Structural neuroimaging in dementia has traditionally served the sole purpose of ruling out (treatable) disease as an alternative explanation for cognitive deterioration, for example a brain tumor or subdural hematoma. However, with more widespread use of magnetic resonance (MR) imaging and the development of more advanced imaging techniques (including diffusion-weighted and susceptibility-weighted imaging, positron emission tomography, or single-photon emission computed tomography), the role of neuroimaging in dementia has shifted gradually from exclusion of disease toward that of a highly valuable aid to the clinical diagnosis and subtyping of dementia.1 To this end, MR imaging is preferred over computed tomography (CT), because it has the advantage of not only assessing (regional) atrophy (for which CT is sufficient) but also depicting other brain changes such as white matter lesions (WMLs) and microbleeds. Furthermore, there is increasing evidence showing that the pathologic process associated with dementia may begin decades before diagnosis. Detecting such preclinical changes by means of imaging could imply a major role for neuroimaging in risk stratification and early disease prevention. Yet, many brain changes seen in dementia also occur in middle-aged and elderly individuals who are cognitively intact, and are considered part of the normal aging process. Distinguishing normal from abnormal aging is therefore a prerequisite when interpreting an imaging examination of an individual suspected of Alzheimer’s disease (AD) or non-Alzheimer’s dementia, and even more so when the goal of imaging shifts toward prediction of development of dementia. Structural MR imaging is the primary neuroimaging technique of choice in clinical practice to support the clinical diagnosis of dementia. This article focuses on structural MR neuroimaging in normal aging and in dementia, more specifically in AD. In the first part, normal versus pathologic brain aging is discussed, focusing on qualitative and quantitative MR imaging markers. In the second part, the role of MR imaging in the (differential) diagnosis of AD is reviewed.

PART I: STRUCTURAL IMAGING IN AGING

To recognize the abnormal, one needs to first know what is normal. With increasing age, the brain may show structural changes to varying degrees. Many of these brain changes overlap with the spectrum of disease present in dementia and AD, and there is a fine line between normal and pathologic brain changes.

KEYWORDS

- Dementia
- Alzheimer’s disease
- Magnetic resonance (MR) imaging
- Normal aging
- Brain
- Atrophy
- Neuroimaging
aging. Moreover, even among those persons considered to age normally, there is a wide range, varying from successful brain aging (ie, retaining normal brain structure and volume up to high age) to the more typical aging or even near-pathologic brain aging (Fig. 1). Also, even although changes such as atrophy or WMLs are to a certain extent considered to be part of the normal aging spectrum, these have consistently been related to vascular risk factors. Furthermore, their presence may be accompanied by subtle cognitive deficits or even an increased risk of neurodegenerative or cerebrovascular disease. Studying the distribution and the time course of alterations that occur in the normal brain with aging is therefore important for understanding the mechanisms leading to these changes and for better characterization of neurologic disorders of which the risk increases with advancing age, such as dementia. Furthermore, because more clinical trials on therapy for AD are investigating imaging measures as surrogate markers for disease outcome, it becomes of particular importance to take into account the normal age-related brain changes that can be expected.

This section describes what changes are commonly found in the aging brain, to what extent these can be regarded as normal, and how these could be interpreted in the context of (suspected) AD.

A summary of common imaging findings in normal aging is presented in Box 1.

**Brain Atrophy and Hippocampal Atrophy**

Insight into changes of total brain volume with aging can be derived from various cross-sectional and longitudinal studies. Several automated image-processing tools have been developed to quantify total brain volume (Box 2), all with high levels of reproducibility.\(^7\) Cross-sectional studies have consistently shown in non-demented persons older than 55 years that brain volumes are smaller with increasing age,\(^8,9\) in persons with cardiovascular risk factors, and even more so when imaging findings consistent with cerebral small vessel disease are present.\(^9,10\) When gray and white matter are studied separately, the rate of decline with age varies according to the age range studied. Several studies report a steady decline in gray matter from early adulthood onwards,\(^11-13\) but others find that in elderly individuals, gray matter loss seems to become less prominent and that it is primarily white matter atrophy that causes the brain to shrink (Fig. 4).\(^9,14\)

There are few longitudinal studies that have examined changes in brain volume within individuals over time. For the purpose of comparison and to correct for head size differences, brain tissue volumes are generally expressed as percentage of intracranial volume. A mean rate of brain volume loss of 0.4% to 0.5% per year in normal middle-aged and elderly individuals has been described,\(^10,14\) and double that rate (1.0%) in individuals who developed dementia during follow-up.\(^12\) Yet, even among individuals remaining free of dementia, there is extensive evidence that total brain volume and separate gray/white matter volumes relate to cognitive performance in various cognitive domains.\(^9,15\)

In the context of AD, hippocampal volume loss in normal aging is of particular interest. Manual

![Fig. 1](https://example.com/fig1.png) Successful versus less-successful brain aging. Coronal T1-weighted images of 2 84-year-old individuals, both with normal Mini Mental State Examination scores. Yet, the brain of the individual on the left shows less atrophy compared with that of the individual on the right (total brain volume expressed as percentage of intracranial volume: 84% for the individual on the left vs 76% on the right).
outlining of hippocampal borders has long been the method of choice to obtain volumetric measures (for a detailed description, see Ref.16). Manual tracing is tedious, resource intensive, and prone to human error. These limitations become particularly relevant when large MR imaging data sets from population-based studies are to be analyzed, arguing for a need for automated measurements. Current automated methods, mainly atlas-based registration, have been shown to yield reliable and valid data, and results are still improving. Using automated segmentation, a longitudinal population-based study in 518 nondemented aging individuals showed a decline of 1.6% in hippocampal volume per year, which is similar to a rate of 1.4% per year that was established found among 200 healthy control individuals in a meta-analysis of AD case-control studies. For comparison, the AD individuals in this meta-analysis had a mean decline in hippocampal volume of 4.7% per year. In the longitudinal study mentioned earlier, individuals who showed a larger rate of decline in hippocampal volume during follow-up more often developed dementia (the odds ratio to develop dementia was 2.3 per standard deviation of volume loss). Among those subjects who stayed free of dementia during follow-up, a faster decline in hippocampal volume was still related to worse performance on memory tests.

