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Chapter 50

# Imaging of neurodegenerative cognitive and behavioral disorders: practical considerations for dementia clinical practice

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**Abstract**

This chapter reviews clinical applications and imaging findings useful in medical practice relating to neurodegenerative cognitive/dementing disorders. The preponderance of evidence and consensus guidelines support an essential role of multitiered neuroimaging in the evaluation and management of neurodegenerative cognitive/dementia syndrome that range in severity from mild impairments to frank dementia. Additionally, imaging features are incorporated in updated clinical and research diagnostic criteria for most dementias, including Alzheimer's disease (AD), Dementia with Lewy bodies (DLB), Frontotemporal Lobar Degenerations/Frontotemporal Dementia (FTD), and Vascular Cognitive Impairment (VCI). Best clinical practices dictate that structural imaging, preferably with magnetic resonance imaging (MRI) when possible and computed tomography when not, be obtained as a first-tier approach during the course of a thorough clinical evaluation to improve diagnostic confidence and assess for nonneurodegenerative treatable conditions that may cause or substantially contribute to cognitive/behavioral symptoms or which may dictate a substantial change in management. These conditions include less common structural (e.g., mass lesions such as tumors and hematomas; normal-pressure hydrocephalus), inflammatory, autoimmune and infectious conditions, and more common comorbid contributing conditions (e.g., vascular cerebral injury causing leukoaraiosis, infarcts, or microhemorrhages) that can produce a mixed dementia syndrome. When, after appropriate clinical, cognitive/neuropsychologic, and structural neuroimaging assessment, a dementia specialist remains in doubt regarding etiology and appropriate management, second-tier imaging with molecular methods, preferably with fluorodexoyglucose positron emission tomography (PET) (or single-photon emission computed tomography if PET is unavailable) can provide more diagnostic specificity (e.g., help differentiate between atypical AD and FTD as the etiology for a frontal/dysexecutive syndrome). The potential clinical utility of other promising methods, whether already approved for use (e.g., amyloid PET) or as yet only used in research (e.g., tau PET, functional MRI, diffusor tensor imaging), remains to be proven for widespread use in community practice. However, these constitute unreimbursed third-tier options that merit further study for clinical and cost-effective utility. In the future, combination use of imaging methods will likely improve diagnostic accuracy.

## INTRODUCTION

Consensus guidelines strongly support the use of structural neuroimaging in clinical practice for the assessment of cognitive/dementia syndromes (CDS) (Knopman et al., 2001; Hort et al., 2010; Scheltens and O'Brien, 2011; Soucy et al., 2014) and imaging criteria have been incorporated into the updated clinical and research

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diagnostic criteria of most dementias. As part of a thorough clinical evaluation, structural imaging, when possible with magnetic resonance imaging (MRI) and if not with computed tomography (CT), can inform regarding potentially treatable or manageable nondegenerative conditions that can cause or substantially contribute to cognitive/behavioral symptoms, and serve to improve diagnostic certainty regarding primary etiology. Molecular imaging, preferably with fluorodeoxyglucose (FDG) positron emission tomography (PET) (with single-photon emission computed tomography (SPECT) as a second option), can be used in cases when a dementia specialist remains in doubt regarding etiology and management. Appropriate use criteria for utility of other PET ligands such as dopamine tracers (to discern a parkinsonian etiology such as Dementia with Lewy bodies (DLB)) and amyloid PET agents (to discern an Alzheimer's disease (AD) etiology) for providing greater diagnostic accuracy have also been suggested, but the use of these ligands by dementia specialists is highly variable and greatly depends on availability, cost, payer, and geocultural considerations.

This chapter will: (1) motivate the "why, who, when, and how" to image patients with CDS; (2) review updated consensus guidelines for use of imaging in the assessment of cognitive impairment/dementia; and (3) briefly outline neuroimaging findings in the most common clinical dementia syndromes, including AD, Vascular Cognitive Impairment (VCI), DLB, Parkinson's disease dementia (PDD), and Frontotemporal Lobar Degeneration (FTLD)/dementia syndromes. Chapter 26 in the previous volume provides an excellent review of imaging methods, imaging findings in various neurodegenerative dementing conditions, and comparison of findings between conditions using several methods.

## THE WHY, WHO, WHEN, AND HOW OF IMAGING PATIENTS WITH COGNITIVE AND BEHAVIORAL DISORDERS

### Why to image patients with CDS

When considering the decision to image a patient presenting with CDS, the clinician needs to consider multiple factors and to tailor personalized advice for the patient and family/caregiver dyad (patient–family dyad), guided by knowledge of patient–family dyad preferences, biopsychosocial circumstances, consensus guidelines, and the principles of medical ethics (e.g., *primum non nocere* (above all do no harm), beneficence, nonmaleficence, autonomy, justice).

Structural imaging is often necessary to eliminate potentially "reversible" or treatable nonneurodegenerative conditions (e.g., mass-occupying lesions; normal-pressure hydrocephalus; and inflammatory, infectious, and immune-mediated conditions) that uncommonly mimic neurodegenerative dementias; and to identify common conditions that can substantially contribute to symptoms (e.g., conditions caused by vascular cerebral injury) – in both situations substantial changes or additions to the management plan may be necessary. Additionally, when present, specific findings on structural imaging (e.g., regionally patterns of atrophy in the "AD signature" regions (see Chapter 26 in the previous volume, and below) and hippocampus atrophy in AD; knife edge/blade atrophy of frontal and/or anterior temporal gyri in FTLD; multiple infarcts or severe leukoaraiosis in VCI with corresponding central atrophy; cortical-subcortical microhemorrhages in Cerebral Amyloid Angiopathy (CAA)) can increase diagnostic accuracy.

It is important to establish etiology, which in cases of diagnostic uncertainty may necessitate molecular imaging, and/or utilization of other biomarkers such as cerebrospinal fluid (CSF), in order to facilitate appropriate recommendations, management, counseling, psychoeducation, and prognostication. Recommendations, approaches, and plans should be tailored to the patient–family dyad for current and future needs regarding medical and psychosocial care, support, safety, and environment; financial and legal affairs; potential participation in clinical trials; and hereditable risk – without high confidence in the diagnosis, the recommendations may be inaccurate and ineffective, and result in unwarranted treatment, undue harm, and unnecessary testing and costs. Imaging methods play a central role in the process of increasing diagnostic confidence.

