echo scans [36].

Although an increased white matter lesion load suggests vascular disease, particularly in combination with lesions in the basal ganglia, a critical clinical challenge in subjects with vascular lesions is determining the relationship of cerebrovascular disease and cognitive symptoms. To appropriately diagnose vascular cognitive impairment or dementia, there should be a clear relationship in the severity and pattern of cognitive impairment and the presence of vascular lesions with neuroimaging [20]. However, this association can be confounded by the frequent co-occurrence of depression on a cerebrovascular basis, as well as by the frequent coexistence with neurodegenerative diseases, especially AD. Small-vessel disease is frequently observed in MRI scans of AD patients in the form of white matter hyperintensities, lacunae and microbleeds. Several studies have indicated that the prevalence of microbleeds in AD ranges from 15% to 32% [37–41]. Microbleeds are also considerably more frequent in AD compared with other neurodegenerative dementia [37].

Alzheimer's disease

In typical late-onset (arbitrarily defined as age at onset >65 years) AD, the medial temporal lobes (MTL), especially the hippocampus and entorhinal cortex, are amongst the earliest sites of pathological involvement [42,43]. Other severely affected regions include the posterior portion of the cingulate gyrus and the precuneus on the medial surface [44–46] and the parietal, posterior superior temporal and frontal regions on the lateral cerebral surfaces [42,47–49].

Structural MRI studies in mild cognitive impairment (MCI) have produced mixed results, in terms of hippocampal as well as posterior cingulate and parietal involvement (absent, unilateral or bilateral) [50–60]. The reasons for this variability may consist of different subject selection (i.e. diverse diagnostic inclusion criteria), small sample size (i.e. studies are not adequately powered to pick up differences even at the group level) and methodological differences. It is also worth noting that the largest source of variance in MCI studies is likely to be the intrinsic heterogeneity of the MCI population, because a relevant proportion of these subjects will not progress to dementia. MCI patients with predominant memory impairment (amnestic MCI), who are at increased risk of developing AD, have atrophy in a consistent set of cortical regions, the 'cortical signature of AD', including the MTL and temporoparietal cortex. Conversely, non-amnestic MCI shows a different pattern of atrophy characterized by a relative sparing of the MTL and a regional involvement which is typically highly consistent with the observed clinical deficits.

Of all the structural markers of AD, hippocampal atrophy assessed on conventional CT or coronal T1-weighted images is the best established and validated. MRI-autopsy studies have convincingly validated that hippocampal volumes measured from antemortem MRI scans correlate with Braak neurofibrillary tangle pathological staging [61–63]. Indeed, MTL atrophy is now one of the supportive biomarkers to make a diagnosis of AD in the presence of memory loss proposed by the new diagnostic criteria [6–8]. MRI is superior to conventional CT in the evaluation of MTL atrophy [10–12]. However, the possibility of evaluating the pattern of atrophy using CT has been improved with the advent of multi-detector row CT, owing to the availability of high-resolution coronally reformatted images [64]. MTL atrophy can be detected by qualitative ratings based on visual scoring,

or by linear measurements and quantitative volumetry of regions of interest (referenced to a well-characterized population with age norms). Several visual rating scales to quantify degree of MTL atrophy have been developed and are widely used [65–68]. On the contrary, at present, accepted standards for quantitative analysis are lacking [69]. Manual hippocampal segmentation is the most validated procedure to estimate a quantitative hippocampal volume, but different laboratories use different anatomical landmarks and measurement approaches [69]. Of note, a harmonized protocol for manual hippocampal segmentation is currently being developed by an international working group (EADC-ADNI), which will be available for general use in 2013 [70]. Furthermore, the utility of structural imaging will certainly be increased further by automated segmentation algorithms developed in the last few years, which are the only feasible methods in the context of large studies [71,72], such as clinical trials.

Clinical population studies have reported that hippocampal volumes in mild AD patients are 15–40% smaller than controls [25], and in MCI the volume is reduced by 10–15% [73]. MTL atrophy can separate mild to moderate AD patients from normal controls with sensitivity and specificity >85% [25]. Structural MRI estimates of tissue loss in MTL are predictive for conversion from amnestic MCI to AD [74–83]. A meta-analysis estimated that MTL atrophy, as assessed on structural MRI, has 73% sensitivity and 81% specificity for predicting whether patients with MCI will convert to AD [84]. Subjects with amnestic MCI who progress to AD also have a greater degree of grey matter atrophy at baseline beyond the MTL than MCI who do not, including the medial and inferior temporal lobes, temporoparietal association neocortex and frontal lobes [50,52,85,86].

It should be emphasized that MTL atrophy may occur in other diseases as well [87–92]; thus, MTL atrophy alone lacks the specificity to confidently exclude other dementia, in particular in patients at the MCI stage.

Early-onset AD patients (i.e. subjects showing onset of symptoms before the age of 65 years) showed less prominent MTL atrophy and greater involvement of the parietal, lateral temporal and frontal regions compared with late-onset AD cases [91,93–95]. Methods such as voxel-based morphometry (VBM) are a popular and successful way to test for groupwise differences in the topography of atrophy beyond the MTL. However, the statistical testing portion of VBM is not designed to provide diagnostic information at the single subject level. A specific visual rating scale has been designed, evaluating the posterior cingulate, precuneus and superior parietal regions [96]. The utility of such a scale has been assessed in pathologically proven (mostly early-onset) AD and frontotemporal lobar degeneration (FTLD) patients [97]. Thirty per cent of AD patients had posterior atrophy in the absence of abnormal MTL atrophy, whereas only 7% of the FTLD group had abnormal posterior atrophy score and normal MTL [97]. Adding the posterior atrophy to the MTL visual rating score improved discrimination of early-onset AD from normal controls and all AD from FTLD cases [97].

Atypical presentations of AD. AD pathology can manifest itself with clinically atypical presentations, that is, in some patients memory is not the primary deficit but visuospatial and visuoperceptual and/or language disturbances are prominent symptoms [98–100]. Atypical presentations are more often seen in early-onset AD patients [99]. In atypical, focal AD presentations, the MTL is relatively spared [99,101]. Two recent quantitative MRI studies in pathology-proven AD cases suggested that a pattern of temporoparietal atrophy or cortical thinning may suggest AD pathology even in subjects presenting with non-amnestic clinical syndromes [101,102]. The temporoparietal cortex volume also provided better discrimination between atypical AD and FTLD groups than the hippocampal volume (81% vs. 74% accuracy) [101]. Two common progressive, focal cortical syndromes associated with AD pathology are posterior cortical atrophy (PCA) and primary progressive aphasia (PPA). Structural MRI scans of patients with PCA show atrophy of parieto-occipital and posterior temporal cortices [99,103]. Compared with typical AD cases, PCA patients had greater right parietal and less left MTL atrophy [99]. For a detailed description of structural neuroimaging features in AD cases with prominent language deficits, see the section on PPA.

Dementia with Lewy bodies

No clear signature pattern of cerebral atrophy associated with dementia with Lewy bodies (DLB) has been established so far. Similar to AD, a diffuse pattern of global grey matter atrophy including temporal, parietal, frontal and insular cortices may occur in DLB [104–106], but at the same time, a pattern of cortical grey matter loss restricted to frontal and parietal lobes has also been reported [107,108]. On the whole, several volumetric studies have not found significant or disproportionate occipital atrophy in DLB [106,107,109].

A relatively robust MR finding in DLB is that of relative preservation of the MTL compared with AD of similar clinical severity [87,104–108,110–115]. This finding is supported by a prospective MRI study with

pathological verification, which found that MTL atrophy on MRI has a robust discriminatory power for distinguishing AD from DLB (sensitivity of 91% and specificity of 94%) [105]. Thus, a relative preservation of MTL structures on CT or MRI supports a diagnosis of DLB in the consensus diagnostic criteria [116].

Subcortical structural alterations in terms of putamen atrophy have been described in some cases of DLB relative to AD [117], whilst no significant atrophy was detected in caudate nucleus [117–119]. A pattern of relatively focused atrophy of the midbrain, hypothalamus and substantia innominata, with a relative sparing of the hippocampus and temporoparietal cortex, has been found in DLB compared with AD cases [107]. However, whether these findings help in recognizing early suspected cases remains unknown. Furthermore, a substantial overlap between DLB and AD with regard to atrophy in these regions detracts from the usefulness of these markers in individual cases.

Frontotemporal dementia

The terms FTLD and FTD describe a group of clinical syndromes which may be produced by a number of histopathologically distinct entities. In these guidelines, the term FTLD will be used to indicate cases with a pathological diagnosis, whilst the term FTD will be used to refer to the clinical syndrome.

The designation of probable behavioural variant of frontotemporal dementia (bvFTD) by the revised diagnostic criteria [120] restricts diagnosis to patients with demonstrable functional decline and typical neuroimaging findings, including frontal and/or temporal atrophy, and hypoperfusion or hypometabolism on PET or SPECT.

Structural MRI studies showed that classical bvFTD presents with a combination of medial frontal, orbital–insular and anterior temporal cortical atrophy [121–128]. Such an atrophy pattern can be readily appreciated on coronal T1-weighted MRI scans (knife-edge atrophy). The MTL is more affected anteriorly, that is, the amygdala is more affected than the hippocampus, and posterior hippocampus often appears normal. Nevertheless, the typical pattern is not necessarily present in all cases [129–131], particularly in patients with FTD and motorneuron disease, and the pattern of atrophy in bvFTD varies significantly across different cohorts [132,133]. In some cases, bvFTD presents with a remarkable atrophy of the right anterior temporal lobe and a lesser involvement of the frontal regions [127,134]. A large VBM study suggested that bvFTD may be divided into four anatomically different subtypes, two of which are associated with a prominent frontal atrophy (i.e. frontal dominant and frontotemporal variants) and two with prominent temporal lobe atrophy (i.e. temporal dominant and temporofrontoparietal subtypes) [127]. Brain atrophy in bvFTD also involves several subcortical structures, such as the striatum [122,125,135], thalamus [125,135,136], bilaterally and hypothalamus [137]. Significant atrophy was also found in the brainstem, including the midbrain and pontine tegmentum in some cases [125,138,139].

Despite variation and overlap of atrophy patterns, visual inspection of regional atrophy on MRI may aid in discriminating FTD from AD. A combined diagnostic criterion based on the finding of either severe frontal atrophy or asymmetry was highly diagnostic (sensitivity 71%, specificity 93%) of bvFTD compared with non-FTD dementia cases (i.e. AD and vascular dementia) [140]. In a study investigating the diagnostic accuracy of visual inspection of MRI scans in patients with pathologically confirmed diagnosis, atrophy of the anterior, inferior and lateral temporal lobes was associated with the highest sensitivity ($\geq$90%) for discriminating FTLD from AD patients, and anterior greater than posterior gradient and hemispheric asymmetry of atrophy were each at least 85% specific for FTLD versus AD [141]. A prospective study in 134 patients with clinically suspected bvFTD demonstrated that evidence of frontotemporal atrophy on structural MRI scans, in the absence of corresponding changes in more posterior areas of the brain, had a sensitivity of 63% and specificity of 70% against a clinical diagnosis after 2 years [130].

Recent quantitative studies have suggested that a cortical thinning of the anterior temporal lobe and frontal lobe is indicative of the presence of FTLD pathology in patients with a clinical diagnosis of bvFTD or PPA during life [102]. Conversely, a cortical thinning or atrophy in the posterior cingulate gyrus, parietal lobe and frontal pole is suggestive of AD pathology independent of clinical presentations (i.e. even in patients with behavioural or language deficits) [101,102] (see also sections on atypical AD presentations and PPA).

Primary progressive aphasia

In patients clinically diagnosed with PPA, who are then divided into clinical variants based on specific speech and language features characteristic for each subtype, an 'imaging-supported' diagnosis can be made if the expected pattern of focal atrophy on structural MRI scans (or functional involvement on SPECT and FDG) is found [142].

Semantic variant PPA is associated with left anterior temporal atrophy (temporal pole), affecting the lateral and ventral temporal surfaces, as well as partic-

ularly the anterior hippocampus, amygdala and fusiform gyrus [121,143–145]. Semantic patients may have left hippocampal atrophy that is at least as severe as that seen in AD patients [49,90,91,144]. In these patients, the hippocampal atrophy is predominantly located anteriorly, with a relative preservation of the posterior hippocampal regions [49,90]. Temporal lobe atrophy is also mainly inferior (often severe involvement of the fusiform gyrus) with relative sparing of the superior temporal gyrus [49,90]. As the disease progresses, the right temporal lobe becomes more involved [146].

The non-fluent PPA variant is associated with a characteristic pattern of left anterior peri-Sylvian atrophy involving inferior, opercular and insular portions of the frontal lobe [145]. Motor and premotor regions and Broca's area are also involved [145]. In non-fluent patients, bilateral atrophy of the basal ganglia [135,145], thalamus [135] and amygdala [135] was observed. Compared with controls, non-fluent patients also have atrophy of the left hippocampus [92]; however, it is less severe than that in AD patients [92].

In the logopenic PPA variant, the pattern of atrophy primarily affects the left temporoparietal junction, including the left posterior superior and middle temporal gyri, as well as the inferior parietal lobule [99,145,147,148]. The involvement of the left MTL is reported less consistently [147]. Such a posterior temporoparietal pattern of atrophy chiefly discriminates this syndrome from the other subtypes of PPA [148].