These findings show that there seems to be a spectrum from normal aging to pathologic brain aging, rather than a distinct separation between healthy and diseased states. Furthermore, it implies that knowledge of normal rates of atrophy in aging is of importance for clinical trials in AD, when the rate of brain atrophy or hippocampal atrophy is used as a surrogate marker of disease progression, but also in a clinical setting taking into account a patient’s age is important to

| Box 1
| Summary of common brain MR imaging findings in aging |

**Brain atrophy**
- Total brain volume: 0.4–0.5% brain tissue loss per year is normal, >1.0% is likely abnormal
- Hippocampus: volume loss 1.6%/y in normal individuals
- Normal volume loss in aging should be taken into account in clinical setting or in trials; reference data derived from normal population may be helpful

**WMLs**
- Punctiform or early confluent lesions (Fazekas score 0–2) in periventricular or subcortical distribution is generally normal in aging
- Confluent lesions are always abnormal (Fazekas score 3)
- MR imaging sequences such as diffusion tensor imaging (DTI) are more sensitive in detecting microstructural changes in normal-appearing white matter

**Cerebral microbleeds**
- T2*-weighted MR imaging sequence needed for depiction
- Common in elderly individuals: prevalence more than 20% in persons older than 60 years
- (Strictly) lobar distribution linked to cerebral amyloid angiopathy (CAA) and AD
- Deep or infratentorial distribution related to hypertensive arteriolosclerosis
- New microbleeds develop yearly in 3%–7% of aging individuals

**Silent brain infarcts**
- Small lacunar strokes that are presumably without symptoms, but have been linked to subtle cognitive deficits and increased risk of stroke and dementia
- Present in 11%–28% of individuals older than 55 years

**Enlarged perivascular spaces (EPVSs)**
- Common around anterior comissure, in centrum semiovale, near vertex of the brain, and in hippocampus
- May be considered normal in most individuals but have also been linked to small vessel disease, cognitive deficits, and risk of dementia
determine whether they show an abnormal degree of brain tissue loss. For this use, reference data on brain tissue volumes derived from a normal aging population are of great value (Fig. 5).

**WMLs and White Matter Microstructure**

In elderly individuals, focal white matter abnormalities occur frequently, seen on CT as mildly hypodense areas and on T2-weighted MR imaging or FLAIR images as hyperintense foci in the white matter (Fig. 6). Commonly used terminology includes WMLs, white matter hyperintensities, or age-related white matter changes. WML load increases with age (Fig. 7) and typically shows a periventricular or subcortical distribution (Box 3, Fig. 10). Although the pathogenesis remains unclear, histopathologic studies point toward hypoxic/ischemic injury caused by hypoperfusion as the underlying cause.26 This theory is further supported by findings that classic cardiovascular risk factors, such as hypertension, smoking, and diabetes, are all related to the presence and progression of WMLs.26,27 Although longitudinal

<table>
<thead>
<tr>
<th>Degree of Atrophy</th>
<th>Gyri</th>
<th>Sulci</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCA = 0</td>
<td>None</td>
<td>Normal volume</td>
</tr>
<tr>
<td>GCA = 1</td>
<td>Mild (may be considered normal in the elderly)</td>
<td>Normal</td>
</tr>
<tr>
<td>GCA = 2</td>
<td>Moderate</td>
<td>Reduced</td>
</tr>
<tr>
<td>GCA = 3</td>
<td>Severe</td>
<td>Severely reduced (knife blade)</td>
</tr>
</tbody>
</table>

studies have shown that lesion load in presumed healthy persons is related to an increased risk of stroke, dementia, and death,\textsuperscript{27,28} cross-sectional reports show only a weak correlation between WML and symptoms, such as cognitive deficits.\textsuperscript{27} This finding may be related to the fact that the underlying extent of tissue disease (ie, myelin loss or axonal damage) may differ between several kinds of lesions that all have a similar appearance on MR imaging. Furthermore, WMLs likely mark underlying vasculopathy that causes changes in normal-appearing brain tissue that are not visible on conventional MR imaging. Various advanced MR techniques have emerged in recent years to assess these hidden abnormalities in apparently normal brain tissue. Examples are magnetic transfer ratio, spectroscopy, or T1 and T2 relaxation measures, the use of which has been described extensively in relation to white matter diseases such as multiple sclerosis.\textsuperscript{29} A more recent emerging technique is DTI, which enables the quantification of random movement of water molecules in brain tissue, by applying strong magnetic gradients in various directions.\textsuperscript{30} Normal brain tissue, especially white matter, hinders the degree and direction of random diffusion because of its highly structured fiber organization. With loss of microstructural integrity of white matter, diffusion properties change to a measurable extent. Parameters derived from DTI that are used commonly to quantify tissue integrity are mean diffusivity (MD, magnitude of diffusion) and fractional anisotropy (FA, degree of anisotropy of diffusion). With increasing age, MD has been consistently found to increase in normal-appearing white matter, and FA to decrease.\textsuperscript{31,32} These changes were found to relate more to WML load and atrophy than to

Fig. 2. Automated brain tissue segmentation. On the left, the T1-weighted image used as input and on the right, the segmentation result in which each voxel has been labeled according to its tissue class.