### Who to image

Once it has been clinically (objectively) established that a patient has substantial change(s) in cognitive function, Mild Cognitive Impairment (MCI), or dementia, the clinician should delineate the CDS, and then determine the etiology. As motivated above, establishing etiology is important. Recently revised diagnostic criteria for the most prevalent dementias, while initially mainly aimed at the dementia clinical research communities, are now beginning to serve as guidance for practicing clinicians. These reports emphasize two major goals: (1) to first establish a diagnostic hypothesis based on a careful clinical evaluation that emphasizes history and examination (including office-based cognitive testing that may be supplemented with formal neuropsychologic testing); and (2) to perform diagnostic testing, including laboratory and imaging studies, to judiciously test the established hypothesis, and increase likelihood of its validity.

### When and how to image

A multitiered approach to imaging is recommended to test an established clinical hypothesis (see above); the

first tier consists of structural imaging. Consensus dementia imaging guidelines uniformly advocate first-line use of structural imaging, particularly brain MRI (see section below and Table 50.1) (Knopman et al., 2001; Hort et al., 2010; Scheltens and O'Brien, 2011; Soucy et al., 2014). An emphasis on structural imaging (supplemented in some instances by selected functional/molecular imaging and/or CSF biomarkers) to increase diagnostic confidence and specificity is part of recently revised diagnostic criteria sets for various dementias, including AD (McKhann et al., 2011), behavioral-variant Frontotemporal Dementia (FTD) (Rascovsky et al., 2011), Primary Progressive Aphasia (PPA) (Gorno-Tempini et al., 2011), and VCI (Gorelick et al., 2011b). While most cases should only require first-tier testing with structural MRI (or head CT), in diagnostically uncertain cases, second-tier (e.g., FDG-PET or SPECT) or third-tier (e.g., amyloid PET, dopamine PET) imaging tests, when appropriately ordered and interpreted by a dementia specialist, can be useful.

In many patients there can be diagnostic uncertainty regarding primary etiology due to large phenotypic overlap in CDS. In these situations imaging can be particularly helpful to better handicap the differential diagnosis. Diagnostic uncertainty can often exist early in the course of symptoms; in very mild stages of many dementias; in atypical presentations of common dementias; in rapidly progressive or early-onset cases; and even in older patients because of a substantial burden of mixed brain pathologies (particularly dementia due to a mix of VCI and AD) – the older the patient, the less likely that only one type of brain pathology is observed. The "added value" of diagnostic imaging over and above the neurocognitive assessment is likely to be least when the pre-imaging diagnostic pretest probability is either very low or very high; a false positive is more likely in the former situation, and a false negative is more likely in the latter situation. Therefore, there is maximum gain from additional neuroimaging (e.g., FDG-PET, SPECT) when there is diagnostic uncertainty (Scheltens et al., 2002; Scheltens and O'Brien, 2011).

While repeated imaging is unnecessary in the vast majority of cases, it can be useful to further corroborate progression of neurodegeneration (see Table 1 in the European Federation of Neurological Societies (EFNS) guidelines "good practice point" on repeated imaging: Hort et al., 2010); this may be of particular utility in early-stage or rapidly progressive syndromes (e.g., prion diseases). However, generally, repeated imaging is often reserved for situations where there is an acute or unexplained clinical condition or change that would merit a substantial modification in approach. Under the latter circumstances structural imaging is the most often indicated approach.

*Table 50.1*

**Structural imaging – computed tomography (CT) and magnetic resonance imaging (MRI) recommendations**

**Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD4) (Soucy et al., 2014)**

- A head MRI when a radiologist/neuroradiologist and/or a cognitive specialist (neurologist, geriatrician, or geriatric psychiatrist) can interpret patterns of atrophy and other features that may provide added diagnostic and predictive value as deemed appropriate by the specialist (grade 2B)
- Standardization of clinical acquisition of core MRI dementia sequences that have radiologists and cognitive specialists with expertise in assessing cognitive disorders, particularly when repeat MRI scans can provide additional diagnostic, prognostic, and safety information (grade 2B)
- In addition to previously listed indications for structural imaging, a CT or MRI scan should be undertaken in the assessment of a person with cognitive impairment if the presence of unsuspected cerebrovascular disease would change the clinical management
- Structural imaging is indicated in most (though not necessarily all) persons with cognitive impairment
- Although more costly and less available, MRI is preferable to CT
- When available in the clinic, cognition specialists should use the computer images of the brain to educate persons with cognitive impairment about changes in the brain. This knowledge may reinforce adherence to vascular risk factor management and to lifestyle modifications to improve brain health (grade 3C)

**European Federation of Neurological Societies (EFNS) (Hort et al., 2010)**

- CT and MRI may be used to exclude treatable causes of dementia
- Multislice CT and coronal MRI may be used to assess hippocampal atrophy to support a clinical diagnosis of AD (level B)
- Follow-up with serial MRI is useful in a clinical setting to document disease progression (good practice point)

## CONSENSUS GUIDELINES REGARDING IMAGING OF COGNITIVE AND BEHAVIORAL DISORDERS ALONG THE DEMENTIA SPECTRUM

### MRI, CT, FDG-PET, and SPECT

While optimal clinical evaluation and management of CDS should be personalized, clinical criteria provide general guidelines for process and application to be used in most patients. The use of imaging during the CDS evaluation

and management process is advised by consensus guidelines which, in some cases (e.g., American Academy of Neurology (AAN) 2001 guidelines: Knopman et al., 2001), have been outdated by rapidly progressing fields. While AAN guidelines are currently under revision, more recent European/EFNS (Hort et al., 2010) and Canadian/Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD4: Soucy et al., 2014) consensus guidelines better address the role of imaging in clinical practice. Table 50.1 summarizes salient consensus guidance regarding structural imaging and Table 50.2 summarizes guidance for molecular imaging. Overall, these guidelines favor a first-tier role for MRI to exclude "treatable" conditions and to assess for regionally specific patterns of atrophy (e.g., hippocampal atrophy in AD), and for FDG-PET in second-tier testing to provide greater specificity for dementia specialists when there is uncertainty in diagnosis and management. Additionally, the EFNS guidelines support the use of second-tier dopamine SPECT testing to differentiate between AD and DLB.

