Pathological ageing of the brain: 
a neuroimaging perspective

António José de Bastos Leite
Apart from patients belonging to a multicentric clinical trial, the clinical examination of the remaining subjects was done at the Alzheimer Centre and the corresponding magnetic resonance imaging scans were performed at the Department of Radiology, VU University Medical Centre (VUmc), Amsterdam, the Netherlands.


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Cover: Untitled III, 1982; Willem de Kooning
(Dutch-American painter; 1904–1997)

“...the possible role of dementia in the changes that occur in de Kooning's artistic production...
...the later paintings may very well be distillations of earlier, more complex works, into the simple lines...”


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“The past is full of uncertainties, woven of controversial interpretations, distorted by the prism of passions... Future, especially when regarded as self-denying... may ennoble the present's directives...”

Reynaldo dos Santos (Portuguese physician; 1880–1970)
## Contents

**Chapter 1**  General introduction, aim, and outline of the thesis  

**Chapter 2**  Pathological ageing of the brain: an overview  

2.1 The problem  

2.2 Choice of imaging modality  

2.3 Alzheimer’s disease  

2.3.1 Imaging findings in Alzheimer’s disease  

2.4 Mild cognitive impairment  

2.5 Alzheimer’s disease with cerebrovascular disease, and other pathologies  

2.6 Dementia with Lewy bodies  

2.7 Parkinson’s disease with dementia  

2.8 Frontotemporal lobar degeneration  

2.9 Dementia and atypical parkinsonian syndromes  

2.10 Vascular dementia  

2.10.1 Imaging findings in vascular dementia  

2.11 Role of neuroimaging in the differential diagnosis of dementia  

2.12 New magnetic resonance techniques and molecular imaging  

**Chapter 3**  Alzheimer’s disease  

3.1 Hippocampal sulcus width and cavities: comparison between patients with Alzheimer’s disease and nondemented elderly subjects
Chapter 1

General introduction, aim, and outline of the thesis
Brain ageing can be classified into successful, usual, and pathological ageing. The most severe consequence of pathological ageing is dementia. Alzheimer’s disease is the most common cause of dementia and is currently considered, by most, as a neurodegenerative disease. Vascular abnormalities are the second most common cause of cognitive impairment, although there is an increasing awareness that both degenerative and vascular pathology usually coexist.

The aim of the thesis is to present a neuroimaging perspective of pathological ageing especially focusing on vascular aspects.

In chapter 2, a review covers the usefulness of several neuroimaging techniques and gives an overview of brain disorders causing dementia. The following chapters correspond to original research studies using magnetic resonance (MR) imaging to detect or assess the severity of brain abnormalities in elderly subjects. Chapter 3 focuses on medial temporal lobe atrophy, a structural neuroimaging feature suggestive of Alzheimer’s pathology. Chapter 4 deals with vascular dementia, namely with the detection of thalamic lesions, the prevalence and clinical relevance of infratentorial abnormalities, and with the relative contribution of medial temporal lobe atrophy and vascular pathology to cognitive impairment. Finally, in chapter 5, a new functional MR perfusion-weighted technique, pulsed arterial spin labelling, is explored to quantify cerebral blood flow in elderly subjects with white matter hyperintensities.
Chapter 2

Pathological ageing of the brain: an overview

António J. Bastos Leite, Philip Scheltens, Frederik Barkhof

Abstract

The number of elderly people is increasing and, therefore, an increase in neurodegenerative and cerebrovascular disorders causing dementia is expected. Alzheimer’s disease is the most common cause of dementia. Vascular dementia, dementia with Lewy bodies, and frontotemporal dementia are the most frequent causes after Alzheimer’s disease, but a large proportion of patients have a combination of degenerative and vascular pathology in the brain. Characteristic magnetic resonance (MR) imaging findings can contribute to the identification of different diseases causing dementia. Structural neuroimaging in dementia is focused on detection of brain atrophy, especially in the medial temporal lobe, for which coronal high resolution T1-weighted images perpendicular to the long axis of the temporal lobe are extremely useful. For the detection of cerebrovascular pathology, the MR imaging protocol should also include axial T2-weighted images, axial fluid-attenuated inversion recovery or proton density-weighted images, and axial gradient-echo T2*-weighted images. In addition, single photon emission computed tomography and positron emission tomography may have added value in the diagnosis of dementia and may become more important in the future, due to the development of radioligands for in vivo detection of Alzheimer’s pathology. New functional MR techniques and serial volumetric imaging studies to identify subtle brain abnormalities may also provide surrogate markers for pathologic processes occurring in diseases causing dementia and, in conjunction with clinical evaluation, may enable to reach more rigorous and early diagnoses, approaching the accuracy of neuropathology.
2.1 The problem

The number of elderly people is increasing rapidly, and this tendency will continue in the near future. As a consequence of the aged population, an increase in neurological diseases is expected, such as neurodegenerative dementias, cerebrovascular disease, and movement disorders.5

In this review, we will focus on dementia, the most severe consequence of pathologic brain ageing. The definition of dementia recommended by the American Academy of Neurology4 as proposed in the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-IIIR)5 states:

“the essential feature of dementia is impairment in short and long term memory, associated with impairment in abstract thinking, impaired judgment, other disturbances of higher cortical function, or personality change… severe enough to interfere significantly with work or usual social activities…”

Since dementia is a growing health problem6,7 with an enormous impact on society, measures should be taken to restructure the diagnostic algorithms and rehabilitation support.7 From the diagnostic point of view, structural neuroimaging with either a noncontrast computed tomography (CT) or magnetic resonance (MR) imaging is already recommended for the initial evaluation of patients with dementia,4 and is increasingly being used to support the clinical diagnosis beyond the traditional exclusionary approach.8 Additionally, there is an increasing urge for an early and more accurate diagnosis of dementia, given the current availability of therapies, such as cholinesterase inhibitors, that for the most frequent dementias,9,12 improve or stabilize cognition, treat behavioural symptoms, and delay institutionalization.13
Moreover, the recognition of conditions that may precede dementia, such as mild cognitive impairment or vascular cognitive impairment,\textsuperscript{14-17} which may be more amenable to intervention, also raises the importance of an earlier diagnosis.

In the future, the introduction of new therapies, for example the anti-amyloid drugs\textsuperscript{18} for Alzheimer’s disease, will reinforce the need of a more rigorous and early diagnosis, given the expectation that the earlier a specific therapy can be started, the more effective it will be in preventing or slowing disease progression.

Alzheimer’s disease is the most common cause of dementia, with prevalence rates higher than 40\% at the age of 85 and a total annual cost approaching 70 billion dollars in the United States of America.\textsuperscript{19-21} It is projected that the prevalence will nearly quadruple over the next 50 years, by which time approximately 1 in 45 Americans will be affected with this disease.\textsuperscript{7}

A large proportion of patients with dementia have a combination of degenerative and vascular pathology in the brain,\textsuperscript{22-30} and there are multiple causes of dementia other than Alzheimer’s disease. Vascular dementia, dementia with Lewy bodies, and frontotemporal dementia are the most common causes after Alzheimer’s disease. Parkinson’s disease can also be associated with dementia, as well as some rare atypical parkinsonian syndromes.\textsuperscript{31} Argyrophilic grain disease is probably an underestimated cause of dementia in old patients.\textsuperscript{32} Huntington’s disease is an autosomal dominant inherited condition characterized by chorea, behavioural disturbances and cognitive deterioration,\textsuperscript{31} whose genetic defect is already known.\textsuperscript{33} One of the main features of prion diseases, like Creutzfeldt-Jacob disease, is rapidly progressive dementia.\textsuperscript{31} Cases of amyotrophic lateral sclerosis and parkinsonism-dementia complex, the so-called Lytico-Bodig disease, are extremely rare and occur almost exclusively in the Chamorran population of southern Guam.\textsuperscript{31, 34} Other causes of dementia include
infections, inflammatory white matter diseases, metabolic disorders, drugs and toxins, heavy metal poisoning, lipophilic substances, renal insufficiency and dialysis, paraneoplastic syndromes, tumours, radiotherapy, cranial trauma, hydrocephalus, and idiopathic calcinosis of Fahr.31

Although there are established clinical criteria for the diagnosis of diseases causing dementia,35,36 the definite diagnosis was always believed to be histopathological. Currently, not even neuropathology can be considered a “gold standard” anymore. There are considerable discrepancies between different post-mortem pathologic criteria and clinical information is still needed for a correct classification.39 For example, Polvikoski et al40 in an autopsy-controlled, prospective, population-based study on the prevalence of Alzheimer's disease in very old people (≥ 85 years) found that 55% of the individuals with neuropathological criteria for Alzheimer's disease were either nondemented during life or classified as having vascular dementia. Conversely, they also found that 35% of those with clinical Alzheimer's disease did not fulfil the neuropathological criteria.

2.2 Choice of imaging modality

Computed tomography without contrast is sufficient to rule out almost all surgically manageable causes of dementia,41 but except in cases where MR is contraindicated, not available, or not affordable, there is no reason to prefer CT over MR.42 When CT is the only alternative, axial thin slices parallel to the long axis of the temporal lobe (using a negative scan angle) should be obtained.43

Magnetic resonance is the preferred imaging modality for dementia, and the protocol should include at least axial T2-weighted images (T2-WI), axial fluid-
attenuated inversion recovery (FLAIR) or proton density-weighted images (PD-WI), axial gradient-echo T2*-weighted images (T2*-WI), and coronal high resolution T1-weighted images (T1-WI) perpendicular to the long axis of the temporal lobe. Axial T2-WI, FLAIR, and PD-WI are crucial for the detection of cerebrovascular pathology and white matter changes. Axial T1-WI facilitate the distinction between lacunar infarcts (hypointense on T1-WI) and focal incomplete infarcts (isointense on T1-WI), and are useful for the assessment of global brain atrophy. Coronal high resolution T1-WI are extremely useful to evaluate medial temporal lobe atrophy (MTA). Axial gradient-echo T2*-WI are needed to detect microbleeds and calcifications.31

Functional imaging techniques have also been applied to the diagnosis of dementia.42, 44-46 Single photon emission computed tomography (SPECT) evaluates brain perfusion, but does not yield absolute quantification of blood flow, and positron emission tomography (PET) is currently used almost exclusively to evaluate the metabolism of glucose in the brain. At present, SPECT and PET are second-line investigations used when MR is inconclusive (e.g., in the early phases of Alzheimer’s disease and frontotemporal dementia). In the future, SPECT and PET may become more important, especially due to the development of radioligands for in vivo detection of Alzheimer’s pathology.47,48 Currently, PET imaging is already reimbursed in the United States of America for dementia patients who have atypical symptoms that preclude a clinical diagnosis.