Fig. 3. Brain atrophy depicted as surface change. Using SIENA,\textsuperscript{5} 2 brain scans from a single individual obtained at different time points (interval 3 years) are segmented into brain and nonbrain tissue and then registered to each other. The resulting image shows regional decrease in volume (in blue) or increase (in red) over time. (Image kindly prepared by Dr Renske de Boer.)
age in itself (Fig. 11), thus supporting the idea that WMLs merely represent the tip of the iceberg and that damage to the white matter is more widespread than can be appreciated on conventional MR images. More importantly, DTI changes in normal-appearing brain tissue relate to cognitive function in community-dwelling elderly individuals, independent of degree of brain atrophy or WML load, suggesting that DTI more sensitively detects clinically significant white matter changes and that this measure may complement traditional volumetric measures. More recent approaches have been directed toward quantification of DTI parameters in distinct white matter tracts that can be identified using tractography methods (Fig. 12). These advances will yield tract-specific information on diffusion properties, which is of relevance to the hypothesis that cognitive decline may in part be caused by disconnection of specific cortical-subcortical connections. It is expected that such methods may aid in detecting more subtle changes in white matter disease over time, which could for example be used as a surrogate marker to evaluate new therapies in clinical trials. Again, reference estimates derived from aging individuals are essential to interpret findings in a clinical setting.

Cerebral Microbleeds

Cerebral microbleeds are small brain hemorrhages that are presumed to result from leakage of blood cells from damaged small vessel walls. They were first detected on MR imaging only in the mid-1990s, as MR imaging sequences sensitive to blood-breakdown products became available (eg, T2*-weighted gradient-echo technique), which are essential for microbleed detection (Fig. 13). Histologically, these small black dots on MR imaging represent hemosiderin-laden macrophages that are clustered around small vessels (Fig. 14). The choice of field strength, sequence parameters (particularly echo time), and postprocessing (eg, susceptibility-weighted imaging technique) have all been found to have a major influence on the detection rate of cerebral microbleeds. With these advances in imaging, the prevalence of microbleeds has been estimated to be more than 20% in persons aged 60 years and
Fig. 5. Normative reference data as an aid for clinical diagnosis. A brain tissue segmentation result is shown (left). The brain volume derived from this segmentation can be compared with reference curves derived from the general aging population (graph). The graph depicts the percentile lines (5%–95%) for brain volume as percentage of intracranial volume, as a function of age (x-axis). The measurement of the individual on the left is plotted in the graph as a gray circle. (Courtesy of Dr Bas Jasperse and Dr Marcel Koek.)

Fig. 6. WMLs seen as hypodense regions on CT (left) and as hyperintensities on FLAIR MR imaging (right).
older, increasing to nearly 40% in those older than 80 years. Microbleed location is generally divided into deep (ie, basal ganglia, thalamus) and infratentorial versus lobar brain regions (Fig. 15). In the aging population, microbleeds in lobar locations share apolipoprotein E (APOE) ε4 genotype as a common risk factor with CAA and AD, suggestive of a potential link between vascular and amyloid neuropathology. This link has further been corroborated by the finding that topography of lobar microbleeds in community-dwelling elderly individuals follows the same posterior distribution as is known from amyloid disease in CAA and AD. Furthermore, recent reports show that presence of microbleeds, and particularly those in lobar locations, relates to worse cognitive function, both in healthy elderly individuals and in patients diagnosed with AD. In contrast, deep or infratentorial microbleeds in aging individuals are primarily linked to classic cardiovascular risk factors and are more likely caused by hypertensive vasculopathy. Longitudinal studies indicate that incident microbleeds commonly occur over time: annually, 3% of presumed healthy elderly individuals develop new microbleeds, increasing to more than 7% of those who already have microbleeds at baseline. In comparison, these rates are doubled in patients attending a memory clinic.

The increasing evidence that microbleeds reflect both vascular disease as well as amyloid angiopathy has led to the belief that these may well represent the missing link between the vascular and amyloid hypotheses in the pathogenesis of AD, which is further elaborated on in part II of this article.

Silent Brain Infarcts
Small lacunar infarcts (Fig. 16) are often found on brain MR imaging in the aging population without previous history of stroke and these have therefore been named silent brain infarcts. Population-based studies have estimated the prevalence of silent infarcts on MR imaging to range from 11% to 28% for those aged 55 years and older. These estimates are likely to vary as a result of large heterogeneity in MR imaging parameters and diagnostic criteria, and the difficulty in distinguishing lacunar infarcts from EPVSs. As expected, silent

Box 3
Assessment of WML load

Visual rating
A large variety of visual rating scales is available to assess the amount and distribution of WMLs. Easiest to use (and therefore most commonly applied in clinical care) is the Fazekas rating scale, which describes WML load separately for periventricular and deep WMLs in a 4-step scale (score 0–3; Fig. 8). A general interpretation of the Fazekas scores is that score 1 (punctiform lesions only) is normal for most individuals, even those aged less than 65 years. Score 2 is considered abnormal for persons aged 70 years and less, whereas score 3 (confluent lesions) should always be viewed as abnormal. The Age-Related White Matter Changes (ARWMC) scale also applies a 4-step scale but on a larger number of regions (Table 2). A more elaborate and semiquantitative scale is that of Scheltens and colleagues.