*Table 50.2*

**Molecular imaging – fluorodeoxyglucose (FDG), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) recommendations**

**Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD4) (Soucy et al., 2014)**

- For a patient with a diagnosis of dementia who has undergone the recommended baseline clinical and structural brain imaging evaluation and who has been evaluated by a dementia specialist but whose underlying pathologic process is still unclear, preventing adequate clinical management, the specialist should obtain an $^{18}$F-FDG PET scan for differential diagnosis purposes (grade 1B)
- If such a patient cannot be practically referred for a FDG-PET scan, a SPECT rCBF study should be performed for differential diagnosis purposes (grade 2C)
- For a patient with MCI evaluated by a dementia specialist and in whom clinical management would be influenced by evidence of an underlying neurodegenerative process, an $^{18}$F-FDG PET scan should be performed or, if not available, then a SPECT rCBF study be performed (partial consensus recommendation)

**European Federation of Neurological Societies (EFNS) (Hort et al., 2010)**

- FDG PET and perfusion SPECT are useful adjuncts when diagnosis remains in doubt (level B)
- Dopaminergic SPECT is useful to differentiate AD from DLB (level A)

rCBF, regional cerebral blood flow; MCI, mild cognitive impairment; AD, Alzheimer's disease.

## β-Amyloid imaging

The US Food and Drug Administration (FDA) and the European Medical Agency have approved several β-amyloid PET ligands for clinical use to support the presence of moderate or frequent neuritic β-amyloid plaques in patients (see Chapter 26 in the previous volume for greater details regarding amyloid PET ligands). However, citing paucity of evidence that use of scans in the broader community setting practice, outside the confines of very subspecialized dementia and imaging centers, will change patient outcomes, insurance coverage for scans remains lacking – scans can be obtained at high out-of-pocket cost, which at this time is still several thousands of dollars (or the equivalent).

The Amyloid Imaging Task Force (Society for Nuclear Medicine and Molecular Imaging and the Alzheimer's Association) has provided consensus criteria for the appropriate use of β-amyloid PET in clinical practice (see Table 50.3 for summary and Johnson et al., 2013a, b, for details). Some limitations of amyloid imaging were noted, including the possibility that a "positive" scan may be incidental given the age-related increase in cerebral amyloid in cognitively normal older adults, and questions regarding specificity,

*Table 50.3*

**Appropriate use criteria for amyloid positron emission tomography (PET) ligand imaging in clinical practice (Johnson et al., 2013a, b)**

| |
|---|
| **Appropriate** |
| Patients with persistent or progressive unexplained MCI |
| AD is a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert and when knowledge of the presence or absence of amyloid pathology is expected to increase diagnostic certainty and alter management |
| Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation |
| Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age) |
| **Inappropriate** |
| Based solely on a positive family history of dementia or presence of apolipoprotein E (APOE) ϵ4 |
| Patients with a cognitive complaint that is unconfirmed on clinical examination |
| In lieu of genotyping for suspected autosomal mutation carriers |
| In asymptomatic individuals |
| Nonmedical use (e.g., legal, insurance coverage, or employment screening) |

MCI, mild cognitive impairment; AD, Alzheimer's disease.

since a positive scan is possible in conditions other than AD, including DLB and CAA (see Johnson et al., 2013a, b, for details). So, while a positive β-amyloid PET scan does not establish a diagnosis of AD or other CDS, a negative scan, in a patient appropriately evaluated by a dementia specialist, may have high negative predictive value since it supports the presence of sparse to no β-amyloid plaques (a core feature of the neuropathologic criteria for AD) and thus reduces the likelihood that the patient's cognitive impairment is due to AD. Theoretically, a negative scan also does not exclude substantial presence or potential effects from other, including oligomeric (and fibrillary), synaptotoxic forms of β-amyloid.

At this time, the US Centers for Medicare and Medicaid Services (CMS) will only cover β-amyloid PET scans under Coverage with Evidence Development patient research programs; these programs aim to assess the utility of β-amyloid PET scans to improve patient outcomes or advance patient treatment options. Using this mechanism, a large $100 million national study, the IDEAS study, has just been launched in the USA. This study aims to assess, in approximately 18,500 Medicare patients 65 years of age and older with MCI or dementia in which etiology remains in doubt by a dementia specialist, whether obtaining a β-amyloid scan using one of three tracers (florbetapir, flutemetamol, or florbetaben) will lead to substantial changes in diagnosis, short-term management, or longer-term clinical trajectory (e.g., testing, hospitalizations, emergency department visits) and costs.

## OVERVIEW OF IMAGING FEATURES OF COMMON DEMENTIAS IN CLINICAL PRACTICE

Characteristic imaging findings in rare or rapidly dementing syndromes, such as non-*ex vacuo* ventriculomegaly in normal-pressure hydrocephalus; diffusion-weighted imaging and fluid-attenuated inversion recovery (FLAIR) cortical ribbon (and basal ganglia) hyperintensities in Creutzfeldt–Jakob disease (CJD); "beads on a string" sign on angiography in primary CNS angiitis; severe white-matter abnormalities in various leukoencephalopathies and leukodystrophies; and MR gadolinium enhancement patterns in limbic and other immune-mediated encephalitides are reviewed in other chapters and elsewhere in the literature (Geschwind et al., 2008; Rosenbloom and Atri, 2011). In this section, the salient imaging features of the most common neurodegenerative dementias will be reviewed, with a focus on MRI as the method of choice for structural imaging, and FDG-PET for metabolic activity. Specialized uses of molecular imaging in clinical practice (e.g., β-amyloid imaging in AD, and dopamine PET in DLB) will also be mentioned.