2.3 Alzheimer’s disease

The criteria of the National Institute of Neurologic, Communicative Disorders and Stroke (NINCDS) – Alzheimer’s disease and Related Disorders Association
(ADRDA) for the diagnosis of Alzheimer's disease include insidious onset and progressive impairment of memory and other cognitive functions in the absence of motor, sensory, or coordination deficits early in the course of disease. They also state that the diagnosis can not be made with laboratory tests, which should be used to identify other possible causes of dementia. Therefore, the NINCDS-ADRDA criteria recognize the lack of a single “gold standard” for the identification of Alzheimer's disease as well as the insufficient knowledge about its cause, except for the extremely rare familial autosomal dominant inherited cases with early onset, whose genetic defects were discovered in the early nineties.

The apolipoprotein E-ε4 (APOE-ε4) allele is genetically associated with the most common late onset familial and sporadic forms of Alzheimer's disease. Although the specificity and positive predictive value of the APOE-ε4 allele were found to be 100% in some series, it is now accepted that APOE genotyping does not provide sufficient sensitivity or specificity to be used as a single diagnostic test.

The neuropathological characteristics of Alzheimer's disease include intraneuronal neurofibrillary tangles (NFTs) and neuropil threads consisting of paired helical filaments whose main component is abnormally phosphorylated tau protein; extracellular deposits of β-amyloid, some associated with dystrophic neurites, activated microglia, and reactive astrocytes – neuritic plaques (NPs); granulovacuolar degeneration; Hirano bodies; corpora amylacea; increased accumulation of lipofuscin in neurons; loss of neurons and synapses; and amyloid angiopathy. NFTs and NPs are the most important pathologic features of this disease. NFTs also occur in other dementias, but their composition varies according to the isoform of abnormal tau protein. NPs are more specific for Alzheimer's disease than other aggregations of β-amyloid.
Braak and Braak\textsuperscript{59} proposed a neuropathological staging of Alzheimer's disease based on the distribution, pattern and density of neurofibrillary changes. These changes develop in only a few types of pyramidal cells, first in the transentorhinal cortex (stages I and II), and then in the entorhinal cortex, hippocampal formation (stages III and IV) and neocortex (stages V and VI), progressing hierarchically in the inverse sequence of cortical myelination, predominantly in neurons with a high density of lipofuscin. They also proposed that the stages of progressive cortical destruction correlate with clinical status of patients with Alzheimer's disease. Stages I and II (transentorhinal stages) are considered to represent the presymptomatic phase of Alzheimer's disease, stages III and IV (limbic stages) are the counterpart of clinically incipient Alzheimer's disease, and stages V and VI (neocortical stages) represent the fully developed cases.\textsuperscript{60,61} Staging classifications for the progression of amyloid deposition were also proposed,\textsuperscript{62,63} but the initial neurofibrillary changes, which may occur several decades before dementia, are believed to indicate the beginning of Alzheimer's disease.\textsuperscript{64}

Current histological criteria for the diagnosis of Alzheimer's disease\textsuperscript{65} are based on both the density of NPs and NFTs in the neocortex and limbic areas, combining previous criteria based only on number of NPs in the neocortex\textsuperscript{66} and the staging criteria of Braak and Braak for neurofibrillary changes.\textsuperscript{59}

Two neural networks are particularly vulnerable to progression of Alzheimer's pathology early in the course of disease.\textsuperscript{67} One is the Papez circuit,\textsuperscript{68} whose disruption starts in the entorhinal cortex and subiculum due to pathology affecting cells that interconnect the hippocampal formation with other brain structures. This results in isolation of the hippocampal formation from most of its connections and accounts for the memory impairment in Alzheimer's disease.\textsuperscript{69} The other affected network is the cortical cholinergic system that originates in neurons within the
basal forebrain, with selective neuronal loss in the substantia innominata’s nucleus basalis of Meynert. It forms the anatomical basis of the cholinergic hypothesis proposed in the mid-seventies for Alzheimer’s disease, and explains the decrease of acetylcholine in the brain of patients with Alzheimer’s disease and other dementias, which is partially responsible for the cognitive and behavioural deficits. Moreover, it serves as the rationale for the use of cholinesterase inhibitors.

2.3.1 Imaging findings in Alzheimer’s disease

Structural neuroimaging in Alzheimer’s disease is focused on detection of MTA, particularly of the hippocampus, parahippocampal gyrus (including the entorhinal cortex), and amygdala. MR and CT are indeed sensitive to MTA in Alzheimer’s disease, correlating with Alzheimer’s pathology at postmortem. MTA can be assessed using visual rating scales, linear measurements of temporal lobe structures, and volumetry of the hippocampus. Volumetric analyses are time-consuming and therefore not well suited for clinical practice. Moreover, MR studies comparing volumetric and visual assessment of MTA found that there is no advantage of volumetry in differentiating patients with Alzheimer’s disease from controls. Linear measurements of the temporal horns are reliable, can be used in routine clinical settings, and have the advantage of being applicable both to CT and MR. The visual rating of MTA is based on subjective evaluation of the choroidal fissure width, the temporal horn width, and the hippocampal height (table 1) using coronal high resolution T1-weighted images perpendicular to the long axis of the temporal lobe (Figure 1). It is easily applicable in clinical practice, but slightly observer dependent. In a recent review of studies using visual rating scales or linear measurements to evaluate MTA, the weighted sensitivity and specificity for detection of patients with Alzheimer’s disease (versus controls) was 85% and 88%, respectively.
Figure 1. Coronal high-resolution T1-weighted images perpendicular to the long axis of the temporal lobe showing the different degrees of medial temporal lobe atrophy (MTA), according to the visual rating scale proposed by Scheltens et al.\textsuperscript{76} (a) absence of atrophy (MTA = 0), (b) minimal atrophy (MTA = 1), (c) mild atrophy on the right side (MTA = 2), severe atrophy on the left (MTA = 4), (d) moderate atrophy (MTA = 3), and (e) severe atrophy (MTA = 4).
Table 1. Visual rating scale for medial temporal lobe atrophy

<table>
<thead>
<tr>
<th>Score</th>
<th>Width of Choroidal Fissure</th>
<th>Width of Temporal Horn</th>
<th>Height of Hippocampus</th>
</tr>
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<tbody>
<tr>
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<td>Normal</td>
<td>Normal</td>
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<tr>
<td>1</td>
<td>↑</td>
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= increased, ↓ = decreased. Reproduced with permission of Scheltens et al.\textsuperscript{76}

Because the initial neuropathological changes in Alzheimer’s disease occur in the entorhinal cortex, some volumetric MR studies compared the discriminative power of measurements in both the entorhinal cortex and hippocampus to identify patients with early stages of Alzheimer’s disease. Although they found that both regions are affected, they did not find advantage by assessing the entorhinal cortex as an alternative for the hippocampus.\textsuperscript{84,85}

Besides the existence of MTA, the most important structural imaging feature of Alzheimer’s disease is progression of such atrophy. Jack et al.\textsuperscript{86} found an yearly decline in hippocampal volume approximately 2.5 times greater in patients with Alzheimer’s disease than in normal aged subjects, and a relationship exists between memory loss and hippocampal damage across the spectrum from normal ageing to dementia.\textsuperscript{87} However, neuroanatomical changes over time may be too mild, diffuse, or topographically complex to be detected by simple visual inspection or even with manually traced measurements of regions of interest. New serial volumetric imaging techniques developed in the past few years represent an added value to identify subtle structural brain changes (Figure 2), which have brought extensive neocortical abnormalities to the fore.\textsuperscript{88,89} In addition, voxel based morphometry (VBM), a voxel-wise, fully automated and unbiased technique that enables comparisons of
the local brain tissue concentration between groups of subjects,\textsuperscript{90} when applied to compare nondemented elderly controls with patients with Alzheimer’s disease, demonstrates in these patients: MTA, global cortical atrophy (with relative sparing of the sensorimotor cortex, occipital poles, and cerebellum), as well as atrophy of the caudate nuclei and medial thalami.\textsuperscript{91} Furthermore, VBM shows that patients with early onset Alzheimer’s disease have greater neocortical atrophy at the temporoparietal junction, but less hippocampal atrophy, than patients with late onset Alzheimer’s disease.\textsuperscript{92}

\textbf{Figure 2.} Coronal high resolution T1-weighted images of a patient with early onset Alzheimer’s disease: (a) baseline scan, (b) scan repeated after 12 months, (c) voxel compression mapping overlay displaying brain volume loss (during the interval of 12 months) in green, and expansion of the cerebrospinal fluid volume in yellow (courtesy of Jasper Sluimer and Nick Fox).

MR studies using thin-section coronal T2-WI have suggested it is possible to demonstrate shrinkage of the substantia innominata, a finding more pronounced in patients with Alzheimer’s disease who respond to cholinesterase inhibitors, but that may also occur in other dementias.\textsuperscript{93-95}

SPECT and PET studies may show hypoperfusion and hypometabolism in several brain regions of patients with Alzheimer’s disease.\textsuperscript{96,97} Studies comparing SPECT with structural MR for the differentiation between patients with Alzheimer’s disease
and nondemented controls almost always found temporoparietal hypoperfusion in Alzheimer’s disease, but there was no clear advantage of SPECT over MR, even though the combination of both significantly improved discrimination. Moreover, the use of MR alone was found to be the most cost-effective approach.