Automated segmentation
Despite the ease of visual rating, studies have shown that there is considerable interrater reliability for the use of these scales, especially concerning WML progression. Alternatively, WML volume can be quantified by manually outlining all lesions and summing these to obtain volumetric measures that may better capture change over time. Yet, this practice is time-consuming and may still be prone to human error. An observer-free and reproducible assessment of WML load may better be obtained by fully automated tissue segmentation procedures (for an example, see Ref.) (Fig. 9).
brain infarct prevalence is higher with increase in age and with risk factors also known to be related to clinical stroke, such as hypertension, atrial fibrillation, carotid intima-media thickness, and increased plasma homocysteine.49 More recent publications also point toward kidney disease as an important risk factor,51 which indicates that cerebral small vessel disease may be a reflection of more systemic vascular damage. Furthermore, silent brain infarcts show a strong association with WML load, again supporting small vessel disease as a common underlying pathophysiology. This finding has been further substantiated by a link between retinal microvascular abnormalities and both lacunar infarcts and WMLs in a large sample of aging individuals.52 Despite their name, the fact that silent infarct presence has been related to subtle cognitive deficits and more than doubles risk of stroke and dementia (in particular AD49) suggests that these are neither silent nor innocuous.

**EPVSs**

Perivascular spaces, also named Virchow-Robin spaces, are extensions of the subarachnoid space that accompany vessels entering the brain parenchyma. EPVSs commonly occur around arteries in the substantia perforata, in the region of the anterior commissure, in the centrum semiovale, or near the vertex of the brain (Fig. 17). Their typical imaging appearance is that of sharply demarcated dotlike or linear CSF-filled spaces. Prominent or dilated perivascular spaces can be seen at all ages, even in the very young,53 in whom they are considered a normal finding. However, with aging, EPVSs may become more prominent54 and have been associated with presence of silent brain infarcts and WML load.54,55 This association with cerebral small vessel disease was further supported by recent evidence that in a large population-based sample of elderly individuals, those with hypertension had more prominent perivascular spaces compared with normotensives.54

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**Table 2**

ARWMC rating scale for WMLs on MR imaging and CT

<table>
<thead>
<tr>
<th>WMLs</th>
<th>ARWMC Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesions (may include symmetric, well-defined caps or bands)</td>
<td>0</td>
</tr>
<tr>
<td>Focal lesions</td>
<td>1</td>
</tr>
<tr>
<td>Beginning confluence of lesions</td>
<td>2</td>
</tr>
<tr>
<td>Diffuse involvement of the entire region, with or without involvement of U-fibers</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Basal ganglia lesions</th>
<th>ARWMC Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesions</td>
<td>0</td>
</tr>
<tr>
<td>1 focal lesion (&gt;5 mm)</td>
<td>1</td>
</tr>
<tr>
<td>&gt;1 focal lesion</td>
<td>2</td>
</tr>
<tr>
<td>Confluent lesions</td>
<td>3</td>
</tr>
</tbody>
</table>

White matter changes on MR imaging are defined as ill-defined hyperintensities $\geq 5$ mm on both T2 and proton density/FLAIR images, and on CT as ill-defined and moderately hypodense areas of $\geq 5$ mm. Lesions are scored for left and right hemisphere separately in the following brain areas: frontal, parieto-occipital, temporal, infratentorial/cerebellum, and basal ganglia (striatum, globus pallidus, thalamus, internal/external capsule, and insula). For each of these regions, the sum score of left and right hemisphere therefore is from 0 to 6.


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**Fig. 8.** Fazekas scale for WMLs. From left to right, Fazekas scale 1 (punctiform lesions), 2 (early confluent lesions), and 3 (confluent lesions) (not shown: score 0 = no lesions).
More importantly, there are suggestions that EPVSs relate to subtle cognitive deficits and even increased risk of dementia, independent of WML volume and presence of brain infarcts. One peculiar location of EPVSs is the hippocampal area, where they may be named hippocampal cavities or hippocampal cysts (see Fig. 17); some consider these to represent failure of closure of the hippocampal sulcus rather than EPVSs. Irrespective of their presumed origin and notwithstanding the interesting location, no clear role has been attributed to the presence of these cyst-like lesions in the hippocampal region.

PART II: STRUCTURAL NEUROIMAGING IN AD

Until recently, the diagnostic criteria for AD, most notably those set out by the National Institute of Neurologic Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA), were based on clinical symptoms only, and antemortem diagnostic certainty was limited to probable AD. In the 2011 revision, the NINCDS-ADRDA criteria include structural and functional biomarkers to provide evidence of AD pathophysiologic process for research purposes. Early diagnosis of AD even with the revised NINCDS-ADRDA criteria is by definition impossible, because the presence of a dementia syndrome is required. Dubois and colleagues propose to discard this severity threshold and reserve the term AD for the in vivo clinicobiological expression of the disease, encompassing the whole severity spectrum of its clinical course. Within this framework, the diagnosis of AD requires the presence of the core diagnostic criterion of early episodic memory impairment, as well as a minimum of 1 supporting biomarker,
derived from structural MR imaging, CSF, metabolic imaging, or genetics. The distinction between possible and probable AD, as made with the NINCDS-ADRDA criteria, is no longer made; instead a distinction is made between typical and atypical AD. Although these criteria are not yet widely accepted as clinical diagnostic criteria, they emphasize the increasing diagnostic role for structural neuroimaging in AD.