### Why MRI is generally preferable to CT in evaluation and management of CDS

If no contraindication exists, the use of MRI in CDS is recommended, particularly when used by a dementia specialist (Soucy et al., 2014). Pasi et al. (2011) review the clinical use of CT in dementia and list several advantages of CT over MRI in the clinical evaluation of CDS, including lower cost, shorter duration of data acquisition, increased availability, and the ability to image patients with metallic devices (e.g., with pacemakers) or with severe claustrophobia (when open MRI is not an option). The use of new-generation CT machines with higher resolution and ability to provide coronal images also diminishes some of the advantages of MRI over CT.

Nevertheless, the advantages of MRI over CT include higher spatial resolution; absence of exposure to ionizing radiation; and better sensitivity to detect cerebrovascular damage, white-matter changes, and microbleeds — the latter are even better detected with the use of 3-T MR systems. Detection of cerebrovascular and white-matter injury and microbleeds is likely to effect changes in clinical management and strategies to reduce risk factors. For example, "silent" chronic cerebral microbleeds associated with CAA can be present in 15–20% of patients presenting for dementia evaluation, and affect cognitive and functional status and dementia severity (Atri et al., 2005). Chronic cerebral microbleeds show several associations with AD across studies (e.g., number of microbleeds is associated with worse dementia severity), are associated with decreased CSF β-amyloid levels and with the ApoE ε4 allele, as well as other imaging manifestations typical for small-vessel disease (Shams and Wahlund, 2016). Such microbleeds would be undetected using CT, and would necessitate a thorough risk–benefit analysis when considering treatment with antiplatelets and anticoagulation, and even when recommending medication, dietary changes, or intake of vitamins that affect platelet function or coagulation pathways, such as high-dose vitamin E treatment for moderation of functional decline in AD dementia. MRI is also more reliable in detecting and differentiating many of the "treatable" as well as the rare (e.g., CJD) causes of CDS. Additionally, better spatial resolution and availability of automated quantitative volumetric and deformation-based methods for MRI allow greater ability to measure specific regional atrophy and patterns associated with particular CDS and pathologies. These patterns, such as hippocampal and medial temporal-lobe (MTL) atrophy and cortical thinning in "AD signature"

regions (see below) in MCI due to AD and AD dementia, and frontal and/or temporal atrophy in FTD, are important in supporting etiology and in the formulation of differential diagnosis.

## Other MR methods – fMRI, DTI, ASL, and MRS

Other MR methods, such as functional MRI (fMRI), diffusion tensor imaging (DTI), arterial spin labeling (ASL), and magnetic resonance spectroscopy (MRS), hold great promise for specialized applications in scientific investigations and clinical trials but require further refinement and validation to be considered for applications in clinical practice (see Chapter 26 in the previous volume). Blood oxygen-level dependent (BOLD) fMRI provides a mirror of fluctuating cerebral blood flow (due to changes in the concentration of oxy- and deoxyhemoglobin that differentially affect magnetic fields) and a neural correlate of local field potentials and synaptic activity; ASL provides a quantitative noninvasive MRI measure of regional perfusion; MRS provides averaged volume concentrations of specific neurochemicals; and DTI reflects "directedness" of microanatomic structures and a sensitive indication of white-matter fiber bundle disruption; for a review of the potential utility of these techniques in CDS, see Ebmeier et al. (2011).

In brain regions with greatest β-amyloid deposition, synaptic dysfunction can be imaged beginning at preclinical stages.

Cognitive or sensory processing task-related (or resting) changes in local field potentials that, on a micro level, reflect alterations in synaptic activity and, on a macro level, dysfunction in regional activity and/or network level cognitive systems connectivity can be quantified at the group level in AD dementia using MRI, specifically BOLD-fMRI (Atri et al., 2011; McLaren et al., 2014), and non-MRI methods, such as Event-related Potentials (ERP) (Olichney et al., 2008; Cecchi et al., 2015) and magnetoencephalography (MEG) (Fernandez et al., 2013). While these (i.e. fMRI, ERP, MEG) methods remain active areas of investigation in research studies/clinical trials in AD (and other CDS) and hold promise for potential future clinical applications, they will require standardization, with respect to acquisition and analyses, and validation in broader population-based studies in clinical settings.

In regions that are not identical to those with greatest β-amyloid deposition but which are heavily connected to them, regional atrophy and loss of white-matter anisotropy can be detected later in the course of the disease, near the time when MCI supervenes. Together with neuropsychologic testing, imaging can improve the prediction of worsening to AD among patients with MCI (Masdeu et al., 2012).

## Practical consideration for use of structural imaging in the clinical dementia setting: identifying protocols and atrophy patterns

It can be difficult to accurately visualize typical atrophy patterns that are characteristic of particular neurodegenerative dementias utilizing relatively thick, two-dimensional axial slices that are used in the routine clinical protocol in community imaging centers (Dickerson, 2014). MRI data with high signal-to-noise properties at resolutions of $1\,mm^3$ or better can now be routinely obtained in the community setting using three-dimensional high-resolution MRI data acquisition methods (which can be reformatted in multiple planes, as opposed to the early scans that were essentially only viewable in one orientation). Furthermore, in collaboration with local radiologists, dementia specialists can implement comprehensive multisequence "dementia/memory loss protocols," in which relatively high-resolution three-dimensional coronal sequences are obtained in addition to routine diagnostic images; using new parallel acquisition techniques that enable faster data collection, such high-resolution sequences can be acquired in 5–8 minutes (i.e., total scanning time of approximately 30–40 minutes).

A dementia/memory loss MR protocol with both T1-weighted and T2-weighted scans can be very useful to inform differential diagnosis. Anatomic details are typically demonstrated clearly with T1-weighted sequences, while T2-weighted sequences provide complementary signals by demonstrating hyperintensities associated with cerebrovascular, gliotic/sclerotic, demyelinative, infective, inflammatory, and neoplastic processes, and damage. In addition to high-resolution T1 anatomic sequences (coronal, axial, and/or sagittal), a minimal dementia/memory loss MR protocol may include a standard axial T2, axial/coronal FLAIR, and axial T2*/susceptibility-weighted (for detection of chronic cerebral microbleeds) as well as a diffusion-weighted sequence (for the detection of cortical or deep gray nuclei changes suggestive of CJD or acute microinfarcts from embolic sources). Images can be manually inspected or measured, or algorithmically computationally quantified, to identify the variety of patterns of pathologic changes, including atrophy and cortical thinning, that are associated with specific neurodegenerative diseases.