A major clinical challenge, to date, is the need to improve the prediction of the specific histopathology causing each of the PPA variants during life (FTLD versus AD). A prominent left frontal and anterior temporal atrophy is seen in semantic PPA patients who have FTLD pathology at autopsy [149–154]. Conversely, semantic patients with AD pathology mostly have hippocampal involvement and a lack of the knife-edge anterior temporal atrophy, as well as a less severe thinning of the temporal lobe in the regions of the collateral sulcus and fusiform gyrus [154]. Some studies evaluating patients with non-semantic PPA associated with AD pathology demonstrated the presence of temporoparietal atrophy [151,152,155,156]. Two recent studies investigated the value of clinical phenotyping, neuropsychological analysis and pattern of MRI atrophy in predicting underlying pathology of non-fluent and logopenic patients [155,156]. In the first study, PPA cases with CSF findings consistent with AD showed a posterior superior temporal atrophy, whilst patients with FTLD pathology had frontal atrophy [155]. The second study showed that a disproportionate or asymmetrical frontotemporal atrophy on structural MRI (knife-edge atrophy) was 100% specific for FTLD pathology but was only present in a minority of patients (sensitivity 40%) [156]. Altogether, these studies in pathologically proven cases suggested that distinct patterns of tissue loss could assist in the *in vivo* prediction of underlying pathology. However, the results of these studies are limited by the small numbers of patients assessed.

Miscellaneous

Midbrain atrophy, better seen on sagittal T1-weighted images, dilatation of the third ventricle, atrophy of the superior cerebellar peduncle and frontal cortical atrophy support a diagnosis of PSP [157]. T2-signal change in the superior cerebellar peduncle can be seen in PSP patients but is less sensitive [157]. Quantitative MRI measurements of brainstem structures have been proposed as potentially useful markers to diagnose PSP on an individual patient basis. In particular, a ratio of linear measurements (e.g. the so-called MR parkinsonism index, which combines measurements of midbrain and pons areas as well as superior and middle cerebellar peduncle widths) has been shown to differentiate accurately PSP from Parkinson's disease (PD) and multiple system atrophy (MSA) cases [158,159].

Other specific imaging signs may include bilateral striatal atrophy in Huntington's disease, sometimes many years before disease onset [160], and striatal or neocortical abnormalities in patients with CJD. In CJD, T2-weighted and especially FLAIR sequences can show a very characteristic pattern of hyperintense signal in the striatum and/or cortex [161]. DWI can show focal changes in CJD not yet apparent on FLAIR images (up to 20% of cases) [161,162]. In sporadic CJD, involvement of either the striatum or neocortex or both is usually found [161]. In variant CJD, there is a selective involvement of the medial and dorsal (pulvinar) thalamic nuclei, leading to the so-called hockey stick sign [163].

Recommendations for structural MRI

1 Structural imaging should be carried out at least once in the diagnostic work-up of patients with cognitive impairment and serves at least three purposes: to exclude other potentially treatable diseases, to recognize vascular lesions and to identify specific findings to help distinguish different forms of neurodegenerative types of dementia (good practice point).

2 MRI is currently the imaging modality of choice for assessing subjects with suspected dementia. However, where MRI is not available or contraindicated, CT scans can usefully exclude major space occupying lesions, large infarcts and hydrocephalus (good practice point). Multi-detector row CT is

the best alternative for patients who cannot undergo MRI (good practice point).

3 A standard MRI protocol should include a high-resolution structural volumetric T1-weighted scan, transverse T2-weighted and FLAIR sequences and transverse T2*-gradient echo sequence (good practice point). Routine contrast administration is not indicated (good practice point). DWI can be useful to identify recent infarcts, as well as cortical and/or basal ganglia changes in CJD patients (good practice point).

4 It is particularly difficult to attribute clinical significance to evidence of cerebrovascular disease in patients with cognitive impairment. Vascular changes on CT or MRI do not preclude a diagnosis of degenerative dementia, especially in older age. A diagnosis of vascular dementia should only be made where the vascular lesion(s) can explain the cognitive deficit (class II, level A). The 'mixed dementia' label should be reserved for those cases in which both clinical features and diagnostic markers point to a mixed aetiology (good practice point).

5 T1-weighted images should be carefully evaluated to assess specific patterns of focal atrophy, especially in the MTL, biparietal regions and posterior cingulate cortex (as seen in AD), temporal pole and/or frontal lobes (as seen in FTD), parietal/occipital lobe (as seen in PCA), putamen, and midbrain and frontal lobe (as seen in PSP) (good practice point).

6 Coronal T1-weighted sequence can be used to assess MTL atrophy to support a clinical diagnosis of AD compared with cognitively normal subjects (class II, level A). Prediction of subsequent AD in individuals with amnestic MCI can also be obtained with MRI volumetric measures of the MTL (class II, level A). However, at present, accepted standards for quantitative MTL volume measurement are lacking. Therefore, quantification must rely on local specific standards (good practice point).

7 Combining MTL measures with other potentially informative markers, such as posterior cingulate cortex and precuneus volumetric measures, are likely to improve diagnostic confidence in AD patients (class II, level B), mainly in younger cases.

8 In cases of atypical AD presentations, the involvement of the MTL is reported less consistently than that of lateral temporal and medial parietal regions (class III, level B).

9 No established structural MRI pattern is characteristic for DLB (class II, level A). However, the absence of MTL atrophy on CT or MRI may be suggestive of a diagnosis of DLB compared with AD (class II, level A).

10 The pattern of atrophy is more useful than atrophy of single regions in the differential diagnosis of FTD compared with AD: knife-edge, severe frontotemporal atrophy combined with dilatation of frontal horn, and an anterior greater than posterior gradient is suggestive of a diagnosis of FTD (class II, level A).

11 A normal structural MRI scan should prompt the clinician to reconsider a diagnosis of bvFTD, if clinically severe, and semantic variant PPA (good practice point).

12 Presence of knife-edge frontal and/or temporal lobe atrophy in patients with PPA is predictive of FTLD pathology, whilst the presence of temporoparietal atrophy is highly associated with AD (class III, level C).

Functional imaging findings

Alzheimer's disease

Cerebral blood flow SPECT and FDG PET scans of typical AD patients demonstrate predominant hypoperfusion or reduced glucose metabolism in the temporoparietal regions, including the precuneus and the posterior cingulate cortex [164]. Functional frontal lobe involvement is also often reported in AD, but usually in conjunction with and characteristically less severe than temporoparietal involvement [165]. Overall, hypoperfusion or hypometabolism in early-onset AD is much greater in magnitude and extent than that of late-onset AD patients with similar dementia severity [166–168]. Early-onset AD patients typically show more severe hypometabolism in parietal, frontal, occipital and subcortical areas [167,168]. The primary visual and sensorimotor cortices, cerebellum, thalamus and basal ganglia are relatively spared in AD [165].

A few studies compared CBF SPECT and FDG PET in their ability to differentiate AD from healthy controls and other dementia, but it seems that FDG PET has both a higher sensitivity and a higher specificity than SPECT [13–16]. The best correspondence was in the temporoparietal and posterior cingulate cortices. However, tracer uptake reductions were significantly more pronounced with PET than with SPECT [13].

Most existing studies compared FDG PET to a clinical diagnosis. Five case–control FDG PET studies using clinical assessment as the reference standard [169–173] revealed an overall diagnostic accuracy of 93% for differentiating AD subjects from healthy subjects, with sensitivity of 96% and specificity of 90% [164]. A prospective study of 102 individuals, presenting consecutively to a primary care centre for examination of suspected early-onset dementia,

showed sensitivity of 78% and specificity of 81% of FDG PET scans against clinical diagnosis of AD [174]. Some studies compared the accuracy of FDG PET with that of clinical and neuropathological diagnosis of dementia [165,175–177]. A multicentre analysis in 138 patients with histopathological diagnoses reported that FDG PET correctly identified the presence or absence of AD in 88% of the cases, with a sensitivity of 94% and a specificity of 73% [175]. A single-centre cohort study of 44 subjects with variable levels of cognitive impairment and autopsy confirmation showed that the diagnostic accuracy available with FDG PET at an initial clinical evaluation (sensitivity, 84%; specificity, 74%) was better than that of initial clinical evaluation alone (sensitivity, 76%; specificity, 58%) and was similar to that of longitudinal clinical diagnosis over approximately 4 years [176]. The diagnosis of AD was associated with a 70% probability of detecting AD pathology, but with a positive PET scan this increased to 84%, and with a negative PET scan this decreased to 31% [176]. A diagnosis of not-AD at an initial clinical evaluation was associated with a 35% probability of AD pathology, increasing to 70% with a positive PET scan [176].

FDG PET differentiates patients with MCI from healthy controls. Amnestic MCI typically shows regional hypometabolism consistent with AD, although the magnitude of reduction is milder than that in clinically probable AD cases [172,178–183]. Longitudinal studies of patients with MCI found that if the baseline FDG PET scan suggests an AD-like pattern, the probability of clinical progression within several years is extremely high [184–187]. A meta-analysis estimated that an AD-like FDG PET pattern observed at baseline in MCI patients had a sensitivity of 89% and a specificity of 85% in distinguishing converters from stable subjects [84]. However, several MCI patients do not have amnestic symptoms. The few CBF SPECT and FDG PET studies that considered amnestic and non-amnestic MCI patients separately provided evidence for a high variability in non-amnestic subjects [172,179,180,188]. A large multicentre study examining FDG PET scans from 114 MCI subjects (amnestic and non-amnestic) found an AD-like PET pattern in 25% of subjects and a DLB- or FTD-like PET pattern in 10% of subjects [172]. The AD pattern was found in the majority (79%) of the MCI patients with deficits in multiple cognitive domains, frequently with additional frontal hypometabolism, and in 31% of amnestic MCI patients [172]. The remaining amnestic MCI patients showed primarily hypometabolism restricted to the hippocampus and posterior cingulate cortex [172]. Non-amnestic MCI patients showed more variable FDG PET profiles, from no hypometabolism (9%) and isolated hippocampal deficits (18%) to widespread FDG uptake consistent with DLB (18%) or with AD and FTLD (9%) [172].

Atypical presentations of AD. The value of functional imaging biomarkers might also differ in the setting of atypical, focal AD presentations, in which the topographical distribution of functional abnormalities needs to be considered separately in each syndrome. Data from functional imaging studies using either CBF SPECT or FDG PET demonstrate a comparable involvement of temporoparietal cortex and precuneus in PCA and typical AD, with extension of hypoperfusion or hypometabolism into occipital and posterior temporal lobes in PCA patients [189–192]. In addition to posterior regions, FDG PET in PCA has indicated specific areas of hypometabolism in the frontal eye fields bilaterally, which can occur secondary to loss of input from occipitoparietal regions and be the cause of oculomotor apraxia in these patients [189,191]. Only a few studies provide guidance about the degree of sensitivity and specificity of CBF SPECT or FDG PET in the diagnostic work-up of atypical AD cases. A retrospective study of 94 patients with a clinical diagnosis of MCI or dementia (typical or atypical), who had an FDG PET within 2 months of their diagnosis, showed that FDG PET findings significantly lowered the number of atypical/unclear diagnoses from 39% to 16% [193]. For a detailed description of functional neuroimaging features in AD cases with prominent language deficits, see the section on PPA.

Dementia with Lewy bodies

Numerous studies reported predominant medial occipital cortex hypoperfusion or hypometabolism in DLB patients compared with AD, with a parietotemporal reduction common to both the diseases [114,165,172,194–199]. Occipital lobe hypometabolism differentiated patients with DLB from AD in both clinically diagnosed [172,196,197,199] and autopsy-confirmed [165,194,195] cohorts. One study comparing FDG PET findings with autopsy results found that occipital hypometabolism, particularly in the primary visual cortex, distinguished DLB from AD with 90% sensitivity and 80% specificity [165]. Furthermore, the sensitivity in discriminating DLB and AD using FDG PET was greater than that with clinical diagnostic criteria applied retrospectively to the data from medical charts [165]. However, on individual SPECT and FDG PET scans, the appearances of DLB and AD can be identical. Moreover, occipital hypometabolism is not a specific marker for DLB and can occasionally be associated with AD. In particular, occipital metab-

olism declines in advanced AD [200] and is associated with atypical AD with PCA [189–192]. The differential diagnosis between DLB and PCA can even be particularly difficult as in some PCA patients there is relative sparing of the hippocampus. In the light of these findings, the McKeith criteria [116] consider a generalized low uptake on SPECT/PET scan with reduced occipital activity as a supportive feature in the diagnostic criteria for DLB, that is, a finding that is commonly present in DLB but lacks sufficient diagnostic specificity to be categorized as core or suggestive. On FDG PET, the cingulate cortex in DLB appears to be relatively spared ('the cingulate island sign') compared with AD cases, but the clinical value of this finding has not been fully investigated [196,201].

Unlike AD, DLB is characterized by nigrostriatal dopaminergic neurodegeneration, making dopaminergic imaging a potentially useful diagnostic tool in this disease [202]. Reduction in striatal uptake of dopamine can be visualized with ^{18}F-L-dihydroxyphenylalanine (^{18}F-DOPA) or by imaging the dopamine transporter using ^{123}I-2beta-carbometoxy-3beta-(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane (^{123}I-FP-CIT) SPECT (known commercially as the DaTSCAN™; GE Healthcare, Waukesha, WI, USA). In a multicentre Phase III trial of ^{123}I-FP-CIT SPECT in 326 patients with a clinical consensus diagnosis of probable ($n = 94$) or possible ($n = 57$) DLB or non-DLB dementia ($n = 147$) [203], mean sensitivity of ^{123}I-FP-CIT SPECT imaging for a clinical diagnosis of probable DLB was 78%, whilst the mean specificity for excluding non-DLB dementia (which was predominantly due to AD) was 90%, giving overall diagnostic accuracy of 86%. Follow-up clinical diagnosis at 12 months, when diagnosis had become clearer in nearly 60% of patients, confirmed the ability of ^{123}I-FP-CIT SPECT imaging to discriminate DLB from non-DLB dementia [204]. Of 44 patients with a clinical diagnosis of possible DLB at baseline, the diagnosis at follow-up remained as possible DLB in 18 but was changed to probable DLB in 19, 12 of whom had abnormal SPECT scans at baseline, and to non-DLB dementia in seven, all of whom had normal baseline scans [204]. ^{123}I-FP-CIT SPECT has demonstrated higher sensitivity and specificity for differentiating DLB from non-DLB than clinical diagnosis in a series of 20 patients who had post-mortem brain examination [205]. In this study, sensitivity of an initial clinical diagnosis of DLB against autopsy diagnosis was 75% and specificity was 42%, in comparison with 88% sensitivity and 100% specificity with ^{123}I-FP-CIT SPECT imaging [205]. These results suggest that an abnormal dopaminergic imaging scan in individuals with possible DLB strongly supports the diagnosis. As a consequence, low dopamine transporter uptake in the basal ganglia demonstrated by SPECT or PET imaging has been included as a suggestive feature in the diagnostic criteria for DLB (one suggestive feature plus one core feature being sufficient to allow a diagnosis of probable DLB) [116]. On the contrary, its negativity does not exclude a clinical diagnosis of probable DLB, as about 20% of probable DLB cases will have a normal or inconclusive scan [204].