**Typical Presentation of AD**

The radiological hallmark finding of AD is cortical atrophy caused by neuronal degeneration and loss. Atrophy is diffuse, but more prominent in the temporal and parietal lobes, with the hippocampus most severely and disproportionately affected (Fig. 18). The primary motor and sensory cortices are relatively spared until late in the disease. Findings are bilateral and generally symmetric, but a certain degree of asymmetry may occur. White matter volume is also reduced, presumed to be secondary to Wallerian degeneration after cortical neuronal cell death. Ventricles and sulci are consequently also enlarged. Widening of the CSF spaces is most prominent surrounding the entorhinal cortex and the hippocampus (ie, the temporal horn and the choroid fissure). The temporospatial distribution of atrophy follows that of the histopathologic characteristics of AD. Neurofibrillary tangles and neuropil threads first appear in the transentorhinal and entorhinal areas (parahippocampal gyrus), increasing in density during the course of the disease and appearing in the hippocampus,
Fig. 13. Microbleed imaging. T1-weighted (left), T2-weighted (middle), and T2*-weighted (right) images. Cerebral microbleeds, depicted by arrows, are visualized only on the T2*-weighted image and not on the T1-weighted or T2-weighted images. The T2*-weighted image is susceptible to paramagnetic properties of hemosiderin, causing the microbleeds to appear as black dots of signal loss.

Fig. 14. Radiologic-pathologic correlation of cerebral microbleeds on MR imaging (3 T). Postmortem brain MR imaging shows on T2*-weighted imaging a hypointense focus on the gray-white matter interface (white arrow). MR image in the middle of the isolated tissue block containing this hypointense focus. Pathologic analysis of this tissue block (hematoxylin and eosin stain) shows macrophages containing hemosiderin (black arrows), confirming that the hypointense lesion on MR imaging is compatible with a microbleed.

Fig. 15. Microbleed location. T2*-weighted MR images showing microbleeds (arrows) in lobar (left), deep (middle), and infratentorial (right) locations.
Fig. 16. Silent brain infarct. T1-weighted (left), T2-weighted (right), and FLAIR images showing a lacunar infarct (arrow) in the left centrum semiovale in an asymptomatic 72-year-old man. Note that the lacune has signal intensity similar to CSF on all sequences and furthermore shows a hyperintense rim on the FLAIR sequence, indicating gliosis.

Fig. 17. T2-weighted images of prominent perivascular spaces (red arrows) in the region of the anterior commissure (left), in the centrum semiovale (middle) and the hippocampus (right).

Fig. 18. Seventy-six-year-old man with AD. Transverse (A) and coronal (B) T1-weighted images show cortical atrophy, more prominently in the parietal than in the frontal lobe (A), with disproportionate hippocampal atrophy (B).
further progressing from the limbic system to the temporal and parietal association cortices and eventually to the entire neocortex. Accordingly, focal entorhinal cortical and hippocampal atrophy occurs early and remains the most prominent feature in the disease process.

**Hippocampal atrophy**

Multiple studies confirm hippocampal volume loss in patients with AD compared with healthy controls. Sensitivity and specificity in distinguishing patients with AD from healthy controls are in the range of 85% and 88%, respectively. Findings regarding entorhinal cortex atrophy are similar, but not more accurate than hippocampal atrophy to distinguish patients with AD from healthy controls.

Although atrophy of the medial temporal lobe is commonly seen in patients with AD (70%–95%), it is also frequently seen in patients with minor cognitive impairment (MCI), although the frequency is lower (60%–80%) and extent of hippocampal atrophy is less pronounced. However, sensitivity and specificity of hippocampal atrophy to identify prodromal AD are only in the range of 70%, indicating limited clinical usefulness. Adding entorhinal cortex measurements may improve accuracy, although findings are inconsistent.

More recently, studies have focused on using hippocampal shape, rather than volume, to predict AD. Preliminary results are promising in that they show that hippocampal shape provides additional predictive value over hippocampal volume.

Hippocampal atrophy may be seen in other conditions, such as hippocampal sclerosis, mesial temporal sclerosis and temporal lobe epilepsy, ischemic insults to the hippocampus, and herpes simplex encephalitis. Furthermore, hippocampal atrophy is common in other types of dementia, such as dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and the Heidenhain variant of Creutzfeldt-Jakob disease (CJD). Consequently, diagnostic accuracy to distinguish AD from other dementias is considerably lower than from healthy controls.

**Medial temporal atrophy rating scale**

The most commonly used and well-validated method to assess hippocampal atrophy is the medial temporal atrophy (MTA) scale. This 5-point visual rating scale ranging from normal (score = 0) to severe atrophy (score = 4) assesses 3 easily recognizable structures on coronal MR images: the width of the choroidal fissure, the width of the temporal horn, and the height of the hippocampal body (Fig. 19, Table 3). A score of 0 to 1 may be considered normal in persons younger than 75 years, whereas a score of 2 may still be considered normal at older than 75 years. The MTA scale correlates well with both linear and volumetric measurements of the hippocampus and has reasonable interobserver agreement, with best results obtained when the scale is dichotomized (MTA = 0–1 vs MTA = 2–4).

In the absence of automated algorithms it is less time-consuming than manual volumetric assessment, but has greater interrater variability. For distinguishing patients with AD from non-dementia patients the MTA scale reaches around 85% sensitivity and specificity. When combined with the Mini Mental State Examination, high sensitivity and specificity of 95% and 98%, respectively, are obtained. MTA also reaches relatively high sensitivity for the diagnosis of other dementias (82%). However, as a consequence, its diagnostic performance in discriminating AD from other dementias is limited. Diagnostic accuracy using volumetric measurements is similar. However, volumetric imaging allows for serial measurements, which may be more specific than single measurements. As also mentioned in part I, from a meta-analysis including nearly 600 patients with AD and more than 200 healthy controls, the rate of hippocampal atrophy per year was estimated to be more than 3-fold higher in patients than in controls. Atrophy rates in patients with MCI are found to be higher than healthy controls but lower than patients with AD, suggesting a continuum of atrophy rate as a function of disease severity.