2.4 Mild cognitive impairment

Mild cognitive impairment is a clinical condition characterized by a prominent but nearly isolated impairment in memory, while other cognitive functions are consistent with normal ageing. Mild cognitive impairment is considered a transitional stage between normal ageing and Alzheimer’s disease, but there is some degree of overlap with both. It seems to represent a heterogeneous group of patients, some progressing to dementia or Alzheimer’s disease, and others stabilizing or even reversing to normal.

Identification of patients with mild cognitive impairment is an area where modern imaging techniques might yield the greatest added value, since clinical criteria may be poorly specific. Hippocampal atrophy determined by MR volumetry was found to predict conversion to Alzheimer’s disease, and entorhinal cortex volumetry might even better distinguish mild cognitive impairment from Alzheimer’s disease. Visual rating of MTA is a good alternative to hippocampal volumetry, although not so accurate. Finally, VBM shows that patients with mild cognitive impairment have less grey matter in the medial temporal lobe, insula, and thalamus than normal elderly controls, but more grey matter in the parietal association areas and cingulate cortex than patients with Alzheimer’s disease.
Functional neuroimaging studies can also accurately identify converters from mild cognitive impairment to Alzheimer’s disease, and even from normal ageing to mild cognitive impairment.\textsuperscript{106-109} Combinations of serial volumetric studies and cognitive or functional imaging assessments may prove to be the best option in the near future.\textsuperscript{110-112} Prospective studies on the effect of white matter lesions in conversion from mild cognitive impairment to dementia are also warranted,\textsuperscript{113, 114} as well as on their impact in transition to disability.\textsuperscript{115}

\section*{2.5 Alzheimer’s disease with cerebrovascular disease, and other pathologies}

The most frequent combination of brain pathologies in dementia is that which results from both degenerative and vascular lesions,\textsuperscript{23-25,27-30} but there are also combinations among different types of degenerative pathologies, namely between Alzheimer’s disease, Parkinson’s disease, and dementia with Lewy bodies.\textsuperscript{22,27,29}

Changes in the endothelium, disruption of the blood-brain barrier, and amyloid angiopathy occur in Alzheimer’s disease, but it is not known whether these vascular changes represent a cause, an effect, or even the consequence of a common pathogenesis of Alzheimer’s disease and cerebrovascular disease.\textsuperscript{116} Nevertheless, recent studies suggest that cerebrovascular disease and late-onset Alzheimer’s disease share common risk factors.\textsuperscript{117}

The recognition of additional pathologies in Alzheimer’s disease is important, because they can lower the threshold for dementia or increase its severity, and may represent an independent target for treatment. For example, the burden of Alzheimer’s pathology is lower in cases of Alzheimer’s disease mixed with other
pathologies than in cases of pure Alzheimer's disease, and patients with brain infarcts fulfilling neuropathological criteria for Alzheimer's disease have poorer cognitive function and higher prevalence of dementia than those without infarcts, especially when they have lacunae in the basal ganglia, thalamus, or in deep white matter. Dementia may also occur in a considerable proportion of post-stroke patients, particularly in those with MTA. Moreover, when there is neuroimaging evidence of mixed pathology (degenerative and vascular) (Figure 3), atrophy predicts or correlates better with dementia than cerebrovascular disease, and may even result from both ischaemic and degenerative injuries.

Figure 3. Coronal T2-weighted image showing severe medial temporal lobe atrophy and extensive white matter hyperintensity, which is suggestive of combination between degenerative and vascular brain pathology.

Neuroimaging is very useful for the diagnosis of cerebrovascular disease, particularly of small vessel disease, which is frequently not suspected clinically and more
often associated with dementia than large vessel disease.\textsuperscript{128} MR signal abnormalities of deep white and grey matter\textsuperscript{129} occurring in Alzheimer's disease, vascular dementia, and usual ageing can be considered as a surrogate marker for small vessel disease.\textsuperscript{8,130} Currently, it is unclear whether cerebrovascular disease, as depicted by MR imaging, should be a separate target for treatment in patients with Alzheimer's disease, but this seems to be quite plausible.

### 2.6 Dementia with Lewy bodies

Formerly considered a variant of Alzheimer's disease, dementia with Lewy bodies is now recognized a common degenerative dementia.\textsuperscript{131} It is clinically characterized by an often rapidly progressive clinical syndrome including dementia, fluctuations in cognitive functioning, and spontaneous parkinsonism. Attention deficits, disproportionate problem solving, and visuospatial difficulties are often prominent and early in the course of disease. Persistent well-formed visual hallucinations are also a feature with diagnostic significance. The patients are particularly responsive to cholinesterase inhibitors, but neuroleptic medication is contraindicated.\textsuperscript{10,37}

Brain stem or cortical Lewy bodies (LB) are the only features considered essential for a pathologic diagnosis of dementia with Lewy bodies, although Lewy-related neurites, Alzheimer's pathology, and spongiform changes may also be seen.\textsuperscript{37} The precise nosological relationships between dementia with Lewy bodies, Alzheimer's disease and Parkinson's disease with dementia are not yet completely clarified. NPs are frequent in both dementia with Lewy bodies and Alzheimer's disease, but neocortical NFTs are rare in dementia with Lewy bodies. In addition, the main component of LB, which are either present in dementia with Lewy bodies, Parkinson's disease, and in Parkinson's disease with dementia, is $\alpha$-synuclein rather than abnormal tau protein.\textsuperscript{37,131}
Magnetic resonance studies comparing dementia with Lewy bodies, Alzheimer’s disease, vascular dementia, and healthy elderly controls found that although MTA was more frequent and severe in all dementia groups than in controls, patients with dementia with Lewy bodies had significantly lower MTA scores and larger temporal lobe, hippocampal, and amygdala volumes than those with Alzheimer’s disease. Therefore, in the differentiation of dementia with Lewy bodies from Alzheimer’s disease, the absence of MTA may be considered suggestive of dementia with Lewy bodies.\textsuperscript{132,133} Conversely, atrophy of the putamen is a feature of dementia with Lewy bodies, but not of Alzheimer’s disease.\textsuperscript{134}

Functional studies found occipital hypoperfusion and hypometabolism in dementia with Lewy bodies\textsuperscript{135,136} that do not seem to be associated with occipital atrophy.\textsuperscript{137}

2.7 Parkinson’s disease with dementia

Contrary to the initial assumption that cognitive function would be spared, it is now recognized that patients with Parkinson’s disease may develop dementia, as their age increases. Clinically, Parkinson’s disease with dementia is characterized by an early impairment of executive functions, but there are no formal criteria for the diagnosis yet.\textsuperscript{138} When fully developed, Parkinson’s disease with dementia and dementia with Lewy bodies overlap both clinically and pathologically. If the previous history is unknown, patients with each of these disorders may be indistinguishable. Currently, an arbitrary rule used for their distinction is to consider that in dementia with Lewy bodies the onset of dementia should occur within 12 months of parkinsonism, and in Parkinson’s disease with dementia only after more than 12 months.\textsuperscript{131,138}
The underlying pathology of Parkinson's disease with dementia has been a matter of controversy, both in terms of site and type, and is currently classified into three groups: subcortical pathology, Alzheimer's type pathology, and LB type pathology. The main pathology seems to be LB type degeneration with cellular and synaptic loss in cortical and limbic structures.\textsuperscript{138}

Whereas Parkinson's disease with dementia was claimed not to be associated with a specific pattern of MR abnormalities,\textsuperscript{139} Laakso et al\textsuperscript{140} found severe hippocampal atrophy in these patients, which is surprising considering the aforementioned resemblance between Parkinson's disease with dementia and dementia with Lewy bodies. Additionally, functional studies found patterns of brain hypoperfusion and hypometabolism in Parkinson's disease with dementia not very different from those described in Alzheimer's disease.\textsuperscript{138} One explanation for these findings may be that patients with Parkinson's disease with dementia have coexistent Alzheimer's pathology.

\subsection*{2.8 Frontotemporal lobar degeneration}

Frontotemporal lobar degeneration (FTLD) accounts for a substantial proportion of primary degenerative dementia cases occurring before the age of 65 years, and includes a heterogeneous group of patients with behavioural or language disturbances usually preceding or overshadowing memory deficits.\textsuperscript{\textsuperscript{\textsuperscript{\textsuperscript{38}}}} Recent clinical criteria proposed by Neary et al\textsuperscript{\textsuperscript{\textsuperscript{\textsuperscript{38}}}} discern three main prototypic syndromes – frontotemporal dementia, progressive nonfluent aphasia (PNA), and semantic dementia (SD), also known as progressive fluent aphasia or temporal variant of FTLD.
Two main histopathological types are considered as the major substrates of FTLD, but clinical presentation reflects the distribution of pathology rather than the exact histopathological type. The commonest pathology is that of neuronal loss and spongiform change (microvacuolation), without other specific features – frontal lobe degeneration type. The other is characterized by severe astrocytic gliosis with or without ballooned cells and inclusion bodies – Pick type. Both Alzheimer’s disease and FTLD, as well as several other neurodegenerative dementias belong to the group of tauopathies, all displaying aggregations of different isoforms of abnormal tau protein. In addition to the sporadic form, there are also familial cases of FTLD, often linked to chromosome 17 abnormalities.

Neuroimaging studies in patients with clinical and pathologic diagnosis of FTLD show a pattern of marked anterior temporal and frontal atrophy resulting in the so-called “knife edge” appearance and in dilatation (ballooning) of the temporal and frontal horns of the lateral ventricles (Figure 4), in some cases associated with predominantly frontal white matter changes. Characteristically, FTLD affects more the temporal pole, but relatively spares the posterior part of the hippocampus.

Asymmetric atrophy is also a distinctive feature of FTLD, particularly of SD and PNA. Selective inferolateral and anterior left temporal atrophy is characteristic of SD. In PNA, atrophy appears to be more diffuse and involves the left frontal and perisylvian structures. One variant of FTLD affecting the right temporal lobe presents with progressive prosopagnosia.