Dopaminergic imaging cannot distinguish DLB from alternative nigrostriatal disorders, such as PD with dementia [206–210], MSA, PSP, corticobasal degeneration, vascular parkinsonism with dementia or FTD with parkinsonism, as all are associated with presynaptic dopaminergic deficiency [211].

Frontotemporal dementia

Behavioural variant of frontotemporal dementia is identified on SPECT or PET scans by patterns of hypoperfusion or hypometabolism in frontal, insular and anterior temporal regions that are typically quite asymmetrically centred into the frontolateral cortex [212–214]. The regions mostly impaired are the medial frontal cortex, followed by the frontolateral and anterior temporal cortices. A prospective study in 134 patients with suspected bvFTD demonstrated that a predominant frontal, anterior temporal or frontotemporal hypoperfusion or hypometabolism on initial SPECT or PET scans has a sensitivity of 90% and specificity of 75% against a clinical diagnosis after 2 years [130]. However, metabolic abnormalities are not limited to these regions. As the severity of dementia increases, the severity and topographical extent of perfusion and metabolic impairments also increase and begin to involve other association areas [215].

The regional pattern of predominantly frontal functional impairment in FTD, with relative sparing of posterior brain regions, usually allows a clear distinction between these patients and those with AD [140,213,216–219]. Using an anterior-to-posterior CBF SPECT ratio (medial superior frontal gyrus/medial temporal lobes), patients with clinical bvFTD were successfully distinguished from AD patients, with a sensitivity of 87% and a specificity of 96% versus early-onset AD patients and 80% versus late-onset AD patients [216]. A few studies have looked at the accuracy of SPECT or FDG PET findings in relation to the pathological diagnoses [177,220]. A reduction in frontal CBF was more common in pathologically confirmed FTLD than in AD cases and was of diagnostic value (sensitivity 80%, specificity 65%) [220]. When the pattern of bilateral frontal CBF reduction was not associated with a bilateral parietal CBF abnormality, the diagnosis was more accurate (sensi-

tivity 80%, specificity 81%) [220]. However, an overlap of abnormalities between the two conditions can be seen, as AD can involve frontal regions and FTLD may not spare temporoparietal cortex [221]. In a study of autopsy-proven FTLD and AD patients, the addition of FDG PET scans particularly improved the accuracy of an FTLD diagnosis more than an AD diagnosis [177]. However, FDG PET scans from FTLD patients had more variability of interpretation compared with those from AD cases, resulting in lower sensitivity (70% for FTLD vs. 98% for AD) and confidence [177]. The disagreement in interpretation of scans in patients with FTLD largely occurred when there was a temporoparietal hypometabolism [221]. Hypometabolism of anterior cingulate and anterior temporal regions indicates a high likelihood of FTLD, even when temporoparietal hypometabolism is present [221].

Primary progressive aphasia

In patients with semantic variant PPA, FDG PET studies showed asymmetrical hypometabolism of the temporal lobes, more marked on the left side [100,222–224]. A functional deficit of the left frontal opercular regions of the brain has been reported in non-fluent variant PPA patients [100,225–228]. In these cases, a functional involvement of bilateral caudate nuclei and thalami was also described [228]. Logopenic PPA patients usually show a pattern of left posterior temporoparietal hypometabolism on FDG PET scans [100].

A study comparing semantic PPA and very early AD patients using structural MRI and FDG PET findings revealed hippocampal atrophy and hypometabolism in both groups, but a strikingly reduced metabolism in the posterior cingulate cortex in patients with AD that was not present in those with semantic variant PPA [222]. A functional imaging study of non-fluent patients demonstrated that a pattern of bilateral temporoparietal involvement is predictive of AD pathology, whilst a unilateral (left), reduced temporoparietal cortex function can be seen in cases with FTLD pathology [229]. On the contrary, a bilaterally normal temporoparietal cortical perfusion or metabolism was predictive of FTLD pathology [229].

Recommendations for functional imaging

1 Although typical cases of dementia may not benefit from routine SPECT or PET imaging, these tools are recommended in those cases where diagnosis remains in doubt after clinical and structural MRI work-up and in particular clinical settings (class II, level A).

2 Functional imaging can be of value to diagnose (or exclude) a neurodegenerative dementia in those subjects with cognitive impairment presenting with severe psychiatric disturbances (including depression and agitation) and in cases where proper cognitive testing is difficult, that is, with no language in common with the clinician (good practice point).

3 Normal FDG PET scan findings, in the presence of the suspicion of dementia, make a neurodegenerative diagnosis less likely (class II, level A).

4 The overall regional pattern of metabolic impairment of the posterior cingulate/precuneus and lateral temporoparietal cortices, more accentuated than frontal cortex deficits, together with the relative preservation of the primary sensorimotor and visual cortices, basal ganglia and cerebellum defines the distinct metabolic phenotype of AD (class II, level A).

5 AD-like metabolic patterns in patients with MCI are predictive of conversion to AD within several years (class II, level A).

6 Occipital hypometabolism, particularly in the primary visual cortex, may be more common in DLB than AD on a group basis (class II, level B). However, on individual scans, the appearances of DLB and AD can be identical. Moreover, occipital hypometabolism is not a specific marker for DLB and can be associated with AD (good practice point).

7 Although an overlap of functional abnormalities between FTD and AD has been shown to occur, the presence of posterior temporal and parietal brain hypoperfusion or hypometabolism is predictive of a pathological diagnosis of AD, whereas a disproportionate reduction in frontal perfusion/metabolism is more common in FTD cases (class II, level A).

8 In PPA patients, bilateral posterior temporoparietal hypometabolism (PET) or hypoperfusion (SPECT) is predictive of AD pathology; normal bilateral posterior temporoparietal function is specific for FTLD (class III, level C).

9 Dopaminergic SPECT is useful to distinguish DLB from AD (class I, level A), especially when there are no clear extrapyramidal symptoms and signs. However, a negative ^{123}I-FP-CIT scan does not necessarily exclude a diagnosis of probable DLB, as around 20% of individuals with probable DLB appear to have normal scans (class I, level A).

10 Dopaminergic SPECT can be useful in differentiating DLB from long-term psychiatric patients on neuroleptic drugs, whose parkinsonism may be drug-induced (good practice point).

Future tools

Amyloid imaging

Vascular dementia

Of particular interest is the potential of PET amyloid imaging (currently just a research tool) to differentiate mixed AD with cerebrovascular disease from pure AD or vascular dementia. Both carbon-11 (^{11}C) and ^{18}F ligands are available. One study found that 69% of patients clinically diagnosed with subcortical vascular dementia were negative for PET ^{11}C-Pittsburgh compound B (PIB) binding [230]. Younger age, a greater number of lacunae and a less severe MTL atrophy predicted a negative amyloid imaging scan [230]. Another small study found high ^{11}C-PIB binding in 40% of patients with post-stroke dementia [231]. Thus, amyloid imaging can be helpful in identifying cognitively impaired patients with high vascular burden who also have comorbid AD. Furthermore, patients with CAA show high^{11}C-PIB binding compared with controls [232], and this can aid differentiation between CAA and brain haemorrhages caused by small-vessel disease.

Alzheimer's disease

Amyloid imaging such as ^{11}C-PIB PET has very high (90% or greater) sensitivity for AD [233]. The amyloid imaging tracers flutemetamol, florbetapir and florbetaben labelled with ^{18}F demonstrated similar accuracy for distinguishing patients with AD from normal subjects and those with other diseases [234–240]. Amyloid tracer binding is diffuse and symmetrical, with high uptake consistently found in the prefrontal cortex, precuneus and posterior cingulate cortex, followed by the lateral parietal, lateral temporal cortex and striatum. This pattern closely mirrors the distribution of plaques found at autopsy [241]. Compared to healthy controls, early-onset AD patients showed increased ^{11}C-PIB uptake throughout frontal, parietal and lateral temporal cortices and striatum and no significant differences in regional or global ^{11}C-PIB binding between early-onset and late-onset patients were found [168]. However, some healthy elderly controls show high ^{11}C-PIB binding. The frequency of increased cortical ^{11}C-PIB binding in controls increases rapidly from 10% or less below the age of 70 to 30–40% at the age of 80 years [242].

As a group, 52–87% of MCI patients show elevated ^{11}C-PIB binding in a similar regional distribution to AD [243,244]. Patients with amnestic MCI are more likely to be ^{11}C-PIB-positive than patients with non-amnestic presentations [244]. Studies using ^{18}F tracers report similar findings, with positive scans found in 45–60% of MCI patients [238,245,246]. In longitudinal studies, ^{11}C-PIB-positive subjects with MCI are significantly more likely to convert to AD than ^{11}C-PIB-negative patients [81,247–249], with 1-year conversion rates to AD ranging from 38% to 47% in ^{11}C-PIB-positive MCI subjects versus. virtually no conversion in ^{11}C-PIB-negative subjects [248,249]. Faster amnestic MCI converters have higher ^{11}C-PIB retention than slower converters in the anterior cingulate, frontal and temporal cortices [248].

Atypical presentations of AD. A few studies have applied amyloid imaging in patients with an atypical clinical presentation of AD. In two studies in which ^{11}C-PIB uptake was compared in large groups of patients with PCA and typical AD, no significant difference was reported in amyloid deposition between these groups. Both showed diffuse ^{11}C-PIB uptake throughout frontal, temporoparietal and occipital cortex [192,250].

Dementia with Lewy bodies

Small case series using amyloid imaging reveal that DLB patients have often an increased cortical amyloid deposition (from 33% up to 87% of cases) similar to that observed in AD [114,251–255]. The regional pattern of ^{11}C-PIB retention in patients with DLB who were ^{11}C-PIB-positive reflects the pattern typically seen in patients with AD, involving the frontal, parietal and superior temporal lobe association cortices. Increased striatal ^{11}C-PIB retention has been reported in patients with DLB [251]. Amyloid imaging with ^{18}F-florbetaben showed cortical binding in 29% of DLB cases [246]. Some degree of amyloid deposition is also observed in a minority of PD with dementia cases (from 17% to 33%), whilst it is more rarely present in PD patients without dementia (from 0% to 23%) [251–255].

Frontotemporal dementia and primary progressive aphasia

Amyloid imaging is expected to provide excellent differentiation of AD from FTD, which is not associated with amyloid deposition – particularly in younger patients. Generally, low cortical ^{11}C-PIB retention [242,256–259] or ^{18}F-florbetaben positivity [237,246] was observed in patients with FTD. Amyloid imaging was used in five bvFTD patients, four semantic variant PPA patients and seven AD patients [256]. Whilst all AD patients experienced an increased ^{11}C-PIB retention, three bvFTD patients, two semantic patients and all healthy controls had ^{11}C-PIB-negative scans. The retrospective revision of clinical and functional neuroimaging data showed that the two ^{11}C-PIB-positive bvFTD patients had a clinical and cognitive

picture consistent with either AD or bvFTD and biparietal hypometabolism on FDG PET. Both ^{11}C-PIB-positive semantic variant PPA patients had FDG PET scans consistent with FTLD; however, one patient had a classic neuropsychological profile for semantic PPA, whilst the other had a cognitive profile that could be consistent with either AD or FTLD. ^{11}C-PIB PET was used to compare 10 clinically diagnosed bvFTD patients with 17 ^{11}C-PIB-positive AD patients and eight PIB-negative healthy controls [257]. Two bvFTD patients showed a positive ^{11}C-PIB retention similar to that of AD cases [257]. The accurate revision of clinical and neuroimaging data showed that, although one of the ^{11}C-PIB-positive patients had a clinical history and an FDG PET scan suggestive of FTLD, the other had a neuropsychological profile which was atypical for bvFTD and developed a global, AD-like cognitive impairment during follow-up, thus suggesting a diagnosis of AD with frontal involvement [257]. In a large study of 62 AD patients and 45 FTD patients, ^{11}C-PIB scans were positive in 87% of AD cases and 16% of FTD cases [259]. ^{11}C-PIB visual reads had a higher sensitivity for AD than FDG PET (89% vs. 77%), with similar specificity (83% vs. 84%). When scans were classified quantitatively, PIB had higher sensitivity (89% vs. 73%), whilst FDG PET had higher specificity (83% vs. 98%) [259]. ^{11}C-PIB outperformed FDG PET in classifying the 12 patients with known pathology (97% vs. 87% overall accuracy combining visual reads and quantitative classification) [259].

In small PPA case series [100,258], the semantic and non-fluent groups show the lowest proportion of ^{11}C-PIB-positive cases, whilst amyloid deposition is more common in patients with the logopenic variant. Logopenic PPA cases show a diffuse ^{11}C-PIB binding pattern that is indistinguishable from typical AD [100,258].

Recommendations for amyloid imaging

1 Amyloid imaging is not yet recommended for routine use in the clinical setting, especially in the diagnostic work-up of patients with straightforward clinical AD as these patients are very likely to have positive scans (class III, level B).

2 Negative amyloid scans indicate absence of AD pathology with a high level of accuracy (class III, level B), but healthy elderly controls might have positive amyloid scans, so their predictive value in isolation is not clear (good practice point).