MTA needs to be rated in both hemispheres separately to assess the presence and degree of

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**Fig. 19.** Coronal T1-weighted images of the hippocampus for stages 0 to 4 of the MTA rating scale (see Table 3). Note progressive widening of the choroid fissure (from stage 1 onwards) and temporal horn (from stage 2 onwards), as well as hippocampal body volume loss (stages 3 and 4).
asymmetry. In a meta-analysis of 700 individuals with AD, 365 with MCI and more than 1000 healthy control individuals asymmetrical hippocampal volume was consistently found, with the hippocampus on the left being smaller than on the right. Asymmetry was least in the AD group, being reduced with disease progression. A certain degree of asymmetry of hippocampal volume may thus be expected, especially at earlier stages of the disease. Asymmetry of the hippocampus does therefore not exclude AD, although marked asymmetry suggests an alternative diagnosis, most notably FTD (see article elsewhere in this issue). However, certain atypical presentations of AD are also accompanied by marked asymmetrical atrophy of brain regions including the hippocampus.

**Atypical Presentation of AD**

Distinctly different patterns of brain atrophy from typical AD may be observed in patients with so-called atypical AD. These are often patients without the APOE ε4 genotype or those presenting younger than 65 years. Atrophy in these patients consists of focal cortical atrophy, which has an estimated relative prevalence of 6% to 14%. Hipocampal atrophy, the hallmark finding in typical AD, is less prominent and may even be absent.

Focal cortical atrophies are associated with the neuropathologic findings of typical AD, but are clinically and radiologically distinct in that a single cognitive domain, not related to memory, is predominantly affected and imaging shows atrophy in the brain region functionally associated to the affected domain. These syndromes include posterior cortical atrophy (PCA) and logopenic progressive aphasia (LPA), both being associated with a posterior pattern of atrophy. Despite more rapid disease progression than in typical AD, longitudinal studies indicate that the pattern of symptoms is relatively stable over time.

**Early-onset AD**

Early-onset AD is arbitrarily defined as AD with an onset of symptoms before the age of 65 years. Patients have been shown to have greater frontal volume loss, with sparing of the medial temporal area, compared with typical, late-onset AD. The disease progresses faster than late-onset AD, with a higher prevalence of neocortical function impairment. Compared with healthy controls, patients with early-onset AD have greater temporoparietal atrophy. One of the areas that is primarily affected in early-onset AD is the precuneus. In a study of 55 patients Karas and colleagues found disproportionate and independent precuneus atrophy in patients with early-onset compared with late-onset AD, and the relative absence of hippocampal atrophy (Fig. 20).

**PCA**

Patients with PCA have an early and prominent impairment of visual and visuospatial skills, with less prominent memory loss, and show associated atrophy of the parieto-occipital and posterior temporal cortices. Atrophy is generally asymmetrical, the right hemisphere being more affected than the left. In the largest histopathologic series to date of 27 patients, AD pathology was present in 14 (67%). AD-specific biomarkers such as amyloid-specific molecular imaging and CSF protein spectra are frequently found to be positive in patients with clinical and imaging findings of PCA, further supporting the concept of AD as the most likely underlying pathology.

Despite the predominance of AD pathology underlying PCA, sometimes coined visual AD, it is undecided whether it should be considered as part of the spectrum of presentations constituting AD or a distinct entity. The syndrome is therefore generally referred to as PCA, independent of the underlying neuropathology, which apart from AD also includes Parkinson disease, DLB, corticobasal degeneration, and prion-associated disease.

### Visual rating scale of MTA

<table>
<thead>
<tr>
<th>Choroid Fissure</th>
<th>Temporal Horn</th>
<th>Hippocampal Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTA = 0</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>MTA = 1</td>
<td>Widened</td>
<td>Normal</td>
</tr>
<tr>
<td>MTA = 2</td>
<td>Moderately widened</td>
<td>Widened</td>
</tr>
<tr>
<td>MTA = 3</td>
<td>Severely widened</td>
<td>Moderately reduced</td>
</tr>
<tr>
<td>MTA = 4</td>
<td>Severely widened</td>
<td>Severely reduced</td>
</tr>
</tbody>
</table>

keeping with the commonly underlying AD pathology, most patients eventually progress to a more global and diffuse pattern of cognitive impairment.

**LPA**

LPA has relatively recently been described as a clinically, neuropathologically, and radiologically distinct subtype of primary progressive aphasia (PPA). The syndrome is characterized by language disorders rather than memory impairment, which consists of slow speech and deficits in sentence repetition. Although speech is slow, it is linguistically still considered fluent because of the lack of grammatical or speech errors. On brain imaging there is marked asymmetrical atrophy of the posterior temporal cortex, including the posterior superior and middle temporal gyri, and the inferior parietal lobule, with the left hemisphere more affected than the right. During the course of the disease, atrophy progresses to the posterior cingulate and into the more anterior and medial parts of the temporal lobe, including the hippocampus. However, early in the disease hippocampal volume may be normal. Similar to patients with typical late-onset AD, most patients with LPA have positive AD molecular imaging and CSF biomarkers.