When MRI scanning is not practical (e.g., due to contraindication, availability, cost), high-resolution CT scanning with multiplanar reformatting is recommended;

this allows inspection of images in multiple planes, including the coronal plane, which provides the clearest view of the MTL and other cortical regions characteristically affected by AD and related neurodegenerative diseases.

Visual inspection of MRI or CT scans for characteristic patterns of atrophy remains the most widely used approach for clinical interpretation of structural neuroimaging scans. In research settings, the gold standard to measure hippocampal volume (HV) is manual segmentation of MR images (Frisoni and Jack, 2011; Jack et al., 2011a). However, HVs are highly protocol-dependent: Boccardi et al. (2011) found 2.5-fold HV differences when comparing 12 highly cited manual segmentation protocols. Quantitative and automated analysis of HV and volumetrics of other salient structures performed by some research groups or FDA-approved commercially available products (e.g., NeuroQuant, Neuroreader), although potentially useful when combined with other clinical data by an experienced dementia imager and clinical specialist, have not been broadly validated in community patient samples, but are in use at several dementia subspecialty clinics. For example, NeuroQuant software compares an individual patient's regional brain volumes with those of a normative database, adjusting for sex, head size, and age. Yet, visual quality review of the results by an imaging expert remains important, and the imaging expert, as well as the referring physician, retains the ability to scroll through segmented three-dimensional MRI images to determine accuracy of the segmentation (McEvoy and Brewer, 2010). Efforts are under way to harmonize automated MR measurements for the purposes of clinical research and trials (Frisoni and Jack, 2011), which will, hopefully, facilitate reproducibility and validation, and ultimately lead to widespread use of quantitative MRI-based morphometry in clinical practice (Dickerson, 2014).

## THE ALZHEIMER'S DISEASE CLINICAL SPECTRUM

Characteristic imaging findings in the AD clinical spectrum, from MCI due to AD through increasing severity of AD dementia (e.g., mild, moderate, and severe AD dementia), typically consist of relatively greater "posterior abnormalities" on structural and metabolic imaging. These include first, atrophy involving MTL structures (particularly the hippocampus, parahippocampal gyrus, and entorhinal cortex) earlier in the course, which then progresses to affect lateral temporal and parietal association cortices, the precuneus, and ultimately frontal regions; and second, hypometabolism on FDG-PET in parietotemporal regions; early hypometabolism in medial and lateral temporal and parietal regions (including the posterior cingulate), and usually later affecting frontal regions. The degree of atrophy and hypometabolism correlates with disease progression, neuronal loss, symptoms, and dementia severity (see McEvoy and Brewer, 2010; Dickerson, 2014, for reviews). A typical "AD signature" pattern of cortical atrophy consistent with AD in groups of individuals with mild dementia or MCI, which is different from atrophy patterns in groups of cognitively normal older individuals, has been identified (Bakkour et al., 2009, 2013; Dickerson et al., 2009). However, individual patterns of MR atrophy and FDG-PET hypometabolism are highly variable, and can significantly depend on the AD clinical syndrome, stage of disease, and individual vulnerabilities. For example, AD-variant syndromes, which are particularly common in early-onset AD, include frontal-dysexecutive and behavioral variants, language/aphasic variants (particularly logopenic-variant of PPA), visuospatial variants (including the posterior cortical atrophy syndrome), and motor-apraxic variants (including the corticobasal syndrome); early in their course, these can produce very different patterns of atrophy and hypometabolism from that of the "typical" AD patterns noted above (see Chapter 26 in the previous volume). Additionally, common AD syndrome variants in late-onset AD include the Lewy body variant of AD, and AD with coexisting VCI. Lewy body variant of AD may involve relatively less hippocampal and MTL atrophy and greater parietal, occipital, and posterior temporal atrophy. AD with coexisting VCI can produce a very heterogeneous pattern of regional, central, or focal atrophy depending on the balance between AD-related pathology and vascular-related damage – vascular and degenerative pathologies can often result in overlapping clinical and imaging phenotypes (Gorelick et al., 2011a). As a final caveat, in late-stage dementia, regardless of etiology, there can often be substantial overlap in clinical and imaging findings with global cognitive deficits and marked atrophy and hypometabolism in frontal, temporal, and parietal regions.

## CONCEPTUAL MODEL OF AD IMAGING (AND CSF) BIOMARKER ABNORMALITY TRAJECTORIES

Jack et al. (2010, 2013) proposed models of AD pathology biomarkers that involve a progressive sequence of measurable biochemical, neurophysiologic, and neuroanatomic alterations that can be potentially detected years prior to psychometrically and clinically noticeable deterioration in cognition, behavior, and function, and with trajectories that typically either plateau (e.g., β-amyloid in CSF and amyloid-PET) or progress (e.g.,