3 Amyloid imaging is likely to find clinical utility in the following fields:

- **i** The stratification of MCI patients into those with and without underlying AD (class III, level B);
- **ii** The evaluation of early-onset AD patients, as these patients often present with atypical symptoms, or patients with clinically atypical presentations (e.g. PPA), as these are pathologically heterogeneous syndromes that are variably associated with AD pathology (class III, level C). Also, below the age of 70 years, frequency of amyloid deposits in controls is low ($< 20\%$);
- **iii** The differential diagnosis between AD and FTD, because amyloid plaques are not part of the FTLD pathological spectrum (class III, level C);
- **iv** The differential diagnosis between CAA and intracranial haemorrhage caused by small-vessel disease, because patients with CAA but not those with small-vessel disease have positive amyloid imaging scans (class III, level C).

Serial structural MRI

Rates of whole-brain atrophy in AD have been estimated at 1.4–2.2% per year, whereas rates of atrophy during normal ageing (for a mean age of 70 years) do not usually exceed 0.7% per year [260]. A meta-analysis showed that mean annualized hippocampal atrophy rates are 4.7% for AD subjects and 1.4% for controls [261]. Atrophy rate from serial MRI studies was found to be associated with time to subsequent clinical conversion to a more impaired state in both cognitively healthy elderly subjects and subjects with amnestic MCI [262,263].

Pathologically proven DLB patients showed a much lower rate of atrophy (similar to that of age-matched controls) compared to the AD group, with rates of whole-brain atrophy of only 0.4% per year [264]. The annual rate of whole-brain volume loss varies from 1.4% to 3.7% in bvFTD patients and from 1.7% to 2.6% in semantic and non-fluent PPA patients [265–267]. Over 1 year, semantic patients had the greatest volume loss in the temporal lobes (5.9% on the left and 4.8% on the right) [268]. The annual rate of whole-brain volume loss in autopsy-proven FTLD patients was significantly higher than the rate observed in AD subjects [269]. The results of a regional analysis of atrophy showed that there were differences between FTLD and AD patients in the rates of tissue loss of both anterior quadrants of the brain, but not in the posterior quadrants [265].

Recommendations for serial structural MRI

1 Changes over a relatively short period (e.g. 6 months to 1 year) that are visible to the naked eye may strengthen the clinical suspicion of

neurodegenerative dementia, particularly in MCI patients (class IV, good practice point).

2 In most cases, advanced image registration techniques are needed to pick up subtle structural changes over time, but these are restricted to research use or clinical trials (class IV, good practice point).

Non-conventional MRI

^{1}H-MRS

Proton magnetic resonance spectroscopic imaging (^{1}H-MRS) studies have reported that the level of *N*-acetylaspartate (NAA) is decreased in AD [270] and MCI patients [271–274] compared with healthy subjects. In addition to neuronal damage, increased glial cell activity, reflected by raised levels of myo-inositol (mI), has been demonstrated in AD patients compared with controls [275]. The NAA/mI ratio enabled the differentiation of patients with AD from cognitively healthy subjects with relatively high sensitivity (57–90%) and specificity (73–95%) [276–279]. NAA/creatine was found to be lower in patients with AD and FTD than in those with DLB [280]. Whilst these findings are robust on a group level, diagnostic value is not robust enough in individual cases.

Diffusion tensor MRI

Diffusion tensor (DT) MRI studies in AD have found altered diffusion properties compared with controls in several brain regions, especially in temporal and frontal lobes, posterior cingulum and corpus callosum [281]. White matter changes in AD generally follow the anatomical pattern of grey matter atrophy [282]. Differences between MCI and controls parallel those between AD and controls, but fewer regions reached statistical significance [281]. The severity of microstructural damage within and beyond the MTL was associated with an increased short-term risk of developing AD in amnestic MCI patients [283–286].

DT MRI is also increasingly being used to examine differences across dementia subtypes [287–289]. For instance, it has been shown that bvFTD is associated with greater diffusion abnormalities in frontal brain regions compared with AD cases, whereas no brain areas in AD showed greater damage than in bvFTD [289]. In addition, DT MRI measures of the anterior corpus callosum and left superior longitudinal fasciculus differentiated bvFTD from non-fluent cases, whilst the best predictors of semantic PPA compared with both bvFTD and non-fluent cases were diffusivity abnormalities of the left uncinate and inferior longitudinal fasciculus [290]. These results suggest that white matter integrity loss measured with DT MRI may offer new markers for the diagnostic differentiation between AD and other neurodegenerative dementia.

Arterial spin labelling

Non-invasive perfusion MRI with arterial spin labelling (ASL) contrast uses magnetically labelled arterial blood water as an endogenous tracer to provide quantitative CBF measurements [291]. The type of information that can be obtained is comparable with that from nuclear medicine examinations, such as HMPAO SPECT and FDG PET, but with higher resolution. A limited number of investigations have employed this technique in the neurodegenerative dementia population. Studies in patients with AD and FTD showed a pattern of hypoperfusion consistent with that of FDG PET hypometabolism [292–294]. Similar findings have been found in amnestic MCI patients [293].

Resting state functional MRI

Resting state functional MRI is a promising new tool for the investigation of the intrinsic connectivity of brain networks in patient populations [295]. The default mode network (DMN), which includes the posterior cingulate, inferior parietal, inferolateral temporal, ventral anterior cingulate and hippocampal regions, has received the greatest attention and has been shown to be less active in AD [296–299] and MCI [300,301] patients than in healthy elderly controls. Sensitivity of RS fMRI measures in differentiating AD patients from healthy elderly controls ranges from 72% to 85% and specificity from 77% to 80% [296,302,303]. The impaired posteromedial cortex deactivation in amnestic MCI patients was also found to be predictive of clinical conversion to AD [304,305].

Unlike AD, bvFTD patients experienced decreased salience network connectivity in the frontal and numerous subcortical nodes, as well as an increased parietal DMN connectivity relative to healthy controls [306,307]. A combination of salience network and DMN connectivity scores was found to be able to classify healthy subjects, AD patients and bvFTD patients with 92% accuracy and to separate AD and bvFTD patients with 100% accuracy [306].

Recommendations for non-conventional MRI

1 At present, advanced MRI techniques do not have a role in the diagnosis or routine assessment or monitoring of neurodegenerative dementia (class IV, good practice point).

2 The reliability and reproducibility of advanced MRI techniques requires further evaluation, and serious efforts are under way to achieve harmo-

nization of both acquisition and post-processing procedures (e.g. http://enigma.loni.ucla.edu/ongoing/dti-working-group/).

Disclosure of conflict of Interest

The authors declare no other conflict of interests. General financial interests are listed in the Appendix.

Appendix

Massimo Filippi received personal compensation for board membership from Teva Pharmaceutical Industries Ltd., and Genmab A/S; for consultancies from Bayer Schering Pharma, Biogen-Dompé, Genmab A/S, Merck Serono, Pepgen Corporation and Teva Pharmaceutical Industries Ltd.; funding for travel from Bayer Schering Pharma, Biogen-Dompé, Genmab A/S, Merck Serono and Teva Pharmaceutical Industries Ltd.; speakers' bureaus from Bayer Schering Pharma, Biogen-Dompé, Genmab A/S, Merck Serono and Teva Pharmaceutical Industries Ltd. His institution has received grants from Bayer Schering, Biogen-Dompé, Genmab A/S, Merck Serono, Teva Pharmaceutical Industries Ltd., and Fondazione Italiana Sclerosi Multipla (FISM).

Federica Agosta received personal compensation for speaking from Bayer Schering Pharma, Sanofi-Aventis and Serono Symposia International Foundation and travel grants from Teva Pharmaceutical Industries Ltd. Her institution has received grants from the Italian Ministry of Health.

Frederik Barkhof received personal compensation for consultancies from Lundbeck, Janssen and Roche.

Bruno Dubois received personal compensation for board membership from Bristol-Myers Squibb, Novartis, Roche, Elan, Eli Lilly, Eisai, GE Healthcare, Janssen and Sanofi-Aventis. His institution has received grants from Novartis, Roche, Eisai and Sanofi-Aventis.

Nick Fox received personal compensation for consultancies from Janssen, Wyeth, GE Healthcare, Bristol-Myers Squibb, Lilly, Bioclinica, AVID and Lundbeck, Eisai Inc. His institution has received grants from Janssen and GE Healthcare and patents for QA Box.

Giovanni B Frisoni received personal compensation for board membership from Lilly, BMS, Bayer, Lundbeck, Elan, Astra Zeneca, Pfizer, Baxter and Wyeth. His institution has received grants from Wyeth, Lilly and Lundbeck Italia.

Clifford Jack received personal compensation for consultancies from Lilly Janssen. His institution has received grants from the NIH.

Peter Johannsen received personal compensation for board membership from AC Immune; for consultancies from Novartis and Roche; for educational materials from Lundbeck Pharma; speakers' bureaus from Lunbeck Pharma, Eisai and Novartis; travel grants from Novartis.

Bruce Miller received personal compensation for board membership from JD French Foundation and LLHillbom Foundation; for consultancies from Tau RX, Ltd. and Allon Therapeutics and royalties from Cambridge University Press. His institution has received grants from the NIH.

Peter Nestor received personal compensation for board membership from Eisai, GE Healthcare and Eli-Lilly. His institution as received grants from Alzheimer's Research UK and the Medical Research Council, UK.

Philip Scheltens received personal compensation for board membership and consultancies from GE Healthcare and AVID/Lilly. His institution has received grants from GE Healthcare.

Sandro Sorbi received personal compensation for speakers bureaus from Novartis and Bayer.

Stefan Teipel: his institution received grants for conducting clinical trials.

Paul Thompson: his institution has received grants from the NIH.

Lars Olof Wahlund has nothing to disclose.

References

1. Waldemar G, Dubois B, Emre M, *et al*. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. *Eur J Neurol* 2007; **14:** e1–e26.
2. Hort J, O'Brien JT, Gainotti G, *et al*. EFNS guidelines for the diagnosis and management of Alzheimer's disease. *Eur J Neurol* 2010; **17:** 1236–1248.
3. (NICE) NIfHaCE. CG42 Dementia: NICE guideline. March 2011.
4. Knopman DS, DeKosky ST, Cummings JL, *et al*. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001; **56:** 1143–1153.
5. Barkhof F, Fox NC, Bastos Leite AJ, Scheltens P. *Neuroimaging in Dementia*, 1st edn. New York: Springer, 2011.
6. Dubois B, Feldman HH, Jacova C, *et al*. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 2007; **6:** 734–746.
7. Dubois B, Feldman HH, Jacova C, *et al*. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* 2010; **9:** 1118–1127.
8. McKhann GM, Knopman DS, Chertkow H, *et al*. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7:** 263–269.
9. Brainin M, Barnes M, Baron JC, *et al*. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *Eur J Neurol* 2004; **11:** 577–581.
10. De Leon MJ, George AE, Golomb J, *et al*. Frequency of hippocampal formation atrophy in normal aging and Alzheimer's disease. *Neurobiol Aging* 1997; **18:** 1–11.
11. Frisoni GB, Geroldi C, Beltramello A, *et al*. Radial width of the temporal horn: a sensitive measure in Alzheimer disease. *AJNR Am J Neuroradiol* 2002; **23:** 35–47.
12. O'Brien JT, Metcalfe S, Swann A, *et al*. Medial temporal lobe width on CT scanning in Alzheimer's disease: comparison with vascular dementia, depression and dementia with Lewy bodies. *Dement Geriatr Cogn Disord* 2000; **11:** 114–118.
13. Herholz K, Schopphoff H, Schmidt M, *et al*. Direct comparison of spatially normalized PET and SPECT scans in Alzheimer's disease. *J Nucl Med* 2002; **43:** 21–26.
14. Messa C, Perani D, Lucignani G, *et al*. High-resolution technetium-99m-HMPAO SPECT in patients with probable Alzheimer's disease: comparison with fluorine-18-FDG PET. *J Nucl Med* 1994; **35:** 210–216.
15. Mielke R, Heiss WD. Positron emission tomography for diagnosis of Alzheimer's disease and vascular dementia. *J Neural Transm Suppl* 1998; **53:** 237–250.
16. Mielke R, Pietrzyk U, Jacobs A, *et al*. HMPAO SPET and FDG PET in Alzheimer's disease and vascular dementia: comparison of perfusion and metabolic pattern. *Eur J Nucl Med* 1994; **21:** 1052–1060.
17. Herholz K, Salmon E, Perani D, *et al*. Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. *Neuroimage* 2002; **17:** 302–316.
18. Bastos Leite AJ, van Straaten EC, Scheltens P, Lycklama G, Barkhof F. Thalamic lesions in vascular dementia: low sensitivity of fluid-attenuated inversion recovery (FLAIR) imaging. *Stroke* 2004; **35:** 415–419.
19. Erkinjuntti T, Inzitari D, Pantoni L, *et al*. Research criteria for subcortical vascular dementia in clinical trials. *J Neural Transm Suppl* 2000; **59:** 23–30.
20. Roman GC, Tatemichi TK, Erkinjuntti T, *et al*. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993; **43:** 250–260.
21. van Straaten EC, Scheltens P, Knol DL, *et al*. Operational definitions for the NINDS-AIREN criteria for vascular dementia: an interobserver study. *Stroke* 2003; **34:** 1907–1912.
22. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* 1987; **149:** 351–356.
23. Scheltens P, Barkhof F, Leys D, *et al*. A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *J Neurol Sci* 1993; **114:** 7–12.
24. Wahlund LO, Barkhof F, Fazekas F, *et al*. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke* 2001; **32:** 1318–1322.
25. Scheltens P, Fox N, Barkhof F, De Carli C. Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion. *Lancet Neurol* 2002; **1:** 13–21.
26. Frisoni GB, Galluzzi S, Pantoni L, Filippi M. The effect of white matter lesions on cognition in the elderly – small but detectable. *Nat Clin Pract Neurol* 2007; **3:** 620–627.
27. Fazekas F, Kleinert R, Roob G, *et al*. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. *AJNR Am J Neuroradiol* 1999; **20:** 637–642.
28. Offenbacher H, Fazekas F, Schmidt R, Koch M, Fazekas G, Kapeller P. MR of cerebral abnormalities concomitant with primary intracerebral hematomas. *AJNR Am J Neuroradiol* 1996; **17:** 573–578.
29. Scharf J, Brauherr E, Forsting M, Sartor K. Significance of haemorrhagic lacunes on MRI in patients with hypertensive cerebrovascular disease and intracerebral haemorrhage. *Neuroradiology* 1994; **36:** 504–508.
30. Haacke EM, DelProposto ZS, Chaturvedi S, *et al*. Imaging cerebral amyloid angiopathy with susceptibility-weighted imaging. *AJNR Am J Neuroradiol* 2007; **28:** 316–317.
31. Goos JD, van der Flier WM, Knol DL, *et al*. Clinical relevance of improved microbleed detection by susceptibility-weighted magnetic resonance imaging. *Stroke* 2011; **42:** 1894–1900.
32. Nandigam RN, Viswanathan A, Delgado P, *et al*. MR imaging detection of cerebral microbleeds: effect of susceptibility-weighted imaging, section thickness, and field strength. *AJNR Am J Neuroradiol* 2009; **30:** 338–343.
33. Greenberg SM, Vernooij MW, Cordonnier C, *et al*. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol* 2009; **8:** 165–174.

34. Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. *Ann Neurol* 2011; **70:** 871–880.
35. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. *Neurology* 2001; **56:** 537–539.
36. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. Cadasil. *Lancet Neurol* 2009; **8:** 643–653.
37. Cordonnier C, van der Flier WM, Sluimer JD, Leys D, Barkhof F, Scheltens P. Prevalence and severity of microbleeds in a memory clinic setting. *Neurology* 2006; **66:** 1356–1360.
38. Pettersen JA, Sathiyamoorthy G, Gao FQ, *et al*. Microbleed topography, leukoaraiosis, and cognition in probable Alzheimer disease from the Sunnybrook dementia study. *Arch Neurol* 2008; **65:** 790–795.
39. Hanyu H, Tanaka Y, Shimizu S, Takasaki M, Abe K. Cerebral microbleeds in Alzheimer's disease. *J Neurol* 2003; **250:** 1496–1497.
40. Atri A, Locascio JJ, Lin JM, *et al*. Prevalence and effects of lobar microhemorrhages in early-stage dementia. *Neurodegener Dis* 2005; **2:** 305–312.
41. Nakata Y, Shiga K, Yoshikawa K, *et al*. Subclinical brain hemorrhages in Alzheimer's disease: evaluation by magnetic resonance T2*-weighted images. *Ann N Y Acad Sci* 2002; **977:** 169–172.
42. Thompson PM, Hayashi KM, de Zubicaray G, *et al*. Dynamics of gray matter loss in Alzheimer's disease. *J Neurosci* 2003; **23:** 994–1005.
43. Bloudek LM, Spackman DE, Blankenburg M, Sullivan SD. Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. *J Alzheimers Dis* 2011; **26:** 627–645.
44. Baron JC, Chetelat G, Desgranges B, *et al*. *In vivo* mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease. *Neuroimage* 2001; **14:** 298–309.
45. Frisoni GB, Testa C, Zorzan A, *et al*. Detection of grey matter loss in mild Alzheimer's disease with voxel based morphometry. *J Neurol Neurosurg Psychiatry* 2002; **73:** 657–664.
46. Jones BF, Barnes J, Uylings HB, *et al*. Differential regional atrophy of the cingulate gyrus in Alzheimer disease: a volumetric MRI study. *Cereb Cortex* 2006; **16:** 1701–1708.
47. Fox NC, Crum WR, Scahill RI, Stevens JM, Janssen JC, Rossor MN. Imaging of onset and progression of Alzheimer's disease with voxel-compression mapping of serial magnetic resonance images. *Lancet* 2001; **358:** 201–205.
48. Thompson PM, Mega MS, Woods RP, *et al*. Cortical change in Alzheimer's disease detected with a disease-specific population-based brain atlas. *Cereb Cortex* 2001; **11:** 1–16.
49. Boxer AL, Rankin KP, Miller BL, *et al*. Cinguloparietal atrophy distinguishes Alzheimer disease from semantic dementia. *Arch Neurol* 2003; **60:** 949–956.
50. Chetelat G, Landeau B, Eustache F, *et al*. Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: a longitudinal MRI study. *Neuroimage* 2005; **27:** 934–946.
51. Karas GB, Scheltens P, Rombouts SA, *et al*. Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. *Neuroimage* 2004; **23:** 708–716.
52. Bozzali M, Filippi M, Magnani G, *et al*. The contribution of voxel-based morphometry in staging patients with mild cognitive impairment. *Neurology* 2006; **67:** 453–460.
53. Pennanen C, Testa C, Laakso MP, *et al*. A voxel based morphometry study on mild cognitive impairment. *J Neurol Neurosurg Psychiatry* 2005; **76:** 11–14.
54. Shiino A, Watanabe T, Maeda K, Kotani E, Akiguchi I, Matsuda M. Four subgroups of Alzheimer's disease based on patterns of atrophy using VBM and a unique pattern for early onset disease. *Neuroimage* 2006; **33:** 17–26.
55. Whitwell JL, Przybelski SA, Weigand SD, *et al*. 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. *Brain* 2007; **130:** 1777–1786.
56. Whitwell JL, Petersen RC, Negash S, *et al*. Patterns of atrophy differ among specific subtypes of mild cognitive impairment. *Arch Neurol* 2007; **64:** 1130–1138.
57. Pengas G, Hodges JR, Watson P, Nestor PJ. Focal posterior cingulate atrophy in incipient Alzheimer's disease. *Neurobiol Aging* 2010; **31:** 25–33.
58. He J, Farias S, Martinez O, Reed B, Mungas D, Decarli C. Differences in brain volume, hippocampal volume, cerebrovascular risk factors, and apolipoprotein E4 among mild cognitive impairment subtypes. *Arch Neurol* 2009; **66:** 1393–1399.
59. Pa J, Boxer A, Chao LL, *et al*. Clinical-neuroimaging characteristics of dysexecutive mild cognitive impairment. *Ann Neurol* 2009; **65:** 414–423.
60. Apostolova LG, Thompson PM, Green AE, *et al*. 3D comparison of low, intermediate, and advanced hippocampal atrophy in MCI. *Hum Brain Mapp* 2010; **31:** 786–797.
61. Gosche KM, Mortimer JA, Smith CD, Markesbery WR, Snowdon DA. Hippocampal volume as an index of Alzheimer neuropathology: findings from the Nun Study. *Neurology* 2002; **58:** 1476–1482.
62. Csernansky JG, Hamstra J, Wang L, *et al*. Correlations between antemortem hippocampal volume and postmortem neuropathology in AD subjects. *Alzheimer Dis Assoc Disord* 2004; **18:** 190–195.
63. Silbert LC, Quinn JF, Moore MM, *et al*. Changes in premorbid brain volume predict Alzheimer's disease pathology. *Neurology* 2003; **61:** 487–492.
64. Wattjes MP, Henneman WJ, van der Flier WM, *et al*. Diagnostic imaging of patients in a memory clinic: comparison of MR imaging and 64-detector row CT. *Radiology* 2009; **253:** 174–183.
65. Scheltens P, Leys D, Barkhof F, *et al*. Atrophy of medial temporal lobes on MRI in 'probable' Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry* 1992; **55:** 967–972.
66. Erkinjuntti T, Lee DH, Gao F, *et al*. Temporal lobe atrophy on magnetic resonance imaging in the diagnosis of early Alzheimer's disease. *Arch Neurol* 1993; **50:** 305–310.
67. Bresciani L, Rossi R, Testa C, *et al*. Visual assessment of medial temporal atrophy on MR films in Alzheimer's disease: comparison with volumetry. *Aging Clin Exp Res* 2005; **17:** 8–13.

68. Duara R, Loewenstein DA, Potter E, *et al*. Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease. *Neurology* 2008; **71:** 1986–1992.
69. Frisoni GB, Jack CR. Harmonization of magnetic resonance-based manual hippocampal segmentation: a mandatory step for wide clinical use. *Alzheimers Dement* 2011; **7:** 171–174.
70. Boccardi M, Ganzola R, Bocchetta M, *et al*. Survey of protocols for the manual segmentation of the hippocampus: preparatory steps towards a joint EADC-ADNI harmonized protocol. *J Alzheimers Dis* 2011; **26** (Suppl 3)**:** 61–75.
71. Leung KK, Barnes J, Ridgway GR, *et al*. Automated cross-sectional and longitudinal hippocampal volume measurement in mild cognitive impairment and Alzheimer's disease. *Neuroimage* 2010; **51:** 1345–1359.
72. Stein JL, Medland SE, Arias Vasquez A, *et al*. Common genetic polymorphisms are associated with human hippocampal and intracranial volumes. *Nat Genetics* 2012; In press.
73. Shi F, Liu B, Zhou Y, Yu C, Jiang T. Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: meta-analyses of MRI studies. *Hippocampus* 2009; **19:** 1055–1064.
74. Jack CR Jr, Petersen RC, Xu YC, *et al*. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology* 1999; **52:** 1397–1403.
75. Devanand DP, Pradhaban G, Liu X, *et al*. Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. *Neurology* 2007; **68:** 828–836.
76. Risacher SL, Saykin AJ, West JD, Shen L, Firpi HA, McDonald BC. Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. *Curr Alzheimer Res* 2009; **6:** 347–361.
77. Apostolova LG, Dutton RA, Dinov ID, *et al*. Conversion of mild cognitive impairment to Alzheimer disease predicted by hippocampal atrophy maps. *Arch Neurol* 2006; **63:** 693–699.
78. DeCarli C, Frisoni GB, Clark CM, *et al*. Qualitative estimates of medial temporal atrophy as a predictor of progression from mild cognitive impairment to dementia. *Arch Neurol* 2007; **64:** 108–115.
79. Desikan RS, Cabral HJ, Fischl B, *et al*. Temporoparietal MR imaging measures of atrophy in subjects with mild cognitive impairment that predict subsequent diagnosis of Alzheimer disease. *AJNR Am J Neuroradiol* 2009; **30:** 532–538.
80. Fleisher AS, Sun S, Taylor C, *et al*. Volumetric MRI vs clinical predictors of Alzheimer disease in mild cognitive impairment. *Neurology* 2008; **70:** 191–199.
81. Jack CR Jr, Wiste HJ, Vemuri P, *et al*. Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease. *Brain* 2010; **133:** 3336–3348.
82. Galluzzi S, Geroldi C, Ghidoni R, *et al*. The new Alzheimer's criteria in a naturalistic series of patients with mild cognitive impairment. *J Neurol* 2010; **257:** 2004–2014.
83. Jack CR Jr, Petersen RC, Grundman M, *et al*. Longitudinal MRI findings from the vitamin E and donepezil treatment study for MCI. *Neurobiol Aging* 2008; **29:** 1285–1295.
84. Yuan Y, Gu ZX, Wei WS. Fluorodeoxyglucose-positron-emission tomography, single-photon emission tomography, and structural MR imaging for prediction of rapid conversion to Alzheimer disease in patients with mild cognitive impairment: a meta-analysis. *AJNR Am J Neuroradiol* 2009; **30:** 404–410.
85. Whitwell JL, Shiung MM, Przybelski SA, *et al*. MRI patterns of atrophy associated with progression to AD in amnestic mild cognitive impairment. *Neurology* 2008; **70:** 512–520.
86. Misra C, Fan Y, Davatzikos C. Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: results from ADNI. *Neuroimage* 2009; **44:** 1415–1422.
87. Barber R, Gholkar A, Scheltens P, Ballard C, McKeith IG, O'Brien JT. Medial temporal lobe atrophy on MRI in dementia with Lewy bodies. *Neurology* 1999; **52:** 1153–1158.
88. Bastos-Leite AJ, van der Flier WM, van Straaten EC, Staekenborg SS, Scheltens P, Barkhof F. The contribution of medial temporal lobe atrophy and vascular pathology to cognitive impairment in vascular dementia. *Stroke* 2007; **38:** 3182–3185.
89. Laakso MP, Partanen K, Riekkinen P, *et al*. Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: an MRI study. *Neurology* 1996; **46:** 678–681.
90. Chan D, Fox NC, Scahill RI, *et al*. Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Ann Neurol* 2001; **49:** 433–442.
91. van de Pol LA, Hensel A, Barkhof F, Gertz HJ, Scheltens P, van der Flier WM. Hippocampal atrophy in Alzheimer disease: age matters. *Neurology* 2006; **66:** 236–238.
92. van de Pol LA, Hensel A, van der Flier WM, *et al*. Hippocampal atrophy on MRI in frontotemporal lobar degeneration and Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2006; **77:** 439–442.
93. Frisoni GB, Pievani M, Testa C, *et al*. The topography of grey matter involvement in early and late onset Alzheimer's disease. *Brain* 2007; **130:** 720–730.
94. Ishii K, Kawachi T, Sasaki H, *et al*. Voxel-based morphometric comparison between early- and late-onset mild Alzheimer's disease and assessment of diagnostic performance of z score images. *AJNR Am J Neuroradiol* 2005; **26:** 333–340.
95. Canu E, Frisoni GB, Agosta F, Pievani M, Bonetti M, Filippi M. Early and late onset Alzheimer's disease patients have distinct patterns of white matter damage. *Neurobiol Aging* 2012; **33:** 1023–1033.
96. Koedam EL, Lehmann M, van der Flier WM, *et al*. Visual assessment of posterior atrophy development of a MRI rating scale. *Eur Radiol* 2011; **21:** 2618–2625.
97. Lehmann M, Koedam EL, Barnes J, *et al*. Posterior cerebral atrophy in the absence of medial temporal lobe atrophy in pathologically-confirmed Alzheimer's disease. *Neurobiol Aging* 2012; **33:** 627.e1–627.e12.
98. Alladi S, Xuereb J, Bak T, *et al*. Focal cortical presentations of Alzheimer's disease. *Brain* 2007; **130:** 2636–2645.
99. Migliaccio R, Agosta F, Rascovsky K, *et al*. Clinical syndromes associated with posterior atrophy: early age at onset AD spectrum. *Neurology* 2009; **73:** 1571–1578.