Clinically, LPA is difficult to distinguish from the other PPA subtypes, which have predominantly underlying FTD disease. Structural brain imaging plays an important role in differential diagnosis (see article elsewhere in this issue). In elderly individuals, cerebrovascular disease is the second most common pathology underlying dementia after AD.

**Differential Diagnoses of AD**

The most important differential diagnoses of AD, depending on age of onset, are vascular dementia (VaD), FTD (see article elsewhere in this issue), nonfluent and semantic subtypes of PPA, DLB (see article elsewhere in this issue), and CJD, in which MR imaging typically shows marked hyperintensity on T2-weighted sequences bilaterally in the caudate nucleus and the putamen, and to a lesser extent in the thalamus and neocortex (Fig. 21). Diffusion-weighted imaging, showing restricted diffusion in the affected gray matter, seems to be the most sensitive sequence to detect CJD-related abnormalities. Overall sensitivity and specificity are reported to be 60% to 90% and 80% to 95%, respectively. VaD is considered separately in the next section, addressing the complex interrelationship of cerebrovascular disease and AD. Especially in the early stages of the disease, when symptoms are often nonspecific, differential diagnosis may be challenging. However, accurate differentiation between the several types of dementia is of especially great relevance in the early stages, when future treatments might have their greatest effect and when most can be gained in terms of symptom reduction and increased quality of life.

**Cerebrovascular Disease and AD**

In elderly individuals, cerebrovascular disease is the second most common pathology underlying dementia after AD.

**VaD**

VaD is a heterogeneous entity, including large and small vessel disease, involving the gray or white matter, and which may arise from local or systemic causes. The most common underlying pathology is small vessel disease, leading to diffuse confluent white matter changes (also known asBinswanger disease) and multiple lacunar infarcts of the deep white and (notably the thalamic) gray matter. Confluent WMLs are caused by incomplete infarction of the white matter, leading to demyelination,
edema, gliosis, spongiosis, and breakdown of the ependymal lining.63 Typically, the subcortical U-fibers are spared. When infarction of the deep perforating arteries is complete, lacunar infarcts occur, which are visualized on MR imaging as small lesions with signal intensity of CSF on all sequences, surrounded by a rim of T2-weighted hyperintensity. A multilacunar state is also known as état lacunaire, not to be confused with état criblé, which is the term used for multiple EPVSs in the basal ganglia, often accompanied by confluent WMLs. Both states are considered pathologic and manifestations of small vessel disease.

Large vessel disease manifests as multiple strategic infarcts, cortical laminar necrosis, or hippocampal necrosis.

Diagnostic criteria for VaD
Because a causative link between cerebrovascular disease and dementia generally cannot be established with certainty, and cerebrovascular changes are common in healthy elderly individuals, as outlined in the first part of this article, there are strict criteria to diagnose VaD set out by the National Institute of Neurologic Disorders and Stroke and Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN).90 A patient must meet the criteria of a dementia syndrome, have evidence of cerebrovascular disease on clinical examination and on imaging, and there has to be a temporal relationship between the onset of dementia and cerebrovascular disease. Radiological criteria are crucial to diagnosis and specified in detail,91 requiring both topographic and severity criteria to be met. Confluent WMLs need to involve at least 25% of the total white matter to reach the diagnosis of VaD (see Fig. 8). Lacunar infarcts need to involve multiple basal ganglia and the frontal white matter, and thalamic lesions need to be bilateral. Strategic large vessel infarcts meet the criteria when they involve the following territories: bilateral anterior cerebral artery, paramedian thalamic, inferior medial temporal lobe, parietotemporal and temporo-occipital association areas and angular gyrus, superior frontal and parietal watershed areas in the dominant hemisphere.91,92

VaD and AD
There seems to be a complex interrelationship between AD and cerebrovascular disease that extends beyond the coexistence of these 2 disease processes. Imaging features of small vessel disease are seen at higher frequency in AD than in healthy controls. Cerebrovascular disease and AD often coexist, whereas stroke often exacerbates preexisting, sometimes previously subclinical,
disease. Furthermore, AD and VaD share common risk factors, such as diabetes and hypertension, as well as genetic factors for brain tissue vulnerability (presenilins, amyloid precursor protein, APOE genes). In patients with MCI, MTA predicts cognitive function better than small vessel disease, although the severity of baseline white matter hyperintensities is a significant predictor of cognitive decline.93

Microbleeds, considered to be a manifestation of CAA, are seen at high frequency in patients with AD (see Figs. 13 and 15). CAA is a microangiopathy with β-amyloid deposition in the vessel walls. On brain imaging, the presence of 3 or more microbleeds (at 1.5 T) in a lobar distribution is suggestive of CAA,94 and other features include subpial siderosis and evidence of past lobar hemorrhage. Although sporadic CAA is commonly seen in elderly individuals, being the leading cause of lobar hemorrhage, in its severe form it is also recognized as a risk factor for dementia. This condition typically constitutes a subcortical VaD, but severe CAA is also considered a feature of AD, sharing the APOE ε4 allele as a common risk factor. The fact that AD patients with many microbleeds perform worse on neuropsychological tests and have higher levels of Aβ-1-42 in their CSF has led to the