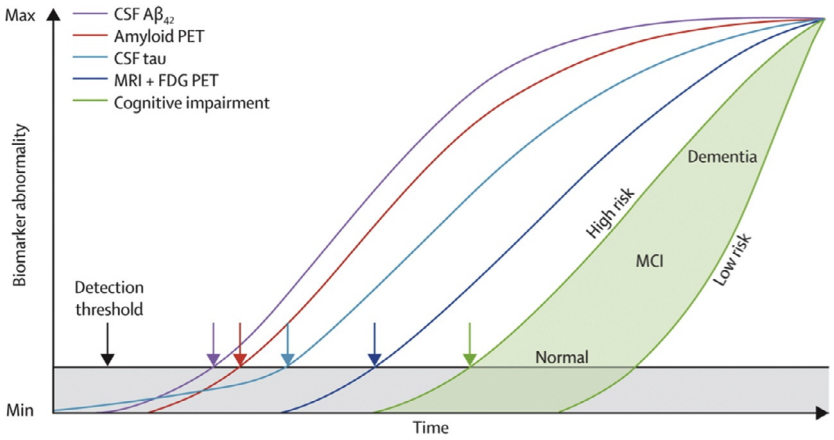


**Fig. 50.1.** The Jack et al. 2013 model of the progression of cognitive, imaging, and cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD). The threshold for biomarker detection of pathophysiologic changes is denoted by the black horizontal line. Trajectories of imaging biomarkers of AD are postulated to be detectably abnormal first via β-amyloid positron emission tomography (PET), and then via fluorodeoxyglucose (FDG)-PET (typically temporal and parietal hypometabolism with or without hypometabolism in midline posterior, posterior cingulated and precuneus, and orbitofrontal regions) and regional atrophy patterns on magnetic resonance imaging (MRI) (typically atrophy in medial temporal-lobe structures, particularly hippocampus, parahippocampal gyrus, and entorhinal cortex, and lateral temporal and parietal association cortices). Trajectory of CSF abnormalities is also depicted. Cognitive, functional, and behavioral impairments become clinically evident (green arrow) with a range of clinical/performance responses (clinical/cognitive level) that depend on the individual's vulnerability-and-resilience (VR risk) profile (light green-filled area). The gray area denotes the zone in which abnormal pathophysiologic changes lie below the biomarker detection threshold. Aβ, amyloid β; MCI, mild cognitive impairment.

tau markers, structural MRI, FDG-PET) in the clinical stages of the AD spectrum. Figure 50.1 depicts the Jack et al. 2013 updated model integrating data from AD immunohistology and biomarkers. In this model, tau pathology is postulated to precede β-amyloid deposition in time, but only early on and at a subthreshold biomarker detection level. β-Amyloid deposition then occurs independently and rises above the biomarker detection threshold (as detected by CSF and β-amyloid PET profiles) (purple and red arrows), which induces acceleration of tauopathy; CSF tau then rises above the detection threshold (light-blue arrow). Later still, FDG-PET (temporal and parietal hypometabolism) and structural MRI (MTL/hippocampal atrophy) (dark-blue arrow) abnormalities rise above the detection threshold. Finally, cognitive, functional, and behavioral impairments become clinically evident (green arrow), with a range of clinical/performance responses (clinical/cognitive level) that depend on the individual's vulnerability and resilience (VR risk) profile (light-green-filled area). It is important to note that, depending on an individual's VR risk profile, two individuals can manifest very similar biomarker profiles but have very different clinical/cognitive levels.

As postulated above and supported by a wealth of data (see Jack et al., 2011b; McKhann et al., 2011; Dickerson, 2014, for a review), the pathobiologic processes that lead to the dementia stage, AD dementia, begin decades prior to the onset of clinical symptoms. Putative biomarkers of these pathobiologic processes have undergone intensive longitudinal study as part of large natural history clinical research observational cohort studies around the world, including the Alzheimer's Disease Neuroimaging Initiative (Mueller et al., 2005; Weiner et al., 2015) and the Australian Imaging, Biomarkers and Lifestyle study of aging (Rowe et al., 2010). Recently revised or developed diagnostic criteria for the AD clinical spectrum acknowledge a slowly progressive clinicobiologic continuum that can be measured via biomarkers, including imaging, and have included use of imaging (as well as CSF) biomarkers to support diagnostic confidence and to increase accuracy (see Jack et al., 2011b; Atri, 2014, for a review). The Dubois Criteria (Dubois et al., 2010) and the National Institute of Aging–Alzheimer's Association criteria for AD (McKhann et al., 2011) incorporate MRI-defined hippocampal atrophy as an important feature. MTL atrophy also predicts progression from MCI to AD.

## THE SPECTRUM OF VASCULAR COGNITIVE IMPAIRMENT

Recent consensus criteria by the American Heart Association/American Stroke Association (AHA/ASA) (Gorelick et al., 2011a) used the term "vascular cognitive impairment" to represent the spectrum of severity from all forms of cognitive impairment associated with cerebrovascular brain injury ranging from

syndromes including subtle symptoms in otherwise cognitively normal individuals, to subtle impairments, to vascular MCI (VaMCI), to impairments in cognition and function severe enough to merit a diagnosis of vascular dementia (VaD). The AHA/ASA consensus criteria state that "the term *VCI* characterizes all forms of cognitive deficits from VaD to MCI of vascular origin" (Gorelick et al., 2011b) and VaD is considered to be the extreme end of the spectrum of VCI (Hachinski et al., 2006; Gorelick et al., 2011b), where vascular disease is felt to be the sole cause for the cognitive impairment. Traditionally, multi-infarct dementia or VaD was only used when cognitive impairment was associated with stroke.

Cerebrovascular and degenerative pathologies, particularly AD-related changes, commonly coexist in later life, each adding to, and possibly synergistically multiplying, the likelihood of cognitive impairment and dementia. There is also a complex interplay between macroscopic and microscopic infarcts, white-matter hyperintensities/leukoaraiosis, and other vascular and degenerative pathologies, including chronic cerebral microbleeds, that contribute to the clinical spectra of AD and VCI. Additionally, cerebrovascular and degenerative pathologies often produce overlapping clinical and imaging phenotypes. Thus the term VCI can encompass syndromes where both cerebrovascular brain injury- and AD-related processes co-occur (Hachinski et al., 2006; Gorelick et al., 2011b). The AHA/ASA consensus criteria state:

> *VCI encompasses all the cognitive disorders associated with cerebrovascular disease, from frank dementia to mild cognitive deficits. Simply put, VCI is a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least 1 cognitive domain. The most severe form of VCI is VaD (Gorelick et al., 2011b).*

The AHA/ASA criteria for diagnosis of VCI are based on two factors: (1) demonstration of the presence of a cognitive disorder by neuropsychologic testing, and evidence of cerebrovascular brain injury by neuroimaging; and (2) determination of the relationship of the cerebrovascular injury (e.g., infarct) to the cognitive symptoms. Therefore, to appropriately diagnose VaD, it is critical to identify the presence of cortical or subcortical infarcts or other stroke lesions, and these should be associated with clinical symptomatology. Some propose that cognitive symptoms should appear within 3 months after a stroke, while others consider this timeframe arbitrary, and state that symptoms can develop even later.