Studies using SPECT for the differential diagnosis between frontotemporal dementia and other dementias found hypoperfusion in the same regions where atrophy occurs, and because hypoperfusion or hypometabolism may precede volume loss, functional studies can be useful in early cases.
Figure 4. Axial fluid-attenuated inversion recovery image of a patient with frontotemporal dementia showing severe anterior temporal lobe atrophy with “knife edge” appearance, dilatation of the temporal horns of the lateral ventricles, and anterior temporal subcortical hyperintensity.

2.9 Dementia and atypical parkinsonian syndromes

The most well-known atypical parkinsonian syndromes are multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Clinical criteria for the diagnosis of PSP include cognitive impairment, and patients with CBD may have dementia as the predominant clinical feature. Both PSP and CBD are sporadic tauopathies that may overlap between each other, as well as with frontotemporal dementia and other disorders. Because dementia is not considered a diagnostic feature of MSA, this disease will not be discussed.
Characteristic findings on routine MR imaging can contribute to the identification of atypical parkinsonian syndromes.\textsuperscript{158,159} Asymmetric atrophy involving the posterior frontal and parietal regions (Figure 5), contralateral to the clinically most affected side, occurs in most of CBD patients. Mild signal changes on FLAIR and PD-WI in the atrophic cortex have been described in some of these patients.\textsuperscript{160} On the other hand, despite the existence of pathologic changes in the basal ganglia, MR imaging abnormalities of these structures were almost never reported.\textsuperscript{160}

**Figure 5.** Coronal high-resolution T1-weighted image of a patient with corticobasal degeneration showing asymmetric atrophy. The atrophy involves predominantly the right parietal lobe.

Midbrain atrophy and diffuse hyperintensity on T2-WI in the mesencephalic tegmentum and tectum (Figure 6a) are characteristic of PSP, and occur due to predominance of tau pathology in these regions.\textsuperscript{161,162} Midbrain atrophy can be simply and accurately assessed measuring the anteroposterior midbrain diameter on axial T2-WI,\textsuperscript{159,163} but visual assessment using sagittal T1-WI should also be done, because when there is midbrain atrophy the mesencephalic caudo-cranial dimension is reduced and the third ventricle’s floor appears more superiorly concave.
than normal (Figure 6b).\textsuperscript{158,160} Besides the infratentorial abnormalities, VBM and serial volumetric imaging studies have also shown a distinct pattern of mesio-frontal atrophy in PSP (Figure 6b).\textsuperscript{164,165}

Although asymmetric frontoparietal atrophy in CBD and midbrain atrophy in PSP are considered the most useful aids to the clinical diagnosis,\textsuperscript{166} other neuroimaging abnormalities were also described. Asymmetric involvement of the corpus striatum and thalamus in CBD was disclosed by PET in addition to asymmetric cortical hypometabolism.\textsuperscript{167} Moreover, patients with PSP and cognitive impairment studied both with MR and PET were found to have predominantly anterior corpus callosum atrophy as well as predominantly frontal cortical hypometabolism.\textsuperscript{168}

![Figure 6.](image)

**Figure 6.** (a) Axial T2-weighted image of a patient with progressive supranuclear palsy (PSP) showing midbrain atrophy and diffuse hyperintensity in the mesencephalic tegmentum and tectum. (b) Sagittal T1-weighted image showing midbrain atrophy (especially of the tectum), dilatation of the cerebral aqueduct, pronounced superior concavity of the third ventricle's floor, and the mesio-frontal atrophy characteristic of PSP.
2.10 Vascular dementia

Vascular dementia is the second most common type of dementia, and it is generally assumed that risk factors for vascular dementia are the same as for simple stroke. Executive dysfunction is commonly seen in vascular dementia and memory impairment is less severe than in Alzheimer’s disease. The most specific diagnostic criteria for vascular dementia are the National Institute of Neurological Disorders and Stroke (NINDS) – Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) criteria. These criteria emphasize the heterogeneity of both clinical syndromes and pathological subtypes of vascular dementia, the need to establish a temporal relation between stroke and the onset of dementia, as well as the importance of brain imaging to support clinical findings.

The main clinicopathological subtypes of vascular dementia are large vessel disease and small vessel disease. Large vessel vascular dementia can be further subdivided into multi-infarct dementia and strategic infarct dementia (caused by vascular lesions located in strategic regions of the brain, such as the hippocampus, paramedian thalamus, and the thalamocortical networks). Small vessel disease may also affect strategic regions. Binswanger’s disease, lacunar state (état lacunaire) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) are examples of subcortical ischaemic small vessel vascular dementia. Cerebral amyloid angiopathies (CAA) are considered as a subtype of cortical-subcortical small vessel disease, but they have associated large vessel pathology as well. Both CADASIL and some forms of CAA have a genetic basis.

Most patients with the diagnosis of vascular dementia have small vessel rather than large vessel disease. Therefore, research criteria were formulated specifically for subcortical ischaemic vascular dementia, now recognized as the most broad and homogeneous subtype.
The pathology of vascular dementia may be described considering either the type of brain lesion or the underlying type of vessel abnormality. Brain lesions include: large vessel cortical-subcortical infarcts, small vessel cortical microinfarcts, small vessel deep infarcts, enlarged perivascular (Virchow-Robin) spaces, haemorrhages, microbleeds, and diffuse white matter lesions. Vessel abnormalities include: atherosclerosis, arteriolosclerosis, amyloid angiopathy, source of emboli, or no obvious structural abnormality at all.\(^{176}\)

Infarcts may either be complete or incomplete. Complete infarcts correspond to areas of tissue destruction, whereas incomplete infarcts may only represent demyelination and oedema. Complete infarcts of deep small vessels are defined as lacunar infarcts, and some authors consider this definition also dependent on size (from 2-3 to 15-20 mm in diameter).\(^{168,177,178}\) In addition, one proposed neuropathological classification of lacunae includes both ischaemic (type I) and haemorrhagic (type II) lesions, as well as enlarged Virchow-Robin spaces (type III).\(^{179}\)

Diffuse white matter lesions include: spongiosis (vacuolation), gliosis, diffuse myelin and axonal loss, breakdown of ependymal lining, oedema, as well as enlarged Virchow-Robin spaces.\(^{180}\)

Given that patients with coexistent Alzheimer’s disease and cerebrovascular disease represent an important and previously underestimated group,\(^{181}\) the causal relation between vascular lesions alone and dementia is only clear in the following circumstances: when patients are young and it is unlikely they have associated Alzheimer’s pathology; when cognitive functions are normal before stroke, impaired immediately after, and do not worsen over time; when vascular lesions are located in strategic regions; and when well-defined vasculopathies known to cause dementia are proven, such as CADASIL or CAA. In other circumstances, it is possible that both degenerative and vascular pathology may contribute to cognitive impairment.\(^{182,183}\)
2.10.1 Imaging findings in vascular dementia

The NINDS-AIREN criteria consider structural neuroimaging crucial for the diagnosis of vascular dementia, and operational definitions for the radiological part of these criteria were recently proposed, both in terms of topography and severity of lesions (table 2). 

T2-weighted MR sequences are far more sensitive for the detection of cerebrovascular disease than CT, although CT was found to be more specific than MR in predicting subsequent symptomatic cerebrovascular disease. Hypointensity on T1-WI usually represents tissue destruction, and may be considered as a surrogate marker for complete infarcts. Therefore, lesions hyperintense on T2-WI and isointense on T1-WI may be considered as incomplete infarcts and probably just correspond to areas of myelin pallor. FLAIR images enable to identify cystic lesions, and the combination of FLAIR with T1-WI may be useful to differentiate the more aggressive lesions from those that might have less power to cause cognitive impairment.

Misclassification between lacunar infarcts and enlarged Virchow-Robin spaces may occur, but most of the enlarged Virchow-Robin spaces measure < 2 mm, and normally surround perforating arteries entering the striatum in the anterior perforated substance. Their appearance in large numbers reflects focal brain atrophy around blood vessels and may lead to the so called état criblé, especially in the basal ganglia (Figure 7). Moreover, the association of enlarged Virchow-Robin spaces and white matter lesions with cognitive impairment occurs, and widening of Virchow-Robin spaces can be considered as a measure of focal atrophy.

White matter changes on MR imaging are visible as diffuse hyperintense abnormalities on T2-WI, FLAIR and PD-WI, but usually they are not prominently hypointense
on T1-WI. On CT, white matter changes appear as mildly hypodense areas. Since their occurrence increases progressively with age, they are usually referred to as age-related white matter changes (ARWMC). ARWMC may be considered as a surrogate marker for ischaemic small vessel disease.\textsuperscript{8,130} Moreover, they are associated with vascular risk factors as well as with other types of cerebrovascular disease.\textsuperscript{195-197} Since the original scale of Fazekas et al,\textsuperscript{129} several others were proposed for rating ARWMC. Currently, the most complete is that proposed by Wahlund et al, applicable both to CT and MR imaging.\textsuperscript{185} According to the NINDS-AIREN criteria, white matter changes alone may be sufficient to cause dementia when at least \( \frac{1}{4} \) of the white matter is involved.\textsuperscript{36} Although this proportion has been defined arbitrarily, it is in accordance with the finding that only severe white matter disease is associated with cognitive dysfunction.\textsuperscript{198} Extensive and diffuse white matter changes affecting predominantly deep and periventricular white matter, but relatively sparing the U-fibres, occur in Binswanger's disease (Figure 8).\textsuperscript{169}

In patients with CADASIL, diffuse white matter signal changes involving the U-fibres occur mainly in the temporal, temporopolar, and frontal regions (Figure 9).\textsuperscript{199-201} Microbleeds, defined by some authors as hypointense foci (< 5 mm) on T2-WI or gradient-echo T2*-WI,\textsuperscript{202,203} are present in a considerable proportion of these patients, as well as in patients with CAA.\textsuperscript{204,205} However, the most typical feature of CAA is the occurrence of cortical-subcortical (lobar) haemorrhages.\textsuperscript{205,206}