100. Rabinovici GD, Jagust WJ, Furst AJ, *et al.* Abeta amyloid and glucose metabolism in three variants of primary progressive aphasia. *Ann Neurol* 2008; **64:** 388–401.
101. Whitwell JL, Jack CR Jr, Przybelski SA, *et al.* Temporoparietal atrophy: a marker of AD pathology independent of clinical diagnosis. *Neurobiol Aging* 2011; **32:** 1531–1541.
102. Lehmann M, Rohrer JD, Clarkson MJ, *et al.* Reduced cortical thickness in the posterior cingulate gyrus is characteristic of both typical and atypical Alzheimer's disease. *J Alzheimers Dis* 2010; **20:** 587–598.
103. Whitwell JL, Jack CR Jr, Kantarci K, *et al.* Imaging correlates of posterior cortical atrophy. *Neurobiol Aging* 2007; **28:** 1051–1061.
104. Beyer MK, Larsen JP, Aarsland D. Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies. *Neurology* 2007; **69:** 747–754.
105. Burton EJ, Barber R, Mukaetova-Ladinska EB, *et al.* Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with Lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis. *Brain* 2009; **132:** 195–203.
106. Burton EJ, Karas G, Paling SM, *et al.* Patterns of cerebral atrophy in dementia with Lewy bodies using voxel-based morphometry. *Neuroimage* 2002; **17:** 618–630.
107. Whitwell JL, Weigand SD, Shiung MM, *et al.* Focal atrophy in dementia with Lewy bodies on MRI: a distinct pattern from Alzheimer's disease. *Brain* 2007; **130:** 708–719.
108. Ballmaier M, O'Brien JT, Burton EJ, *et al.* Comparing gray matter loss profiles between dementia with Lewy bodies and Alzheimer's disease using cortical pattern matching: diagnosis and gender effects. *Neuroimage* 2004; **23:** 325–335.
109. Middelkoop HA, van der Flier WM, Burton EJ, *et al.* Dementia with Lewy bodies and AD are not associated with occipital lobe atrophy on MRI. *Neurology* 2001; **57:** 2117–2120.
110. Barber R, Ballard C, McKeith IG, Gholkar A, O'Brien JT. MRI volumetric study of dementia with Lewy bodies: a comparison with AD and vascular dementia. *Neurology* 2000; **54:** 1304–1309.
111. Camicioli R, Moore MM, Kinney A, Corbridge E, Glassberg K, Kaye JA. Parkinson's disease is associated with hippocampal atrophy. *Mov Disord* 2003; **18:** 784–790.
112. Hashimoto M, Kitagaki H, Imamura T, *et al.* Medial temporal and whole-brain atrophy in dementia with Lewy bodies: a volumetric MRI study. *Neurology* 1998; **51:** 357–362.
113. Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT. Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. *Brain* 2004; **127:** 791–800.
114. Kantarci K, Lowe VJ, Boeve BF, *et al.* Multimodality imaging characteristics of dementia with Lewy bodies. *Neurobiol Aging* 2012; **33:** 2091–2105.
115. Tam CW, Burton EJ, McKeith IG, Burn DJ, O'Brien JT. Temporal lobe atrophy on MRI in Parkinson disease with dementia: a comparison with Alzheimer disease and dementia with Lewy bodies. *Neurology* 2005; **64:** 861–865.
116. McKeith IG, Dickson DW, Lowe J, *et al.* Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005; **65:** 1863–1872.
117. Cousins DA, Burton EJ, Burn D, Gholkar A, McKeith IG, O'Brien JT. Atrophy of the putamen in dementia with Lewy bodies but not Alzheimer's disease: an MRI study. *Neurology* 2003; **61:** 1191–1195.
118. Almeida OP, Burton EJ, McKeith I, Gholkar A, Burn D, O'Brien JT. MRI study of caudate nucleus volume in Parkinson's disease with and without dementia with Lewy bodies and Alzheimer's disease. *Dement Geriatr Cogn Disord* 2003; **16:** 57–63.
119. Barber R, McKeith I, Ballard C, O'Brien J. Volumetric MRI study of the caudate nucleus in patients with dementia with Lewy bodies, Alzheimer's disease, and vascular dementia. *J Neurol Neurosurg Psychiatry* 2002; **72:** 406–407.
120. Rascovsky K, Hodges JR, Knopman D, *et al.* Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011; **134:** 2456–2477.
121. Rosen HJ, Gorno-Tempini ML, Goldman WP, *et al.* Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology* 2002; **58:** 198–208.
122. Boccardi M, Sabattoli F, Laakso MP, *et al.* Frontotemporal dementia as a neural system disease. *Neurobiol Aging* 2005; **26:** 37–44.
123. Perry RJ, Graham A, Williams G, *et al.* Patterns of frontal lobe atrophy in frontotemporal dementia: a volumetric MRI study. *Dement Geriatr Cogn Disord* 2006; **22:** 278–287.
124. Du AT, Schuff N, Kramer JH, *et al.* Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. *Brain* 2007; **130:** 1159–1166.
125. Seeley WW, Crawford R, Rascovsky K, *et al.* Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. *Arch Neurol* 2008; **65:** 249–255.
126. Richards BA, Chertkow H, Singh V, *et al.* Patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. *Neurobiol Aging* 2009; **30:** 1626–1636.
127. Whitwell JL, Przybelski SA, Weigand SD, *et al.* Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study. *Brain* 2009; **132:** 2932–2946.
128. Rabinovici GD, Seeley WW, Kim EJ, *et al.* Distinct MRI atrophy patterns in autopsy-proven Alzheimer's disease and frontotemporal lobar degeneration. *Am J Alzheimers Dis Other Demen* 2007; **22:** 474–488.
129. Knopman DS, Boeve BF, Parisi JE, *et al.* Antemortem diagnosis of frontotemporal lobar degeneration. *Ann Neurol* 2005; **57:** 480–488.
130. Mendez MF, Shapira JS, McMurtray A, Licht E, Miller BL. Accuracy of the clinical evaluation for frontotemporal dementia. *Arch Neurol* 2007; **64:** 830–835.
131. Pijnenburg YA, Mulder JL, van Swieten JC, *et al.* Diagnostic accuracy of consensus diagnostic criteria for frontotemporal dementia in a memory clinic population. *Dement Geriatr Cogn Disord* 2008; **25:** 157–164.

132. Mahoney CJ, Beck J, Rohrer JD, *et al*. Frontotemporal dementia with the C9ORF72 hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features. *Brain* 2012; **135:** 736–750.
133. Whitwell JL, Weigand SD, Boeve BF, *et al*. Neuroimaging signatures of frontotemporal dementia genetics: C9ORF72, tau, progranulin and sporadics. *Brain* 2012; **135:** 794–806.
134. Shimizu H, Hokoishi K, Fukuhara R, Komori K, Ikeda M. Two cases of frontotemporal dementia with predominant temporal lobe atrophy. *Psychogeriatrics* 2009; **9:** 204–207.
135. Garibotto V, Borroni B, Agosti C, *et al*. Subcortical and deep cortical atrophy in frontotemporal lobar degeneration. *Neurobiol Aging* 2011; **32:** 875–884.
136. Borroni B, Brambati SM, Agosti C, *et al*. Evidence of white matter changes on diffusion tensor imaging in frontotemporal dementia. *Arch Neurol* 2007; **64:** 246–251.
137. Piguet O, Petersen A, Yin Ka Lam B, *et al*. Eating and hypothalamus changes in behavioral-variant frontotemporal dementia. *Ann Neurol* 2011; **69:** 312–319.
138. Cardenas VA, Boxer AL, Chao LL, *et al*. Deformation-based morphometry reveals brain atrophy in frontotemporal dementia. *Arch Neurol* 2007; **64:** 873–877.
139. Chao LL, Schuff N, Clevenger EM, *et al*. Patterns of white matter atrophy in frontotemporal lobar degeneration. *Arch Neurol* 2007; **64:** 1619–1624.
140. Varma AR, Adams W, Lloyd JJ, *et al*. Diagnostic patterns of regional atrophy on MRI and regional cerebral blood flow change on SPECT in young onset patients with Alzheimer's disease, frontotemporal dementia and vascular dementia. *Acta Neurol Scand* 2002; **105:** 261–269.
141. Likeman M, Anderson VM, Stevens JM, *et al*. Visual assessment of atrophy on magnetic resonance imaging in the diagnosis of pathologically confirmed young-onset dementias. *Arch Neurol* 2005; **62:** 1410–1415.
142. Gorno-Tempini ML, Hillis AE, Weintraub S, *et al*. Classification of primary progressive aphasia and its variants. *Neurology* 2011; **76:** 1006–1014.
143. Mummery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RS, Hodges JR. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. *Ann Neurol* 2000; **47:** 36–45.
144. Galton CJ, Patterson K, Graham K, *et al*. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology* 2001; **57:** 216–225.
145. Gorno-Tempini ML, Dronkers NF, Rankin KP, *et al*. Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol* 2004; **55:** 335–346.
146. Brambati SM, Rankin KP, Narvid J, *et al*. Atrophy progression in semantic dementia with asymmetric temporal involvement: a tensor-based morphometry study. *Neurobiol Aging* 2009; **30:** 103–111.
147. Gorno-Tempini ML, Brambati SM, Ginex V, *et al*. The logopenic/phonological variant of primary progressive aphasia. *Neurology* 2008; **71:** 1227–1234.
148. Rohrer JD, Ridgway GR, Crutch SJ, *et al*. Progressive logopenic/phonological aphasia: erosion of the language network. *Neuroimage* 2010; **49:** 984–993.
149. Kim EJ, Rabinovici GD, Seeley WW, *et al*. Patterns of MRI atrophy in tau positive and ubiquitin positive frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry* 2007; **78:** 1375–1378.
150. Whitwell JL, Josephs KA, Rossor MN, *et al*. Magnetic resonance imaging signatures of tissue pathology in frontotemporal dementia. *Arch Neurol* 2005; **62:** 1402–1408.
151. Grossman M, Libon DJ, Forman MS, *et al*. Distinct antemortem profiles in patients with pathologically defined frontotemporal dementia. *Arch Neurol* 2007; **64:** 1601–1609.
152. Josephs KA, Whitwell JL, Duffy JR, *et al*. Progressive aphasia secondary to Alzheimer disease vs FTLD pathology. *Neurology* 2008; **70:** 25–34.
153. Rohrer JD, Warren JD, Modat M, *et al*. Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. *Neurology* 2009; **72:** 1562–1569.
154. Pereira JM, Williams GB, Acosta-Cabronero J, *et al*. Atrophy patterns in histologic vs clinical groupings of frontotemporal lobar degeneration. *Neurology* 2009; **72:** 1653–1660.
155. Hu WT, McMillan C, Libon D, *et al*. Multimodal predictors for Alzheimer disease in nonfluent primary progressive aphasia. *Neurology* 2010; **75:** 595–602.
156. Xiong L, Xuereb JH, Spillantini MG, Patterson K, Hodges JR, Nestor PJ. Clinical comparison of progressive aphasia associated with Alzheimer versus FTD-spectrum pathology. *J Neurol Neurosurg Psychiatry* 2011; **82:** 254–260.
157. Litvan I, Agid Y, Calne D, *et al*. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology* 1996; **47:** 1–9.
158. Quattrone A, Nicoletti G, Messina D, *et al*. MR imaging index for differentiation of progressive supranuclear palsy from Parkinson disease and the Parkinson variant of multiple system atrophy. *Radiology* 2008; **246:** 214–221.
159. Longoni G, Agosta F, Kostic VS, *et al*. MRI measurements of brainstem structures in patients with Richardson's syndrome, progressive supranuclear palsy-parkinsonism, and Parkinson's disease. *Mov Disord* 2011; **26:** 247–255.
160. Weir DW, Sturrock A, Leavitt BR. Development of biomarkers for Huntington's disease. *Lancet Neurol* 2011; **10:** 573–590.
161. Young GS, Geschwind MD, Fischbein NJ, *et al*. Diffusion-weighted and fluid-attenuated inversion recovery imaging in Creutzfeldt–Jakob disease: high sensitivity and specificity for diagnosis. *AJNR Am J Neuroradiol* 2005; **26:** 1551–1562.
162. Vitali P, Maccagnano E, Caverzasi E, *et al*. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. *Neurology* 2011; **76:** 1711–1719.
163. Collie DA, Summers DM, Sellar RJ, *et al*. Diagnosing variant Creutzfeldt-Jakob disease with the pulvinar sign: MR imaging findings in 86 neuropathologically confirmed cases. *AJNR Am J Neuroradiol* 2003; **24:** 1560–1569.
164. Bohnen NI, Djang DS, Herholz K, Anzai Y, Minoshima S. Effectiveness and safety of 18F-FDG PET in the