## Neuroimaging in VCI

Neuroimaging methods, particularly MR modalities, provide excellent tools for identifying different types of cerebrovascular-related brain injury and vascular pathologies. The AHA/ASA VCI consensus criteria recommend the use of brain imaging with MRI, or CT, as reasonable in making a diagnosis of VCI; imaging evidence of cerebrovascular disease-related injury is a requirement for the diagnoses of probable VaD and probable vascular MCI. The diagnosis of possible VaD and possible VaMCI, which require a lower level of evidence, do not require imaging characterization of this type of injury.

In the evaluation of VCI using MR techniques, high-resolution T1 sequence can accurately delineate brain anatomy, while FLAIR sequences can sensitively detect white-matter and gliotic tissue changes (Gorelick et al., 2011a). The AHA/ASA criteria also provide a recommendation (class IIa; level of evidence B) for use of MRI with T2*-weighted gradient-echo sequences in patients with progressive cognitive impairment for detection of the multiple strictly lobar hemorrhagic lesions characteristic of probable CAA. CT provides a less costly and more available alternative to MR with less sensitivity and specificity to detect the diversity of imaging changes related to cerebrovascular brain injury.

Clinical criteria do not recommend use of FDG-PET and SPECT in the routine evaluation of VCI. Clinical heterogeneity of VCI phenotypes, along with likelihood of coexisting neurodegenerative pathology in older individuals, can yield a mixed picture of metabolic abnormalities. However, in more classic "pure" forms of VCI due to microvascular disease, the metabolic abnormalities involve the thalamus, caudate, and frontal lobes: a pattern concordant with neuropsychologic findings of impaired executive function that are often a prominent feature of typical VCI syndromes (Pascual et al., 2010).

At centers with expertise, additional techniques (see Chapter 26 in the previous volume) including DTI, ASL, magnetization transfer methods, and hydrogen spectroscopy, are sometimes utilized to better delineate the nature and effects of cerebrovascular-related brain injury. The neuroimaging evaluation of acute and subacute infarcts/stroke and vasculature (e.g., with CT and MRI methods such as diffusion-weighted imaging, apparent diffusion coefficient, CT angiography/MR angiography, CT venography/MR venography) and hemorrhages are reviewed in other chapters.

There are several limitations to imaging methods in the assessment of VCI. A significant limitation is that clinically available scans only detect macroscopic infarcts of 3 mm in size or greater; microscopic infarcts and small-vessel disease are currently not within the

resolution of most scans. Another limitation is that some vascular pathologies may represent either vascular or degenerative processes. For instance, neuroimaging studies have shown that white-matter degeneration, as measured by both FLAIR and DTI, and microbleeds are associated with both VCI and clinical AD. Similarly, metabolic imaging can yield diverse or overlapping patterns of abnormalities depending on local and distant effects (connected synaptic networks) of cerebrovascular brain injury.

## DEMENTIA WITH LEWY BODIES

The Third Report of the DLB consortium (McKeith et al., 2005a) provides the most recent updated clinical criteria for DLB. DLB, a synucleinopathy that in many cases can show considerable neuropathologic and phenotypic overlap with the AD spectrum (as well as with the less common condition of PDD), is reported in 15–30% of autopsy cases of dementia and <1–5% of community samples (see Hanağası, 2014, for a review).

### Neuroimaging in DLB

While structural imaging is obtained as part of the standard CDS assessment (see above), there are no DLB-specific findings on MRI or CT. DLB clinical criteria state that suggestive evidence, sufficient to support a diagnosis of possible DLB, is provided by "low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging" (McKeith et al., 2005). The criteria also state that supportive features that are commonly present but do not provide diagnostic value include: (1) relative preservation of MTL on CT or MRI scan; (2) decreased tracer uptake on SPECT or PET imaging in occipital regions; (3) abnormal (low-uptake) metaiodobenzylguanidine (MIBG) myocardial scintigraphy (a cardiac imaging marker of postganglionic cardiac sympathetic innervation); and (4) prominent slow waves on electroencephalogram (EEG) with temporal-lobe transient sharp waves (McKeith et al., 2005).

DLB, similarly to AD, is considered a neurodegenerative disease with a "posterior" predilection, at least in the initial and milder stages. While findings on structural imaging, including MTL and parietal atrophy, can considerably overlap with those of AD, groups of patients with DLB may display a milder degree of hippocampal and MTL atrophy compared to groups of patients with AD (Sabattoli et al., 2008; Burton et al., 2009). In DLB, greater MRI hippocampal atrophy may be associated with presence of coexisting neurofibrillary tangle pathology (Kantarci et al., 2012). Presence of cortical Lewy bodies has been associated with smaller amygdalar size (Burton et al., 2012). Cortical and subcortical atrophy has also been reported in the striatum, dorsal midbrain, substantia innominata, and hypothalamus (Kantarci et al., 2012).

Tier-2 neuroimaging in equivocal cases of DLB may include findings of low striatial $^{18}$F-fluorodopa PET uptake (Hu et al., 2000), and low dopamine transporter $^{123}$I-beta-CIT SPECT binding in the caudate and posterior putamen (McKeith et al., 2007; O'Brien et al., 2009) in DLB compared to AD; these findings are less useful in differentiating DLB from PDD. Meanwhile, 80% of patients with DLB but only 20% of patients with PDD were found to have abnormal amyloid binding on amyloid-PET (Edison et al., 2008; Gomperts et al., 2008; Foster et al., 2010).

While occipital, as well as parietal, FDG-PET hypometabolism and SPECT hypoperfusion have been observed in DLB (Albin et al., 1996; Lobotesis et al., 2001), occipital abnormalities are not always present, and there is substantial overlap in the FDG-PET and SPECT patterns of abnormality seen in DLB and AD, reflecting the common presence of AD-type pathology in cases of DLB. Some studies suggest that the posterior cingulate gyrus, by the splenium of the corpus callosum, is uniformly hypometabolic or hypoperfused in AD, but is less so in DLB (Goker-Alpan et al., 2012; Graff-Radford et al., 2014) (see Fig. 26.26, in Chapter 26 in the previous volume).

Prominent slowing of EEG background activity and transient temporal sharps and slow waves, while a supportive feature that may be more common in DLB than AD, do not provide diagnostic value (McKeith et al., 2005b; Bonanni et al., 2008; Roks et al., 2008).