Deep venous thrombosis and dural arteriovenous fistulae are vascular abnormalities that may rarely cause venous hypertensive encephalopathy or bilateral thalamic congestion (Figure 10), and lead to dementia. MR or conventional angiography are crucial for their diagnosis.\textsuperscript{207-209} Conventional angiography is also very useful for the interventional therapy of these abnormalities.\textsuperscript{207,208,210}
**Table 2.** Operational definitions for the imaging guidelines of the National Institute of Neurological Disorders and Stroke (NINDS) – Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) criteria for vascular dementia (VaD)

<table>
<thead>
<tr>
<th><strong>Topography</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large vessel stroke – arterial territorial infarct involving the cortical grey matter</strong></td>
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</tr>
<tr>
<td>– Anterior cerebral artery (ACA) – only bilateral ACA infarcts are sufficient to meet the NINDS-AIREN criteria</td>
<td></td>
</tr>
<tr>
<td>– Posterior cerebral artery (PCA) – infarcts in the PCA territory can only be included when they involve the following regions:</td>
<td></td>
</tr>
<tr>
<td>1. Paramedian thalamus</td>
<td></td>
</tr>
<tr>
<td>2. Inferior medial temporal lobe</td>
<td></td>
</tr>
<tr>
<td>– Association areas – a middle cerebral artery (MCA) infarct needs to involve the following regions:</td>
<td></td>
</tr>
<tr>
<td>1. Parietotemporal (e.g., angular gyrus)</td>
<td></td>
</tr>
<tr>
<td>2. Temporo-occipital</td>
<td></td>
</tr>
<tr>
<td>– Watershed territories – an infarct occurring in the watershed territory between MCA and PCA or between MCA and ACA needs to involve the following regions:</td>
<td></td>
</tr>
<tr>
<td>1. Superior frontal region</td>
<td></td>
</tr>
<tr>
<td>2. Parietal region</td>
<td></td>
</tr>
<tr>
<td><strong>Small vessel disease</strong></td>
<td></td>
</tr>
<tr>
<td>– Ischaemic pathology resulting from occlusion of small perforating arteries may become apparent as white matter lesions or as small vessel deep infarcts (e.g., lacunar infarcts):</td>
<td></td>
</tr>
<tr>
<td>1. White matter lesions</td>
<td></td>
</tr>
<tr>
<td>2. Multiple basal ganglia, thalamic, and frontal white matter lacunar infarcts – the criteria are met when there are at least two lacunar infarcts in the basal ganglia, thalamus or internal capsule, and at least two lacunar infarcts in the frontal white matter</td>
<td></td>
</tr>
<tr>
<td>3. Bilateral thalamic lesions</td>
<td></td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td></td>
</tr>
<tr>
<td>– Large vessel disease of the dominant hemisphere – if there is a large vessel infarct, the criteria are only met when the infarct is located in the dominant hemisphere. In the absence of clinical information, the left hemisphere is considered dominant</td>
<td></td>
</tr>
<tr>
<td>– Bilateral large vessel hemispheric strokes – the infarct located in the non-dominant hemisphere should involve an area listed under topography. The infarct located in the dominant hemisphere does not need to meet the topography criteria</td>
<td></td>
</tr>
<tr>
<td>– Extensive white matter lesions or leukoencephalopathy involving at least ¼ of the total white matter. Extensive white matter lesions are considered to involve at least ¼ of the total white matter when they are confluent – grade 3 in the age-related white matter changes (ARWMC) scale$^{185}$ – in at least two regions, and beginning confluent – grade 2 in the ARWMC scale – in two other regions. A lesion is considered confluent when it measures &gt; 20 mm or it consists of ≥ 2 smaller lesions fused by connecting bridges</td>
<td></td>
</tr>
</tbody>
</table>
Fulfilment of radiological criteria for probable VaD

- Large vessel disease – a lesion must be scored in at least one subsection of both topography and severity (both the topography and severity criteria should be met)
- Small vessel disease – for white matter lesions, both the topography and severity criteria should be met; for multiple lacunar infarcts and bilateral thalamic lesions, only the topography criterion is sufficient

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Figure 7. Axial fluid-attenuated inversion recovery images showing numerous enlarged Virchow-Robin spaces in the basal ganglia (état criblé) associated with extensive white matter lesions.
Figure 8. Axial fluid-attenuated inversion recovery images showing extensive and diffuse white matter lesions involving predominantly the deep and periventricular white matter, but relatively sparing the U-fibres, a pattern typical of Binswanger’s disease.
Figure 9. Axial fluid-attenuated inversion recovery images of a patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The images show diffuse white matter hyperintensities involving the U-fibres, mainly in the temporal, temporopolar, and frontal regions.

Figure 10. (a) Axial fluid-attenuated inversion recovery image showing bilateral thalamic hyperintensity due to venous congestion caused by a straight sinus thrombosis, confirmed by digital subtraction angiography (b).
2.11 Role of neuroimaging in the differential diagnosis of dementia

Magnetic resonance studies performed to investigate the value of MTA for the differential diagnosis of dementia did not find unequivocal results. O’Brien et al.\textsuperscript{211} carried out a study to determine the specificity of hippocampal atrophy for the differentiation between Alzheimer’s disease and other conditions associated with cognitive impairment, such as vascular dementia and major depression. They found that ratings of MTA were useful to differentiate Alzheimer’s disease from other groups. Conversely, Laakso et al.\textsuperscript{140} found that hippocampal atrophy was not specific to differentiate Alzheimer’s disease from vascular dementia or Parkinson’s disease with dementia, although they could not rule out the existence of Alzheimer’s pathology in all of their patients. More recently, Barber et al.\textsuperscript{132,133} found different degrees of hippocampal atrophy occurring in Alzheimer’s disease, vascular dementia, and dementia with Lewy bodies – the most severe in Alzheimer’s disease, the less severe in dementia with Lewy bodies, and although there was a trend towards less atrophy in dementia with Lewy bodies compared with vascular dementia, no significant volumetric difference between those two groups was observed. Most likely, these discrepancies reflect studies of different populations, illustrating that the diagnostic accuracy of MTA depends on disease severity.

SPECT and PET studies have also been applied to the differential diagnosis of dementia. Although they are considered useful for the differentiation between Alzheimer’s disease, vascular dementia and frontotemporal dementia, the discrimination between Alzheimer’s disease and dementia with Lewy bodies was found to be difficult on the basis of cerebral metabolism and blood flow.\textsuperscript{212,213} In the future, VBM and serial volumetric imaging studies evaluating global brain atrophy may also be useful for the differential diagnosis. However, one should always keep in mind that imaging overlap between different diseases may reflect a
combination of different pathologies, or even result from differences in the pathology
distribution.\textsuperscript{214,215}

The pattern of white matter signal abnormalities on MR is very useful for the
differentiation between ischaemic lesions and inflammatory demyelinating lesions. Multiple sclerosis is the most common inflammatory demyelinating disease and occurs mainly in young people, but it may lead to cognitive dysfunction due to accumulation of white matter lesions, or due to the occurrence of cortical and juxtacortical lesions.\textsuperscript{31} The most specific MR diagnostic criteria for multiple sclerosis were proposed by Barkhof et al,\textsuperscript{216} and currently a modification of them makes part of the guidelines from the International Panel on the diagnosis of multiple sclerosis.\textsuperscript{217} MR is also very useful for the diagnosis of other disorders that may lead to dementia and primarily affect white matter, such as herpes simplex encephalitis, human immunodeficiency virus encephalitis, and progressive multifocal leukoencephalopathy.\textsuperscript{31}

Apart from the imaging findings described for the most frequent diseases causing dementia, MR may still show specific imaging patterns of atrophy or signal abnormalities in other disorders. Atrophy of the striatum, most conspicuous on visual inspection in the caudate nucleus, is typical of Huntington’s disease (Figure 11),\textsuperscript{31} although putaminal atrophy is a better predictor of disease onset in presymptomatic subjects.\textsuperscript{218} Rapidly progressive brain atrophy, as well as striatal and cortical hyperintensity on FLAIR, PD-WI, or T2-WI (Figure 12) preceded by signal abnormalities on diffusion-weighted imaging (DWI) occur in patients with Creutzfeldt-Jakob disease.\textsuperscript{219-222} Additionally, in the new variant of Creutzfeldt-Jakob disease, bilateral hyperintensity of the pulvinar is a very specific imaging finding.\textsuperscript{223}
Figure 11. Axial (a) and coronal (b) T2-weighted images showing severe atrophy of the striatum, most conspicuous in the caudate nucleus, typical of Huntington’s disease.

Figure 12. Axial proton density-weighted image of a patient with Creutzfeldt-Jacob disease. The image shows hyperintensity in the striatum, periventricular white matter, septum pellucidum, and cerebral cortex, particularly in the claustrum, insula, and frontal lobe.
Normal pressure hydrocephalus is a rare disorder that, even more rarely, causes dementia. By definition, it includes the clinical triad of gait disturbance, urinary incontinence, and dementia. Gait impairment is the cardinal symptom, while mental deterioration may be subtle or even unrecognized. Initially, normal pressure hydrocephalus was considered to be an idiopathic form of communicating hydrocephalus, but currently other forms of communicating hydrocephalus, and even a few non-communicating forms make part of its spectrum.\textsuperscript{224-226} MR is the best imaging modality to evaluate the pulsatile motion of cerebrospinal fluid (CSF) in the cerebral aqueduct, either visually, as a low intensity signal on T2-WI (flow void), or using quantitative phase-contrast measurements. In normal pressure hydrocephalus, both flow void and phase-contrast measurements are increased due to reduced ventricular compliance,\textsuperscript{227,228} and it seems that only when they are prominently increased there is prediction of a positive response to shunt therapy.\textsuperscript{226,229-231} Given the frequent coexistence of normal pressure hydrocephalus with deep and periventricular white matter ischaemic changes,\textsuperscript{232,233} it is matter of controversy whether normal pressure hydrocephalus alone represents a true disease entity causing dementia.