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<table>
<thead>
<tr>
<th>Sequence</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D T1-weighted</td>
<td>Atrophy</td>
</tr>
<tr>
<td></td>
<td>Coronal plane: hippocampal atrophy</td>
</tr>
<tr>
<td></td>
<td>Sagittal plane: precuneus atrophy</td>
</tr>
<tr>
<td>Two-dimensional (2D)/3D</td>
<td>Atrophy, white and gray matter signal abnormalities</td>
</tr>
<tr>
<td>T2-FLAIR</td>
<td>Coronal plane: hippocampal signal abnormalities</td>
</tr>
<tr>
<td></td>
<td>White and gray matter signal abnormalities, particularly thalamus and posterior fossa</td>
</tr>
<tr>
<td>2D transverse TSE/FSE</td>
<td>Diffusion restriction</td>
</tr>
<tr>
<td>T2-weighted</td>
<td>Microbleeds, subpial hemosiderosis</td>
</tr>
<tr>
<td>2D transverse diffusion-weighted imaging</td>
<td>Diffusion restriction</td>
</tr>
<tr>
<td>2D transverse T2*-weighted</td>
<td>Microbleeds, subpial hemosiderosis</td>
</tr>
</tbody>
</table>

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Fig. 22. For optimal assessment of the hippocampus, coronal reconstructions need to be made perpendicular to the plane of the hippocampus. The thin line is aligned along the hippocampus in the sagittal T1-weighted image (left), with the thick and dashed lines indicating the plane of coronal reconstruction. Right-hand image shows the resulting coronal section at the level of the thick line.
idea that CAA reflects the combination of AD and vascular damage.\textsuperscript{63}

It is not clear how to interpret the interrelationship between vascular disease and AD, whether they happen to coexist in 1 patient, or whether they have a synergistic relationship aggravating each other’s effect.

**Imaging Protocol and Report in AD**

We recommend that the MR imaging scanning protocol includes T1-weighted, T2-weighted, T2-FLAIR, diffusion-weighted, and T2*-weighted sequences (Table 4). Contrast is not indicated routinely, although it is indicated if granulomatous disease, vasculitis, and infection are considered as differential diagnoses.

Three-dimensional (3D) T1-weighted sequences are best suited to assess presence and degree of atrophy and can be reformatted in any plane, including the coronal plane, aligned perpendicular to the plane of the hippocampus, to assess MTA (Fig. 22) and the sagittal plane to assess atrophy of the precuneus in early AD. WMLs are best visualized on a T2-FLAIR sequence, preferably using a 3D sequence, which again allows for the reconstruction in the coronal plane to scrutinize the hippocampus for focal signal abnormalities, and

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**Box 4**

**Summary of structural MR imaging findings in the (differential) diagnosis of AD**

**Typical AD**
- Disproportionate hippocampal atrophy with temporoparietal atrophy
- Relative sparing of the primary motor and sensory cortex
- Bilateral, more or less symmetric
- Microbleeds in a lobar, subcortical distribution

**Atypical AD**
- No or little hippocampal atrophy
- Focal cortical atrophy
  - Precuneus: early-onset AD
  - Parieto-occipital and posterior temporal lobe: PCA
  - Posterior temporal cortex and the inferior parietal lobule: LPA
- Marked asymmetry of atrophy
  - Right more than left: PCA
  - Left more than right: LPA

**FTD**
- Bilateral frontal and temporal atrophy with anterior to posterior gradient
  - Left more than right anterior perisylvian region: NFPA
  - Left more than right ventrolateral temporal region: SD
- (Asymmetrical) hippocampal atrophy, more pronounced anteriorly
- Disproportionate widening of the frontal horns.
- Relative sparing of the parietal and occipital lobes

**CJD**
- T2-hyperintensity and diffusion restriction bilaterally in the caudate nucleus and putamen, and to a lesser extent in the thalamus and neocortex

**DLB**
- Medial temporal lobe and GCA
- Relative sparing of the primary motor and sensory cortex
- Less extensive than AD when accounting for disease severity

**Abbreviations:** NFPA, non-fluent progressive aphasia; SD, semantic dementia.
significantly reduces the CSF flow artifact in the posterior fossa and third ventricle. However, because of reduced sensitivity of FLAIR in the posterior fossa and the diencephalon, specifically the thalamus, a standard T2-weighted sequence also needs to be included. Diffusion-weighted imaging allows for the detection of recent ischemic changes, as well as for visualization of those areas of diffusion restriction characteristic of CJD. T2*-weighted imaging, with low flip angle and long echo time to increase susceptibility sensitivity, is required to detect microbleeds occurring in the context of CAA.

Reporting MR imaging findings in dementia includes both those pointing toward the pathology underlying the dementia syndrome and those suggesting an alternative cause of neurocognitive degeneration. The latter include focal abnormalities such as brain tumor or subdural hematoma. The hippocampus needs to be scrutinized for signal abnormality on T2-weighted sequences to diagnose ischemia or sclerosis. Areas of diffusion restriction may indicate pathology such as acute ischemia, herpes simplex encephalitis, alcoholic encephalopathy, or CJD. T2-weighted hyperintensity in certain brain regions may point to a specific diagnosis, such as in the periaqueductal gray or mammillary bodies in case of alcoholic encephalopathy.

The radiological report further needs to include a structured and standardized assessment of the GCA, the medial temporal lobe and WML load, according to, for instance, the GCA, MTA, and ARWMC visual rating scales, respectively (see Tables 1–3). Atrophy should always be rated on the same imaging sequence, preferably the FLAIR or T1-weighted sequence. The degree of asymmetry, as well as focal regions of atrophy, should be reported separately. Both the number and distribution of microbleeds needs to be reported. Large and small vessel cerebrovascular changes need to be specified according to the topographic and severity operational NINDS-AIREN criteria to enable diagnosis of VaD.

A summary of findings (Box 4) aids to reach a likely and differential diagnosis of the disease underlying the patient’s dementia syndrome.

REFERENCES