## PARKINSON'S DISEASE DEMENTIA

The Movement Disorder Society Task Force established clinical diagnostic criteria for PDD (Emre et al., 2007), a dementia that occurs in the context of well-established Parkinson disease. In the clinical setting DLB can be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present), while in the research setting, a stricter, existing 1-year rule between the onset of dementia and parkinsonism is often employed. The general term "Lewy body disease" is sometimes used in clinical practice when parkinsonism with dementia on the PPD-DLB spectrum is present, and when a differentiation between DLB and PDD is not being made. A Task Force of the Movement Disorder Society has also published diagnostic criteria for MCI in PD (Litvan et al., 2012).

Structural imaging obtained as part of the standard CDS assessment (see above) does not provide PDD-specific findings on MRI or CT, but may help differentiate vascular parkinsonism with VCI – a diagnosis that would exclude a diagnosis of probable PDD. While dopamine transporter-related abnormalities on PET and

SPECT can be suggestive of "Lewy body disease" in general (thus differentiating them from AD), they do not help differentiate between DLB and PDD. In contrast to DLB, where up to 80–85% of patients may have significantly elevated amyloid PET binding, there is often relatively low binding in PDD, with only 20% or fewer of PDD patients displaying coexisting cortical amyloid burden (Edison et al., 2008; Gomperts et al., 2008; Maetzler et al., 2008).

## FRONTOTEMPORAL LOBAR DEGENERATION SYNDROMES

FTLD syndromes comprise a loosely knit group of clinically (and neuropathologically) heterogeneous neurodegenerative diseases that preferentially affect the "anterior" brain regions, the frontal and anterior temporal lobes, and, in many cases, relatively spare other cortical regions. FTLDs often also affect subcortical regions, including the basal ganglia, and in some cases can affect basal forebrain and brainstem nuclei (see Chapter 26 in the previous volume for neuroimaging findings, and Dickerson, 2014, for a review). International consensus diagnostic criteria developed for three FTLD clinical subtypes (frontotemporal dementia, progressive nonfluent aphasia, and semantic dementia) (Neary et al., 1998), PPA (Gorno-Tempini et al., 2011), and behavioral-variant FTD (Rascovsky et al., 2011) identify structural and functional (PET/SPECT) abnormalities in these disorders.

### Neuroimaging in FTLD

Structural imaging, preferably with MRI, is critical in the diagnostic workup of suspected FTLD. Structural imaging can help exclude other potential causes of slowly progressive frontal-lobe syndromes, including tumors (e.g., frontal meningioma) and stroke/VCI, and to identify typical abnormalities consistent with FTLD neurodegenerative syndromes. Atrophy of frontal and/or anterior temporal regions is typical in FTDs; "knife edge" or "knife blade" atrophy represents extreme atrophic thinning of frontal and/or anterior temporal gyri in severe FTLD. In behavioral-variant FTD, atrophy is usually more prominent in the right hemisphere, while in PPA syndromes it is often more prominent in the left hemisphere – the left temporal tip in semantic-variant PPA (Fig. 26.29 in Chapter 26, previous volume); the left anterior perisylvian area in nonfluent-variant PPA (Fig. 26.5); and the left posterior perisylvian area in logopenic-variant PPA (Fig. 26.22) (which is most often associated with AD, rather than FTD, pathology: Mesulam et al., 2014). FTD can also co-occur with motor neurone disease, and atypical parkinsonian disorders, such as progressive supranuclear palsy and corticobasal degeneration syndrome (see Chapter 26 for more details).

Progressive supranuclear palsy, characterized by marked axial postural instability with early falls, dysarthria, and downward-gaze palsy, later progressing to a frontal-lobe syndrome, is often characterized radiographically by the presence of the hummingbird sign (see Fig. 26.30), best seen on sagittal T1 MRI that reflects striking midbrain atrophy and a decreased midbrain-to-pons area ratio (Massey et al., 2013); frontal atrophy may also be seen. In CBD, atrophy of posterior frontal and superior parietal areas as well as decreased metabolism in the superior parietal lobule can be seen (see Fig. 26.31).

In the USA, CMS approved clinical reimbursement for FDG-PET scans in 2004 for the differential diagnosis of FTD versus AD in clinical practice. In some frontal cognitive, behavioral, and/or aphasic syndromes, structural imaging may appear relatively normal early in the course; in such cases, FDG-PET (or SPECT) may identify abnormalities when anatomic changes are subtle or undetectable. The relatively specific abnormality pattern of lateral temporoparietal and posterior cingulate FDG-PET hypometabolism in typical AD (Jagust et al., 1988; Herholz et al., 2002) versus predominantly frontal (medial prefrontal, posterior orbitofrontal, dorsolateral prefrontal), anterior temporal, or insular abnormalities (and abnormalities in deep nuclei, including the basal ganglia and thalamus is some cases) in non-AD FTD syndromes has been shown to improve diagnostic confidence, and to be of practical utility in clinically uncertain cases (Foster et al., 2007; Womack, 2011). Tier-2 use of FDG-PET scanning is warranted when ordered by a dementia specialist in cases where the diagnosis still remains in doubt after the initial clinical, cognitive/neuropsychologic, and MRI evaluation.

## CONCLUSION

Neuroimaging is an essential adjunct to clinical and cognitive assessments in the evaluation of cognitive and behavioral disorders. A multitiered approach to imaging is recommended to test an established clinical hypothesis; the first tier consists of structural imaging, preferably with MRI. Consensus guidelines strongly support the use of structural neuroimaging in clinical practice and imaging criteria are incorporated into the diagnostic criteria of most neurodegenerative dementias. Molecular imaging (usually with FDG-PET) can be used as a second-tier option in cases where a dementia specialist remains in doubt regarding etiology and management. The clinical utility of third-tier options, such as amyloid PET, is yet to be determined. Many promising methods are under research investigation (e.g., tau PET, fMRI, ASL, DTI). In the future, combination use of imaging

methods is likely to better elucidate the underlying pathobiology of the dementia clinical phenotype at the level of the individual, thus improving diagnostic accuracy, and empowering more efficient and effective management and care of the patient.

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