2.12 New magnetic resonance techniques and molecular imaging

The big future challenge of neuroimaging techniques in the diagnosis of dementia will be to demonstrate pathologic processes occurring at a microscopic level, and therefore help to recognize subjects at risk of developing dementia before the occurrence of atrophy as an indicator of substantial tissue loss.

Neuronal loss and dysfunction are the major pathologic consequences at the cellular level. Proton MR spectroscopy (MRS) is reliable to demonstrate these abnormalities,
by means of showing low levels of N-acetylaspartate – the metabolite considered to be a neuroaxonal marker.\textsuperscript{234-253} Additionally, most single voxel proton MRS studies performed in the parieto-occipital cortex of patients with Alzheimer’s disease have also shown high levels of myo-inositol, a finding believed to represent gliosis or increased tissue osmolality.\textsuperscript{234,235,238,245} The same results were found in the frontal lobe of patients with frontotemporal dementia.\textsuperscript{240} Furthermore, phosphorous MRS studies have shown low levels of phosphocreatine and high levels of phosphomonoesters in the early stages of Alzheimer’s disease,\textsuperscript{239,247,254,255} but their meaning is uncertain. In spite of the reported findings, the role of MRS for the diagnosis of dementia is limited,\textsuperscript{243,253} mainly because the technique is difficult to standardize and can not be used on an individual basis. Perhaps in the future, the chemical shift imaging approach may become more useful as a diagnostic tool, since the regional distribution of metabolites can be evaluated.

Perfusion-weighted imaging (PWI) is an MR technique which constitutes a good alternative to nuclear medicine for the evaluation of microvascular changes in patients with dementia.\textsuperscript{256,257} The experience with PWI is still limited, and most studies have used a rapid gradient-echo T2*-weighted sequence during intravenous injection of a paramagnetic contrast bolus. This dynamic susceptibility contrast (DSC) PWI shows a degree of temporoparietal hypoperfusion in patients with Alzheimer’s disease comparable to the degree of hypometabolism revealed by PET, even after correction for brain atrophy. In addition, whereas the sensitivity of both DSC-PWI and PET to detect changes is comparable, DSC-PWI is much more rapid, and has the advantage of avoiding ionizing radiation.\textsuperscript{258,259} In the future, DSC-PWI may be useful for diagnostic purposes or even tried to identify persons at risk of developing dementia.
Arterial spin labelling (ASL) represents an alternative MR technique to evaluate brain perfusion, and obviates the use of an exogenous contrast bolus injection. ASL uses water as a diffusible tracer and inverts the inflowing water proton spins in the arterial blood to obtain a measure of flow.\textsuperscript{260} One ASL study comparing patients with Alzheimer’s disease with control subjects demonstrated blood flow decreases in Alzheimer’s disease occurring in the temporal, parietal, frontal, and posterior cingulate cortices.\textsuperscript{261}

Functional MR imaging (fMRI) is a powerful research technique to evaluate brain activation on the basis of local changes in blood deoxyhaemoglobin concentration – the so-called blood oxygen level dependent (BOLD) effect.\textsuperscript{262} Usually, the BOLD effect is measured in relation to various stimuli and tasks, but a new fMRI approach applied to study brain connectivity during a “no task condition” is currently under development.\textsuperscript{263} Findings of fMRI studies applied to dementia include decreased activation in the medial temporal lobe of patients with Alzheimer’s disease during learning tasks requiring the encoding of new information, as well as loss of frontal activation in patients with frontotemporal dementia during a working memory task.\textsuperscript{264,265} In the future, the major application of fMRI perhaps will be to identify subjects at risk of developing dementia. So far, fMRI studies undertaken to identify subjects at risk of developing Alzheimer’s disease (carrying the APOE-\(\epsilon\)4 allele) have shown conflicting results. They found either decreased or increased brain activation in regions involving the temporal lobe, which possibly means these regions are either already affected subclinically or trying to assume a compensatory role.\textsuperscript{266,267}

Diffusion-weighted MR imaging is a technique sensitive to the microscopic motion of water molecules in tissue.\textsuperscript{268} It is already very useful in clinical practice for the diagnosis of recent onset ischaemia, and may detect recent infarcts responsible for the so called “stepwise decline” in patients with vascular dementia.\textsuperscript{269} Moreover,
the apparent diffusion coefficients of the temporal white matter and hippocampus are higher in mild cognitive impairment and patients with Alzheimer’s disease than in control subjects, probably due to decreased axonal density, disruption and loss of axonal membranes or myelin, and to Wallerian degeneration secondary to grey matter pathology.270-272 High b value DWI is more sensitive to white matter degeneration than conventional DWI.273

Diffusion tensor imaging (DTI) enables the measurement of directionality (anisotropy) of the microscopic motion of water, and allows visualization of white matter tracts due to the longitudinal diffusion of water in fibres.274 Decreased fractional anisotropy was found in the temporal lobes and deep posterior white matter of patients with Alzheimer’s disease,270,271,275 and a reduction in the integrity of association white matter tracts, such as the splenium of the corpus callosum, superior longitudinal fasciculus, and cingulum, also occurs in Alzheimer’s disease.276 Increases of water diffusion and a parallel loss of anisotropy in hyperintensities identified on T2-WI, in normal-appearing white matter, and in normal-appearing grey matter (especially the thalamus) were found in CADASIL,277,278 as well as increases of water diffusion in lesions and normal-appearing white matter in patients with ARWMC.279 Therefore, DTI may provide a better index of white matter damage than conventional MR imaging.

Magnetization transfer (MT) is an MR technique that modulates image contrast by selectively saturating protons bound to macromolecules (e.g., proteins) using off-resonance radiofrequency (RF) pulses.280 The difference in signal intensity with and without application of the RF pulses can be measured as an MT ratio (MTR). When there is protein destruction, bound protons become less suppressed by the RF pulses, and the MTR decreases.281 This occurs in patients with Alzheimer’s disease, Parkinson’s disease with dementia, PSP, and ARWMC.282-285 Since microscopic
abnormalities extend beyond the macroscopic lesions visualized on conventional MR images, MT may be helpful to evaluate diffuse brain damage in patients with dementia.

Studies about T1 and T2 relaxation time measurements in elderly subjects with or without dementia are scarce. Age-related increases of T1 relaxation times in the white matter, putamen, and thalamus were found, as well as increases of T1 relaxation times in the temporoparietal white matter of patients with Alzheimer’s disease. Concerning T2 relaxation time measurements, the results from studies in patients with Alzheimer’s disease are conflicting. Some studies found prolongation of the T2 relaxation times in the temporoparietal white matter, hippocampus, and amygdala, as well as a correlation between this prolongation and the severity of dementia, while other studies did not find any use for T2 relaxometry in the diagnosis of Alzheimer’s disease. Both T1 and T2 relaxation times are dependent on the free water content. Therefore, the CSF may contribute to increase the relaxation times, particularly in patients with brain atrophy. One study using a bi-exponential model to separate brain tissue water from CSF showed reduction of the T2 relaxation times in the right hippocampus of patients with Alzheimer’s disease, and proposed that these patients may have a reduced water content in the brain tissue. These results are consistent with the neuropathological features of Alzheimer’s disease that increase tissue osmolality, such as the intraneuronal deposition of lipofuscin and neurofibrillary changes, as well as the extracellular deposition of β-amyloid.

Magnetic resonance microscopy (MRM) requires higher field scanners, stronger gradients, and much longer sequences than conventional MR to create images with very high resolution. MRM is ideally suited for studying small animals and embryos, and may even depict images of single neurons in vitro. One MRM
study in formalin fixed brain tissue sections of patients with Alzheimer’s disease detected β-amyloid plaques using a 7.1 Tesla (T) magnet and gradient strengths as high as 850 mT/m, by means of a gradient-echo T2*-weighted sequence. This sequence created images with isotropic voxels of approximately 40 µm, and required scanning times as high as 20 hours. Another post-mortem MRM study using a multislice fast-spin-echo T2-weighted sequence could also detect β-amyloid plaques in the brain of a transgenic mouse model of Alzheimer’s disease, with scanning times approaching what may be considered reasonable for in vivo imaging.

Finally, molecular imaging represents an important advance of the neuroimaging techniques applied to the diagnosis of neurodegenerative diseases, due to the possibility of targeting non-invasively specific abnormal proteins that represent biological markers of disease. Moreover, in the future, it may allow monitoring the effects of new therapies aimed at modifying the course of these diseases. Currently, most of the efforts are focused on the development of radioligands for in vivo detection of β-amyloid using PET and SPECT. However, the development of these new agents revealed to be a major challenge, since the employed molecules should not be toxic, need to be labelled by a radioactive tracer, must be able to cross the blood-brain barrier, and then must specifically bind to β-amyloid. The molecular imaging probes examined for PET include derivatives of histological dyes for β-amyloid (Congo red and thioflavins), stilbene derivatives, acridine analogues, serum amyloid protein (SAP), and the radiofluorinated 6-dialkylamino-2-naphthylethylidene (DDNP) analogues. In addition, rhenium complexes, Congo red derivatives, SAP, antibodies to amyloid, and fragments of β-amyloid itself have been examined for SPECT. The DDNP derivative 2-(1-{6-[2-[18F]fluoroethyl](methyl)amino]-2-naphthyl}ethylidene)malononitrile (18FDDNP), and the thioflavin T derivative 11C labelled Pittsburgh Compound-B were shown to label β-amyloid in living humans, both visualized by PET. Moreover, 18FDDNP also targets NFTs, and prion
plaques\textsuperscript{302} in human autopsy brain tissue. Very recently, novel compounds were presented for in vivo imaging of $\beta$-amyloid with PET,\textsuperscript{303,304} as well as dual agents that may be used both with PET and SPECT.\textsuperscript{305} MRM also enables imaging of $\beta$-amyloid after injection of magnetically labelled peptides in transgenic mice,\textsuperscript{306,307} and because MR provides much higher spatial resolution than PET or SPECT without ionizing radiation, it may become a good alternative to nuclear medicine.
Chapter 3

Alzheimer’s disease

3.1

Hippocampal sulcus width and cavities: comparison between patients with Alzheimer’s disease and nondemented elderly subjects

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Abstract

Background and purpose: The hippocampal fissure is a foetal sulcus that, except for its most medial part (the superficial hippocampal sulcus), is normally obliterated. Hippocampal cavities are residual cysts attributable to lack of hippocampal fissure obliteration. We hypothesized that either hippocampal sulcus enlargement or an increase in number or size of hippocampal cavities could be associated with medial temporal lobe atrophy (MTA) occurring in Alzheimer’s disease.