evaluation of dementia: a review of the recent literature. *J Nucl Med* 2011; **53:** 59–71.
165. Minoshima S, Foster NL, Sima AA, Frey KA, Albin RL, Kuhl DE. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. *Ann Neurol* 2001; **50:** 358–365.
166. Kemp PM, Holmes C, Hoffmann SM, *et al.* Alzheimer's disease: differences in technetium-99m HMPAO SPECT scan findings between early onset and late onset dementia. *J Neurol Neurosurg Psychiatry* 2003; **74:** 715–719.
167. Kim EJ, Cho SS, Jeong Y, *et al.* Glucose metabolism in early onset versus late onset Alzheimer's disease: an SPM analysis of 120 patients. *Brain* 2005; **128:** 1790–1801.
168. Rabinovici GD, Furst AJ, Alkalay A, *et al.* Increased metabolic vulnerability in early-onset Alzheimer's disease is not related to amyloid burden. *Brain* 2010; **133:** 512–528.
169. Mosconi L, Tsui WH, Pupi A, *et al.* (18)F-FDG PET database of longitudinally confirmed healthy elderly individuals improves detection of mild cognitive impairment and Alzheimer's disease. *J Nucl Med* 2007; **48:** 1129–1134.
170. Ng S, Villemagne VL, Berlangieri S, *et al.* Visual assessment versus quantitative assessment of 11C-PIB PET and 18F-FDG PET for detection of Alzheimer's disease. *J Nucl Med* 2007; **48:** 547–552.
171. Chen WP, Samuraki M, Yanase D, *et al.* Effect of sample size for normal database on diagnostic performance of brain FDG PET for the detection of Alzheimer's disease using automated image analysis. *Nucl Med Commun* 2008; **29:** 270–276.
172. Mosconi L, Tsui WH, Herholz K, *et al.* Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. *J Nucl Med* 2008; **49:** 390–398.
173. McMurtray AM, Licht E, Yeo T, Krisztal E, Saul RE, Mendez MF. Positron emission tomography facilitates diagnosis of early-onset Alzheimer's disease. *Eur Neurol* 2008; **59:** 31–37.
174. Panegyres PK, Rogers JM, McCarthy M, Campbell A, Wu JS. Fluorodeoxyglucose-positron emission tomography in the differential diagnosis of early-onset dementia: a prospective, community-based study. *BMC Neurol* 2009; **9:** 41.
175. Silverman DH, Small GW, Chang CY, *et al.* Positron emission tomography in evaluation of dementia: regional brain metabolism and long-term outcome. *JAMA* 2001; **286:** 2120–2127.
176. Jagust W, Reed B, Mungas D, Ellis W, Decarli C. What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia? *Neurology* 2007; **69:** 871–877.
177. Foster NL, Heidebrink JL, Clark CM, *et al.* FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. *Brain* 2007; **130:** 2616–2635.
178. Nestor PJ, Fryer TD, Smielewski P, Hodges JR. Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. *Ann Neurol* 2003; **54:** 343–351.
179. Mosconi L, De Santi S, Li Y, *et al.* Visual rating of medial temporal lobe metabolism in mild cognitive impairment and Alzheimer's disease using FDG-PET. *Eur J Nucl Med Mol Imaging* 2006; **33:** 210–221.
180. Mosconi L, Tsui WH, De Santi S, *et al.* Reduced hippocampal metabolism in MCI and AD: automated FDG-PET image analysis. *Neurology* 2005; **64:** 1860–1867.
181. Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol* 1997; **42:** 85–94.
182. Drzezga A, Lautenschlager N, Siebner H, *et al.* Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. *Eur J Nucl Med Mol Imaging* 2003; **30:** 1104–1113.
183. Mosconi L, Perani D, Sorbi S, *et al.* MCI conversion to dementia and the APOE genotype: a prediction study with FDG-PET. *Neurology* 2004; **63:** 2332–2340.
184. Arnaiz E, Jelic V, Almkvist O, *et al.* Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment. *Neuro Report* 2001; **12:** 851–855.
185. Anchisi D, Borroni B, Franceschi M, *et al.* Heterogeneity of brain glucose metabolism in mild cognitive impairment and clinical progression to Alzheimer disease. *Arch Neurol* 2005; **62:** 1728–1733.
186. Chetelat G, Desgranges B, de la Sayette V, Viader F, Eustache F, Baron JC. Mild cognitive impairment: can FDG-PET predict who is to rapidly convert to Alzheimer's disease? *Neurology* 2003; **60:** 1374–1377.
187. Drzezga A, Grimmer T, Riemenschneider M, *et al.* Prediction of individual clinical outcome in MCI by means of genetic assessment and (18)F-FDG PET. *J Nucl Med* 2005; **46:** 1625–1632.
188. Huang C, Wahlund LO, Almkvist O, *et al.* Voxel- and VOI-based analysis of SPECT CBF in relation to clinical and psychological heterogeneity of mild cognitive impairment. *Neuroimage* 2003; **19:** 1137–1144.
189. Nestor PJ, Caine D, Fryer TD, Clarke J, Hodges JR. The topography of metabolic deficits in posterior cortical atrophy (the visual variant of Alzheimer's disease) with FDG-PET. *J Neurol Neurosurg Psychiatry* 2003; **74:** 1521–1529.
190. Schmidtke K, Hull M, Talazko J. Posterior cortical atrophy: variant of Alzheimer's disease? A case series with PET findings. *J Neurol* 2005; **252:** 27–35.
191. Kas A, de Souza LC, Samri D, *et al.* Neural correlates of cognitive impairment in posterior cortical atrophy. *Brain* 2011; **134:** 1464–1478.
192. Rosenbloom MH, Alkalay A, Agarwal N, *et al.* Distinct clinical and metabolic deficits in PCA and AD are not related to amyloid distribution. *Neurology* 2011; **76:** 1789–1796.
193. Laforce R Jr, Buteau JP, Paquet N, Verret L, Houde M, Bouchard RW. The value of PET in mild cognitive impairment, typical and atypical/unclear dementias: a retrospective memory clinic study. *Am J Alzheimers Dis Other Demen* 2010; **25:** 324–332.
194. Albin RL, Minoshima S, D'Amato CJ, Frey KA, Kuhl DA, Sima AA. Fluoro-deoxyglucose positron emission tomography in diffuse Lewy body disease. *Neurology* 1996; **47:** 462–466.
195. Higuchi M, Tashiro M, Arai H, *et al.* Glucose hypometabolism and neuropathological correlates in

brains of dementia with Lewy bodies. *Exp Neurol* 2000; **162:** 247–256.
196. Imamura T, Ishii K, Sasaki M, *et al*. Regional cerebral glucose metabolism in dementia with Lewy bodies and Alzheimer's disease: a comparative study using positron emission tomography. *Neurosci Lett* 1997; **235:** 49–52.
197. Ishii K, Imamura T, Sasaki M, *et al*. Regional cerebral glucose metabolism in dementia with Lewy bodies and Alzheimer's disease. *Neurology* 1998; **51:** 125–130.
198. Ishii K, Soma T, Kono AK, *et al*. Comparison of regional brain volume and glucose metabolism between patients with mild dementia with Lewy bodies and those with mild Alzheimer's disease. *J Nucl Med* 2007; **48:** 704–711.
199. Teune LK, Bartels AL, de Jong BM, *et al*. Typical cerebral metabolic patterns in neurodegenerative brain diseases. *Mov Disord* 2010; **25:** 2395–2404.
200. Ishii K, Sasaki M, Kitagaki H, *et al*. Reduction of cerebellar glucose metabolism in advanced Alzheimer's disease. *J Nucl Med* 1997; **38:** 925–928.
201. Lim SM, Katsifis A, Villemagne VL, *et al*. The 18F-FDG PET cingulate island sign and comparison to 123I-beta-CIT SPECT for diagnosis of dementia with Lewy bodies. *J Nucl Med* 2009; **50:** 1638–1645.
202. Cummings JL, Henchcliffe C, Schaier S, Simuni T, Waxman A, Kemp P. The role of dopaminergic imaging in patients with symptoms of dopaminergic system neurodegeneration. *Brain* 2011; **134:** 3146–3166.
203. McKeith I, O'Brien J, Walker Z, *et al*. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. *Lancet Neurol* 2007; **6:** 305–313.
204. O'Brien JT, McKeith IG, Walker Z, *et al*. Diagnostic accuracy of 123I-FP-CIT SPECT in possible dementia with Lewy bodies. *Br J Psychiatry* 2009; **194:** 34–39.
205. Walker Z, Jaros E, Walker RW, *et al*. Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. *J Neurol Neurosurg Psychiatry* 2007; **78:** 1176–1181.
206. Colloby SJ, Williams ED, Burn DJ, Lloyd JJ, McKeith IG, O'Brien JT. Progression of dopaminergic degeneration in dementia with Lewy bodies and Parkinson's disease with and without dementia assessed using 123I-FP-CIT SPECT. *Eur J Nucl Med Mol Imaging* 2005; **32:** 1176–1185.
207. Hilker R, Thomas AV, Klein JC, *et al*. Dementia in Parkinson disease: functional imaging of cholinergic and dopaminergic pathways. *Neurology* 2005; **65:** 1716–1722.
208. Klein JC, Eggers C, Kalbe E, *et al*. Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia *in vivo*. *Neurology* 2010; **74:** 885–892.
209. O'Brien JT, Colloby S, Fenwick J, *et al*. Dopamine transporter loss visualized with FP-CIT SPECT in the differential diagnosis of dementia with Lewy bodies. *Arch Neurol* 2004; **61:** 919–925.
210. Rossi C, Volterrani D, Nicoletti V, *et al*. 'Parkinson-dementia' diseases: a comparison by double tracer SPECT studies. *Parkinsonism Relat Disord* 2009; **15:** 762–766.
211. Brooks DJ, Piccini P. Imaging in Parkinson's disease: the role of monoamines in behavior. *Biol Psychiatry* 2006; **59:** 908–918.
212. Miller BL, Cummings JL, Villanueva-Meyer J, *et al*. Frontal lobe degeneration: clinical, neuropsychological, and SPECT characteristics. *Neurology* 1991; **41:** 1374–1382.
213. Ishii K, Sakamoto S, Sasaki M, *et al*. Cerebral glucose metabolism in patients with frontotemporal dementia. *J Nucl Med* 1998; **39:** 1875–1878.
214. Jeong Y, Cho SS, Park JM, *et al*. 18F-FDG PET findings in frontotemporal dementia: an SPM analysis of 29 patients. *J Nucl Med* 2005; **46:** 233–239.
215. Diehl-Schmid J, Grimmer T, Drzezga A, *et al*. Decline of cerebral glucose metabolism in frontotemporal dementia: a longitudinal 18F-FDG-PET-study. *Neurobiol Aging* 2007; **28:** 42–50.
216. Sjogren M, Gustafson L, Wikkelso C, Wallin A. Frontotemporal dementia can be distinguished from Alzheimer's disease and subcortical white matter dementia by an anterior-to-posterior rCBF-SPET ratio. *Dement Geriatr Cogn Disord* 2000; **11:** 275–285.
217. Ibach B, Poljansky S, Marienhagen J, Sommer M, Manner P, Hajak G. Contrasting metabolic impairment in frontotemporal degeneration and early onset Alzheimer's disease. *Neuroimage* 2004; **23:** 739–743.
218. Charpentier P, Lavenu I, Defebvre L, *et al*. Alzheimer's disease and frontotemporal dementia are differentiated by discriminant analysis applied to (99m)Tc HmPAO SPECT data. *J Neurol Neurosurg Psychiatry* 2000; **69:** 661–663.
219. Kanda T, Ishii K, Uemura T, *et al*. Comparison of grey matter and metabolic reductions in frontotemporal dementia using FDG-PET and voxel-based morphometric MR studies. *Eur J Nucl Med Mol Imaging* 2008; **35:** 2227–2234.
220. McNeill R, Sare GM, Manoharan M, *et al*. Accuracy of single-photon emission computed tomography in differentiating frontotemporal dementia from Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2007; **78:** 350–355.
221. Womack KB, Diaz-Arrastia R, Aizenstein HJ, *et al*. Temporoparietal hypometabolism in frontotemporal lobar degeneration and associated imaging diagnostic errors. *Arch Neurol* 2011; **68:** 329–337.
222. Nestor PJ, Fryer TD, Hodges JR. Declarative memory impairments in Alzheimer's disease and semantic dementia. *Neuroimage* 2006; **30:** 1010–1020.
223. Diehl J, Grimmer T, Drzezga A, Riemenschneider M, Forstl H, Kurz A. Cerebral metabolic patterns at early stages of frontotemporal dementia and semantic dementia. A PET study. *Neurobiol Aging* 2004; **25:** 1051–1056.
224. Drzezga A, Grimmer T, Henriksen G, *et al*. Imaging of amyloid plaques and cerebral glucose metabolism in semantic dementia and Alzheimer's disease. *Neuroimage* 2008; **39:** 619–633.
225. Nestor PJ, Graham NL, Fryer TD, Williams GB, Patterson K, Hodges JR. Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula. *Brain* 2003; **126:** 2406–2418.
226. Zahn R, Buechert M, Overmans J, *et al*. Mapping of temporal and parietal cortex in progressive nonfluent aphasia and Alzheimer's disease using chemical shift imaging, voxel-based morphometry and positron emission tomography. *Psychiatry Res* 2005; **140:** 115–131.
227. Panegyres PK, McCarthy M, Campbell A, Lenzo N, Fallon M, Thompson J. Correlative studies of struc-