Methods: Two observers assessed the maximal hippocampal sulcus width by means of the fimbriosubicular distance at the anterior part of the hippocampal body; as well as the occurrence, number, and size of hippocampal cavities; and the visual rating score of MTA on magnified coronal high-resolution T1-weighted magnetic resonance images of 21 patients with Alzheimer’s disease and 15 nondemented elderly controls.

Results: Both observers found the maximal hippocampal sulcus width significantly larger in patients with Alzheimer’s disease than in controls ($P < 0.0001$). The interobserver averaged fimbriosubicular distance in patients with Alzheimer’s disease was 2.84 mm (standard deviation [SD] = 0.94), approximately twice that of the corresponding distance in nondemented subjects (1.41 mm; SD = 0.58). Both observers found a significant correlation between the fimbriosubicular distance and MTA score (observer 1 $r_s = 0.71$; observer 2 $r_s = 0.74$; $P < 0.0001$). None of the observers found significant differences between patients with Alzheimer’s disease and nondemented subjects with respect to occurrence, number, or size of hippocampal cavities, nor did they find a significant correlation between the number or size of hippocampal cavities and MTA. Interobserver agreement ranged from moderate to very good.

Conclusion: Enlargement of the hippocampal sulcus, assessed by the fimbriosubicular distance, is associated with MTA in Alzheimer’s disease, but enlargement of the hippocampal cavities is not.
Introduction

The most common cause of dementia is Alzheimer’s disease. Neuropathological changes underlying Alzheimer’s disease first occur in the medial temporal lobe.59 Therefore, structural neuroimaging in Alzheimer’s disease is focused on detection of medial temporal lobe atrophy (MTA), particularly of the hippocampus, parahippocampal gyrus (including the entorhinal cortex), and amygdala.308

The hippocampal fissure is a foetal sulcus around which occurs the hippocampal folding. It begins as a small indentation in the primitive hippocampus at approximately the 10th week of foetal development. Later, the sulcus deepens, but between the 18th and the 21st week of foetal development, it is obliterated almost completely by fusion between the cornu ammonis and the dentate gyrus.309 No more than the most medial part of the hippocampal fissure persists as an open and shallow groove between the dentate gyrus and the subiculum, just below the fimbria and the fimbriodentate sulcus, on the medial surface of the hippocampus310,311 – the superficial hippocampal sulcus.311 Hippocampal cavities are generally considered residual cysts resulting from lack of hippocampal fissure obliteration. Therefore, hippocampal cavities are most commonly localized laterally, at the apex of the hippocampal fold, between the cornu ammonis and the dentate gyrus. Hippocampal cavities are regularly found in routine magnetic resonance (MR) imaging studies and are believed to represent a normal variant reflecting cerebrospinal fluid (CSF) collection.312,313

Because brain atrophy results in enlargement of the CSF spaces, we hypothesized that either hippocampal sulcus enlargement or an increase in the number or size of hippocampal cavities could be associated with medial temporal lobe atrophy (MTA) occurring in Alzheimer’s disease.
Methods

Subjects
Between 2000 and 2002, 21 patients (7 men, 14 women) fulfilling the National Institute of Neurologic, Communicative Disorders and Stroke (NINCDS) – Alzheimer’s disease and Related Disorders Association (ADRDA) criteria for probable Alzheimer’s disease, and 15 elderly nondemented controls (9 men, 6 women) were selected for this study. The patients were randomly selected from the outpatient memory clinic of the Alzheimer Centre (VU University Medical Centre, Amsterdam, the Netherlands), as part of a prospective study on brain ageing and dementia approved by the local ethics committee. Control subjects were relatives of the patients and provided informed consent to be included. To evaluate cognitive function, we administered the mini-mental state examination (MMSE) (possible range of scores: 0 to 30) to all subjects. On the basis of the MMSE, patients with Alzheimer’s disease were classified as having mild-to-moderate (MMSE scores ≥ 10) or severe (MMSE scores < 10) dementia. No patients were under antidementia therapy before they underwent MR imaging examination.

Magnetic Resonance Imaging Protocol
MR imaging examinations were performed using a superconductive magnet operating at 1.0 Tesla (Impact, Siemens, Erlangen, Germany) and a routine imaging protocol for dementia. For this study, we used a high-resolution 3D T1-weighted gradient-echo sequence (echo time = 7 ms; repetition time = 15 ms; number of excitations = 1; flip angle = 8°; effective slice thickness = 1.49 mm).

Image Assessment
Two observers (A.J.B.-L. and J.H.v.W.) rated the images, blinded to clinical information, with the use of digital image files displayed at full resolution, without pixel interpolation.
Because the identifiable part of the hippocampal sulcus is normally a shallow groove just below the fimbria and above the subiculum, we used magnified coronal high-resolution T1-weighted images (T1-WI) perpendicular to the long axis of the temporal lobe to better visualize it and took the fimbriosophikus distance as a linear measurement to evaluate its maximal width. We measured this distance perpendicular to the visible longitudinal extent of the hippocampal sulcus on both sides, at the anterior part of the hippocampal body, after choosing the best section displaying the fimbria. In those cases in which the hippocampal sulcus was too shallow to be measured, we considered it to equal 0 mm. In the other cases, we took the measurement either vertically or obliquely, according to the relative position between the fimbria and the subiculum (Figure 1). Hippocampal cavities were defined as sharply demarcated cystic structures (isointense with CSF) localized at the apex of the hippocampal fold. The greatest dimension of each of the hippocampal cavities was determined on coronal T1-WI. We also used a visual rating scale to evaluate MTA76 on coronal T1-WI (possible range of scores for each side: 0 to 4).

Focal abnormalities measuring < 1 mm were not included. Cyst-like structures localized medially in the hippocampus and appearing to be the hippocampal sulcus continuation in contiguous sections were considered part of the sulcus, not hippocampal cavities. Care was taken to avoid the inclusion of pulsation artifacts, recognizable by linear patterns of signal-intensity banding attributable to phase misregistration.315

**Statistical Analysis**

Statistical analysis was performed by means of SPSS 11.0 (SPSS for Windows, Chicago, Ill) and MedCalc (MedCalc Software, Mariakerke, Belgium). We used the Fisher’s exact test to compare categorical variables and the Mann-Whitney U test to compare scores between independent groups of subjects. For comparisons of
discrete and continuous variables, we used the independent-samples Student’s *t* test, because the distribution of data was approximately normal. Correlations were tested by using the Spearman rank correlation coefficient (*r*). Statistical significance was considered when *P* values were < 0.05.

**Figure 1.** Magnified coronal high-resolution T1-weighted images (T1-WI) of the hippocampal region.

**A** and **B**, Coronal T1-WI of a 68 year-old nondemented control showing discrete enlargement of the choroidal fissures (cf), suggesting medial temporal lobe atrophy (MTA) grade 1, and hippocampal cavities bilaterally (vertical arrows). Note that both hippocampal sulci are not enlarged (horizontal arrows).

**C** and **D**, Coronal T1-WI of a 54 year-old patient with Alzheimer’s disease showing enlargement of the hippocampal sulcus, measured between the fimbria and the subiculum (vertical measurement overlays), and enlargement of the choroidal fissures (cf) (MTA grade 1).
E and F, Coronal T1-WI of a 76 year-old patient with Alzheimer's disease showing enlargement of the hippocampal sulcus (vertical measurement overlays), moderate to severe MTA (grade 3) and hippocampal cavities bilaterally (vertical arrows).

G and H, Coronal T1-WI of a 93 year-old patient with Alzheimer's disease showing severe MTA (grade 4), and a small hippocampal cavity on the right side (vertical arrow). Note that the fimbria appears laterally displaced. This displacement contributes to an increase of the fimbriosubicular distance (oblique measurement overlays).

To assess interobserver agreement, we used the kappa (K) coefficient for nominal variables, the weighted K coefficient for ordinal and discrete variables, and the intraclass correlation coefficient (ICC) for continuous variables. Strength of agreement was interpreted according to adapted guidelines proposed by Landis and Koch.316

We also calculated the statistical power of the study on the basis of the standardized difference for the most relevant variable.

**Results**

Table 1 summarizes the clinical and radiological characteristics of the patients and controls. All patients had Alzheimer's disease of mild-to-moderate severity.

Both observers found the maximal hippocampal sulcus width significantly larger in patients with Alzheimer's disease than in controls (P < 0.0001). The interobserver averaged fimbriosubicular distance in patients with Alzheimer's disease was 2.84 mm (standard deviation [SD] = 0.94), approximately twice that of the corresponding distance in nondemented subjects (1.41 mm; SD = 0.58) (Figure 1). Both observers found higher MTA scores significantly associated with Alzheimer's disease (P < 0.01),
as well as a significant correlation between the fimbriosubicular distance and MTA (observer 1 $r_s = 0.71$; observer 2 $r_s = 0.74$; $P < 0.0001$) (Figure 2). Table 2 shows the correspondence between fimbriosubicular measurements and visual rating grades of MTA.