tural and functional imaging in primary progressive aphasia. *Am J Alzheimers Dis Other Demen* 2008; **23:** 184–191.
228. Perneczky R, Diehl-Schmid J, Pohl C, Drzezga A, Kurz A. Non-fluent progressive aphasia: cerebral metabolic patterns and brain reserve. *Brain Res* 2007; **1133:** 178–185.
229. Nestor PJ, Balan K, Cheow HK, *et al*. Nuclear imaging can predict pathologic diagnosis in progressive non-fluent aphasia. *Neurology* 2007; **68:** 238–239.
230. Lee JH, Kim SH, Kim GH, *et al*. Identification of pure subcortical vascular dementia using 11C-Pittsburgh compound B. *Neurology* 2011; **77:** 18–25.
231. Mok V, Leung EY, Chu W, *et al*. Pittsburgh compound B binding in poststroke dementia. *J Neurol Sci* 2010; **290:** 135–137.
232. Johnson KA, Gregas M, Becker JA, *et al*. Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. *Ann Neurol* 2007; **62:** 229–234.
233. Herholz K, Ebmeier K. Clinical amyloid imaging in Alzheimer's disease. *Lancet Neurol* 2011; **10:** 667–670.
234. Barthel H, Gertz HJ, Dresel S, *et al*. Cerebral amyloid-beta PET with florbetaben (18F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. *Lancet Neurol* 2011; **10:** 424–435.
235. Clark CM, Schneider JA, Bedell BJ, *et al*. Use of florbetapir-PET for imaging beta-amyloid pathology. *JAMA* 2011; **305:** 275–283.
236. Nelissen N, Van Laere K, Thurfjell L, *et al*. Phase 1 study of the Pittsburgh compound B derivative 18F-flutemetamol in healthy volunteers and patients with probable Alzheimer disease. *J Nucl Med* 2009; **50:** 1251–1259.
237. Rowe CC, Ackerman U, Browne W, *et al*. Imaging of amyloid beta in Alzheimer's disease with 18F-BAY94-9172, a novel PET tracer: proof of mechanism. *Lancet Neurol* 2008; **7:** 129–135.
238. Vandenberghe R, Van Laere K, Ivanoiu A, *et al*. 18F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: a phase 2 trial. *Ann Neurol* 2010; **68:** 319–329.
239. Wong DF, Rosenberg PB, Zhou Y, *et al*. In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (florbetapir [corrected] F 18). *J Nucl Med* 2010; **51:** 913–920.
240. Tolboom N, van der Flier WM, Boverhoff J, *et al*. Molecular imaging in the diagnosis of Alzheimer's disease: visual assessment of [11C]PIB and [18F]FDDNP PET images. *J Neurol Neurosurg Psychiatry* 2010; **81:** 882–884.
241. Braskie MN, Klunder AD, Hayashi KM, *et al*. Plaque and tangle imaging and cognition in normal aging and Alzheimer's disease. *Neurobiol Aging* 2008; **31:** 1669–1678.
242. Rowe CC, Ng S, Ackermann U, *et al*. Imaging beta-amyloid burden in aging and dementia. *Neurology* 2007; **68:** 1718–1725.
243. Kemppainen NM, Aalto S, Wilson IA, *et al*. PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. *Neurology* 2007; **68:** 1603–1606.
244. Pike KE, Savage G, Villemagne VL, *et al*. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain* 2007; **130:** 2837–2844.
245. Fleisher AS, Chen K, Liu X, *et al*. Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. *Arch Neurol* 2011; **68:** 1404–1411.
246. Villemagne VL, Ong K, Mulligan RS, *et al*. Amyloid imaging with (18)F-florbetaben in Alzheimer disease and other dementias. *J Nucl Med* 2011; **52:** 1210–1217.
247. Forsberg A, Engler H, Almkvist O, *et al*. PET imaging of amyloid deposition in patients with mild cognitive impairment. *Neurobiol Aging* 2008; **29:** 1456–1465.
248. Okello A, Koivunen J, Edison P, *et al*. Conversion of amyloid positive and negative MCI to AD over 3 years: an 11C-PIB PET study. *Neurology* 2009; **73:** 754–760.
249. Wolk DA, Price JC, Saxton JA, *et al*. Amyloid imaging in mild cognitive impairment subtypes. *Ann Neurol* 2009; **65:** 557–568.
250. de Souza LC, Corlier F, Habert MO, *et al*. Similar amyloid-beta burden in posterior cortical atrophy and Alzheimer's disease. *Brain* 2011; **134:** 2036–2043.
251. Edison P, Rowe CC, Rinne JO, *et al*. Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. *J Neurol Neurosurg Psychiatry* 2008; **79:** 1331–1338.
252. Foster ER, Campbell MC, Burack MA, *et al*. Amyloid imaging of Lewy body-associated disorders. *Mov Disord* 2010; **25:** 2516–2523.
253. Gomperts SN, Rentz DM, Moran E, *et al*. Imaging amyloid deposition in Lewy body diseases. *Neurology* 2008; **71:** 903–910.
254. Maetzler W, Liepelt I, Reimold M, *et al*. Cortical PIB binding in Lewy body disease is associated with Alzheimer-like characteristics. *Neurobiol Dis* 2009; **34:** 107–112.
255. Villemagne VL, Okamura N, Pejoska S, *et al*. Differential diagnosis in Alzheimer's disease and dementia with Lewy bodies via VMAT2 and amyloid imaging. *Neurodegener Dis* 2012; **10:** 161–165.
256. Rabinovici GD, Furst AJ, O'Neil JP, *et al*. 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. *Neurology* 2007; **68:** 1205–1212.
257. Engler H, Santillo AF, Wang SX, *et al*. In vivo amyloid imaging with PET in frontotemporal dementia. *Eur J Nucl Med Mol Imaging* 2008; **35:** 100–106.
258. Leyton CE, Villemagne VL, Savage S, *et al*. Subtypes of progressive aphasia: application of the International Consensus Criteria and validation using beta-amyloid imaging. *Brain* 2011; **134:** 3030–3043.
259. Rabinovici GD, Rosen HJ, Alkalay A, *et al*. Amyloid vs FDG-PET in the differential diagnosis of AD and FTLD. *Neurology* 2011; **77:** 2034–2042.
260. Frisoni GB, Fox NC, Jack CR Jr, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. *Nat Rev Neurol* 2010; **6:** 67–77.
261. Barnes J, Bartlett JW, van de Pol LA, *et al*. A meta-analysis of hippocampal atrophy rates in Alzheimer's disease. *Neurobiol Aging* 2009; **30:** 1711–1723.
262. Geroldi C, Rossi R, Calvagna C, *et al*. Medial temporal atrophy but not memory deficit predicts progression to dementia in patients with mild cognitive impairment. *J Neurol Neurosurg Psychiatry* 2006; **77:** 1219–1222.
263. Jack CR Jr, Shiung MM, Weigand SD, *et al*. Brain atrophy rates predict subsequent clinical conversion in

normal elderly and amnestic MCI. *Neurology* 2005; **65:** 1227–1231.
264. Whitwell JL, Jack CR Jr, Parisi JE, *et al*. Rates of cerebral atrophy differ in different degenerative pathologies. *Brain* 2007; **130:** 1148–1158.
265. Chan D, Fox NC, Jenkins R, Scahill RI, Crum WR, Rossor MN. Rates of global and regional cerebral atrophy in AD and frontotemporal dementia. *Neurology* 2001; **57:** 1756–1763.
266. Knopman DS, Jack CR Jr, Kramer JH, *et al*. Brain and ventricular volumetric changes in frontotemporal lobar degeneration over 1 year. *Neurology* 2009; **72:** 1843–1849.
267. Gordon E, Rohrer JD, Kim LG, *et al*. Measuring disease progression in frontotemporal lobar degeneration: a clinical and MRI study. *Neurology* 2010; **74:** 666–673.
268. Krueger CE, Dean DL, Rosen HJ, *et al*. Longitudinal rates of lobar atrophy in frontotemporal dementia, semantic dementia, and Alzheimer's disease. *Alzheimer Dis Assoc Disord* 2010; **24:** 43–48.
269. Whitwell JL, Jack CR Jr, Pankratz VS, *et al*. Rates of brain atrophy over time in autopsy-proven frontotemporal dementia and Alzheimer disease. *Neuroimage* 2008; **39:** 1034–1040.
270. Kantarci K. 1H magnetic resonance spectroscopy in dementia. *Br J Radiol* 2007; **80**(Spec No. 2)**:** S146–S152.
271. Kantarci K, Reynolds G, Petersen RC, *et al*. Proton MR spectroscopy in mild cognitive impairment and Alzheimer disease: comparison of 1.5 and 3 T. *AJNR Am J Neuroradiol* 2003; **24:** 843–849.
272. Falini A, Bozzali M, Magnani G, *et al*. A whole brain MR spectroscopy study from patients with Alzheimer's disease and mild cognitive impairment. *Neuroimage* 2005; **26:** 1159–1163.
273. Wang Z, Zhao C, Yu L, Zhou W, Li K. Regional metabolic changes in the hippocampus and posterior cingulate area detected with 3-Tesla magnetic resonance spectroscopy in patients with mild cognitive impairment and Alzheimer disease. *Acta Radiol* 2009; **50:** 312–319.
274. Chantal S, Braun CM, Bouchard RW, Labelle M, Boulanger Y. Similar 1H magnetic resonance spectroscopic metabolic pattern in the medial temporal lobes of patients with mild cognitive impairment and Alzheimer disease. *Brain Res* 2004; **1003:** 26–35.
275. Kantarci K, Jack CR Jr, Xu YC, *et al*. Regional metabolic patterns in mild cognitive impairment and Alzheimer's disease: a 1H MRS study. *Neurology* 2000; **55:** 210–217.
276. Kantarci K, Xu Y, Shiung MM, *et al*. Comparative diagnostic utility of different MR modalities in mild cognitive impairment and Alzheimer's disease. *Dement Geriatr Cogn Disord* 2002; **14:** 198–207.
277. Zhu X, Schuff N, Kornak J, *et al*. Effects of Alzheimer disease on fronto-parietal brain N-acetyl aspartate and myo-inositol using magnetic resonance spectroscopic imaging. *Alzheimer Dis Assoc Disord* 2006; **20:** 77–85.
278. Martinez-Bisbal MC, Arana E, Marti-Bonmati L, Molla E, Celda B. Cognitive impairment: classification by 1H magnetic resonance spectroscopy. *Eur J Neurol* 2004; **11:** 187–193.
279. Fernandez A, Garcia-Segura JM, Ortiz T, *et al*. Proton magnetic resonance spectroscopy and magnetoencephalographic estimation of delta dipole density: a combination of techniques that may contribute to the diagnosis of Alzheimer's disease. *Dement Geriatr Cogn Disord* 2005; **20:** 169–177.
280. Kantarci K, Petersen RC, Boeve BF, *et al*. 1H MR spectroscopy in common dementias. *Neurology* 2004; **63:** 1393–1398.
281. Sexton CE, Kalu UG, Filippini N, Mackay CE, Ebmeier KP. A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* 2011; **32:** 2322.e5–2322.e18.
282. Agosta F, Pievani M, Sala S, *et al*. White matter damage in Alzheimer disease and its relationship to gray matter atrophy. *Radiology* 2011; **258:** 853–863.
283. Fellgiebel A, Dellani PR, Greverus D, Scheurich A, Stoeter P, Muller MJ. Predicting conversion to dementia in mild cognitive impairment by volumetric and diffusivity measurements of the hippocampus. *Psychiatry Res* 2006; **146:** 283–287.
284. Kantarci K, Petersen RC, Boeve BF, *et al*. DWI predicts future progression to Alzheimer disease in amnestic mild cognitive impairment. *Neurology* 2005; **64:** 902–904.
285. Muller MJ, Greverus D, Weibrich C, *et al*. Diagnostic utility of hippocampal size and mean diffusivity in amnestic MCI. *Neurobiol Aging* 2007; **28:** 398–403.
286. Scola E, Bozzali M, Agosta F, *et al*. A diffusion tensor MRI study of patients with MCI and AD with a 2-year clinical follow-up. *J Neurol Neurosurg Psychiatry* 2010; **81:** 798–805.
287. Kantarci K, Avula R, Senjem ML, *et al*. Dementia with Lewy bodies and Alzheimer disease: neurodegenerative patterns characterized by DTI. *Neurology* 2010; **74:** 1814–1821.
288. Firbank MJ, Blamire AM, Krishnan MS, *et al*. Diffusion tensor imaging in dementia with Lewy bodies and Alzheimer's disease. *Psychiatry Res* 2007; **155:** 135–145.
289. Zhang Y, Schuff N, Du AT, *et al*. White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI. *Brain* 2009; **132:** 2579–2592.
290. Agosta F, Scola E, Canu E, *et al*. White matter damage in frontotemporal lobar degeneration spectrum. *Cereb Cortex* 2011; doi:10.1093/cercor/bhr288.
291. Detre JA, Alsop DC. Perfusion magnetic resonance imaging with continuous arterial spin labeling: methods and clinical applications in the central nervous system. *Eur J Radiol* 1999; **30:** 115–124.
292. Alsop DC, Dai W, Grossman M, Detre JA. Arterial spin labeling blood flow MRI: its role in the early characterization of Alzheimer's disease. *J Alzheimers Dis* 2010; **20:** 871–880.
293. Dai W, Lopez OL, Carmichael OT, Becker JT, Kuller LH, Gach HM. Mild cognitive impairment and alzheimer disease: patterns of altered cerebral blood flow at MR imaging. *Radiology* 2009; **250:** 856–866.
294. Hu WT, Wang Z, Lee VM, Trojanowski JQ, Detre JA, Grossman M. Distinct cerebral perfusion patterns in FTLD and AD. *Neurology* 2010; **75:** 881–888.
295. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 2007; **8:** 700–711.
296. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A* 2004; **101:** 4637–4642.

297. Zhang HY, Wang SJ, Liu B, *et al*. Resting brain connectivity: changes during the progress of Alzheimer disease. *Radiology* 2010; **256:** 598–606.
298. Agosta F, Pievani M, Geroldi C, Copetti M, Frisoni G, Filippi M. Resting state fMRI in Alzheimer's disease: beyond the default mode network. *Neurobiol Aging* 2012; **33:** 1564–1578.
299. Binnewijzend MA, Schoonheim MM, Sanz-Arigita E, *et al*. Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging* 2012; **33:** 2018–2028.
300. Qi Z, Wu X, Wang Z, *et al*. Impairment and compensation coexist in amnestic MCI default mode network. *Neuroimage* 2010; **50:** 48–55.
301. Sorg C, Riedl V, Muhlau M, *et al*. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. *Proc Natl Acad Sci U S A* 2007; **104:** 18760–18765.
302. Li SJ, Li Z, Wu G, Zhang MJ, Franczak M, Antuono PG. Alzheimer disease: evaluation of a functional MR imaging index as a marker. *Radiology* 2002; **225:** 253–259.
303. Supekar K, Menon V, Rubin D, Musen M, Greicius MD. Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Comput Biol* 2008; **4:** e1000100.
304. Petrella JR, Prince SE, Wang L, Hellegers C, Doraiswamy PM. Prognostic value of posteromedial cortex deactivation in mild cognitive impairment. *PLoS ONE* 2007; **2:** e1104.
305. Petrella JR, Sheldon FC, Prince SE, Calhoun VD, Doraiswamy PM. Default mode network connectivity in stable vs progressive mild cognitive impairment. *Neurology* 2011; **76:** 511–517.
306. Zhou J, Greicius MD, Gennatas ED, *et al*. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain* 2010; **133:** 1352–1367.
307. Whitwell JL, Josephs KA, Avula R, *et al*. Altered functional connectivity in asymptomatic MAPT subjects: a comparison to bvFTD. *Neurology* 2011; **77:** 866–874.