Table 1. Characteristics of patients with Alzheimer’s disease (AD) ($n = 21$) and nondemented elderly subjects ($n=15$) including age, mini-mental state examination (MMSE), hippocampal sulcus (HS) width, number and size of hippocampal cavities (HC), and medial temporal lobe atrophy (MTA) score.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (Standard deviation)</th>
<th>AD patients</th>
<th>Controls</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>69.3 (10.9)</td>
<td>68.9 (8.0)</td>
<td>$P = 0.91$</td>
</tr>
<tr>
<td>MMSE score$^1$</td>
<td></td>
<td>18.8* (4.5)</td>
<td>27.9* (1.9)</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>HS width$^2$ (mm) – observer 1</td>
<td></td>
<td>2.9 (1.0)</td>
<td>1.4 (0.6)</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>HS width$^2$ (mm) – observer 2</td>
<td></td>
<td>2.8 (1.1)</td>
<td>1.4 (0.7)</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>HS width$^2$ (mm) – interobserver average</td>
<td></td>
<td>2.8 (0.9)</td>
<td>1.4 (0.6)</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Number of HC – observer 1</td>
<td></td>
<td>2.6 (3.2)</td>
<td>3.6 (2.8)</td>
<td>$P = 0.32$</td>
</tr>
<tr>
<td>Number of HC – observer 2</td>
<td></td>
<td>1.9 (2.4)</td>
<td>3.6 (2.9)</td>
<td>$P = 0.06$</td>
</tr>
<tr>
<td>Number of HC – interobserver average</td>
<td></td>
<td>2.2 (2.7)</td>
<td>3.6 (2.8)</td>
<td>$P = 0.15$</td>
</tr>
<tr>
<td>Mean size of HC (mm) – observer 1</td>
<td></td>
<td>1.7 (1.0)</td>
<td>2.0 (1.1)</td>
<td>$P = 0.29$</td>
</tr>
<tr>
<td>Mean size of HC (mm) – observer 2</td>
<td></td>
<td>1.3 (1.1)</td>
<td>2.0 (0.8)</td>
<td>$P = 0.06$</td>
</tr>
<tr>
<td>Mean size of HC (mm) – interobserver average</td>
<td></td>
<td>1.5 (0.9)</td>
<td>2.0 (0.9)</td>
<td>$P = 0.10$</td>
</tr>
<tr>
<td>MTA score$^{2,3}$ – observer 1</td>
<td></td>
<td>2.2* (1.0)</td>
<td>1.1* (0.7)</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>MTA score$^{2,3}$ – observer 2</td>
<td></td>
<td>1.7* (1.1)</td>
<td>0.6* (0.7)</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>MTA score$^{2,3}$ – interobserver average</td>
<td></td>
<td>2.0* (1.1)</td>
<td>0.8* (0.6)</td>
<td>$P &lt; 0.01$</td>
</tr>
</tbody>
</table>

$^*$ Please note that means of scores are presented, whereas we used the Mann-Whitney U test to compare differences between groups.

$^1$ Lower values indicate greater severity.

$^2$ Values are left/right averages.

$^3$ Higher values indicate greater severity.
Figure 2. Scatterplots displaying the averaged left/right hippocampal sulcus width (fimbriosubicular distance) plotted against the medial temporal atrophy score. Triangles represent patients with Alzheimer’s disease, and circles correspond to control subjects.

One of the observers found hippocampal cavities in 14 (66.7%) of the 21 patients, and in 14 (93.3%) of the 15 controls ($P = 0.10$). The other found hippocampal cavities in 16 (76.2%) patients, and in 13 (86.7%) controls ($P = 0.67$). None of the observers found significant differences between patients with Alzheimer’s disease and nondemented subjects with respect to number or size of hippocampal cavities, nor did they find a significant correlation between number or size of hippocampal cavities and MTA.

The interobserver reliability analysis revealed a very good agreement in the assessment of the number of hippocampal cavities (weighted Kappa [$K$] = 0.90) and hippocampal sulcus width (intra-class correlation coefficient [ICC] = 0.85), good agreement in the assessment of MTA (weighted $K$ = 0.80), and moderate agreement in the judgment of presence ($K$ = 0.58) and size of hippocampal cavities (ICC =
On the basis of a standardized difference of 1.34 for the hippocampal sulcus width, the statistical power of the study was approximately 0.90 ($P = 0.01$).

**Discussion**

Our results show that enlargement of the hippocampal sulcus, assessed by a linear measurement between the fimbria and the subiculum, is significantly associated with Alzheimer's disease and that hippocampal sulcus enlargement is significantly correlated with higher visual rating scores of MTA. The early involvement of both the entorhinal cortex and the subiculum by Alzheimer’s pathology\(^5\) resulting in disruption of the perforant pathway,\(^6\) which conveys most of the input connections from the neocortex to the hippocampus and partially transverses the obliterated hippocampal fissure,\(^3\) explains, in part, the tissue loss leading to hippocampal sulcus enlargement. In addition, it is also conceivable that the consequent loss of hippocampal efferences may well cause atrophy of the fimbria. Finally, in certain patients with severe hippocampal atrophy, the fimbria appears to be laterally displaced; therefore, an additional increase of the fimbriosubicular distance occurs (Figure 1H).

MTA can be assessed by using visual rating scales, linear measurements of temporal lobe structures, and volumetry of the hippocampus.\(^3\) Previous studies using computed tomography (CT) axial thin sections parallel to the long axis of the temporal lobe found enlargement of the choroidal/hippocampal fissure complex in Alzheimer’s disease, assessed either by visual rating of the medial hippocampal lucency or by using a quantitative stereological approach. Other studies found linear measurements of the temporal horn width reliable for the detection of
Alzheimer’s disease. We used a linear measurement between the fimbria and the subiculum on magnified coronal high-resolution T1-WI to estimate the maximal hippocampal sulcus width. Because both the fimbria and the subiculum correspond to hippocampal structures, this measurement may reflect purely hippocampal atrophy better than the choroidal fissure width or the temporal horn width, both surrounded superiorly and laterally by white matter of the temporal lobe. We also used a visual rating scale for MTA based on the subjective evaluation of the choroidal fissure width, the temporal horn width, and the hippocampal height. Because this scale does not currently consider the hippocampal sulcus width, its inclusion as an item to rate MTA may perhaps have diagnostic significance for the detection of patients with Alzheimer’s disease. In fact, we found the fimbriosubicular distance significantly larger in patients with Alzheimer’s disease than in controls with similar MTA scores (Table 2).

**Table 2.** Interobserver averaged hippocampal sulcus (HS) width (fimbriosubicular distance) according to grade of medial temporal lobe atrophy (MTA) in patients with Alzheimer’s disease (AD) (n = 21) and nondemented elderly control subjects (n = 15)

<table>
<thead>
<tr>
<th>MTA score</th>
<th>Mean HS width* (Standard deviation)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD patients</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>0 (n=3)</td>
<td>−</td>
<td>1.4 (0.5)</td>
<td></td>
</tr>
<tr>
<td>1 (n=18)</td>
<td>2.1 (0.5)</td>
<td>1.3 (0.7)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>2 (n=6)</td>
<td>2.5 (0.1)</td>
<td>1.7 (0.4)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>3 (n=6)</td>
<td>3.5 (0.4)</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>4 (n=3)</td>
<td>4.1 (1.1)</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

‘Values in mm

Hippocampal cavities are usually defined as cystic remnants of the primitive hippocampal fissure, although some authors believe they also represent enlarged
perivascular (Virchow-Robin) spaces. In any case, their presence, increased number, or enlargement could reflect focal hippocampal atrophy, and one would expect them to be more frequent or larger in patients with Alzheimer’s disease than in healthy elderly subjects. Actually, enlarged Virchow-Robin spaces reflecting focal brain atrophy around perforating arteries in the striatum and centrum semiovale are associated with white matter lesions and cognitive impairment. Furthermore, enlarged Virchow-Robin spaces were recently found to be a sensitive indicator of cerebral microvascular disease. Nevertheless, we did not find a significant difference between patients with Alzheimer’s disease and nondemented subjects with respect to occurrence, number, or size of hippocampal cavities. We also did not find a significant correlation between number or size of hippocampal cavities and MTA. However, hippocampal cavities are less commonly seen in younger than in elderly subjects, and their number and size were found to be higher in nondemented subjects carrying apolipoprotein E genotypes conferring risk for the development of degenerative and vascular brain pathology. One explanation for the apparent disagreement between these findings and our results is perhaps the existence of a cancellation effect between MTA and hippocampal cavities, either because some hippocampal cavities may disappear by merging with the hippocampal sulcus as this enlarges or because small hippocampal simply can not harbour too many cavities.

On the basis of the standardized difference for the hippocampal sulcus width, the statistical power of this study is high, but the relatively small sample size still represents a limitation to detect (as significant) other less-marked differences. Another limitation is the fact that some of the performed measurements were very small and, therefore, possibly influenced by the existence of partial volume effects. To avoid this problem, we used magnified coronal high-resolution T1-WI displayed without pixel interpolation, which enabled us to identify the exact number of pixels for each individual measurement. Nevertheless, we recognize that both a larger sample size and the use of MR imaging sequences acquired at higher field strengths
(enabling more spatial resolution) would be important to confirm our findings.

**Conclusion**

Enlargement of the hippocampal sulcus, assessed by the fimbriosubicular distance on coronal T1-WI, is associated with MTA in patients with Alzheimer’s disease and may serve as a measure to rate MTA severity. By contrast, hippocampal cavities were not found to be significantly associated with MTA or Alzheimer’s disease and do not seem to have pathologic value.
Chapter 4

Vascular dementia

4.1

Thalamic lesions in vascular dementia: low sensitivity of fluid-attenuated inversion recovery (FLAIR) imaging

António J. Bastos Leite, Elisabeth C.W. van Straaten, Philip Scheltens, Geert Lycklama, Frederik Barkhof

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Abstract

**Background and Purpose:** The criteria of the National Institute of Neurological Disorders and Stroke (NINDS) – Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) include thalamic lesions for the diagnosis of vascular dementia. It is generally believed that either T2-weighted images (T2-WI) or fluid-attenuated inversion recovery (FLAIR) images may depict supratentorial ischaemic abnormalities. However, to our knowledge no study compared the sensitivity of these sequences to depict thalamic lesions. Our purpose was to compare their sensitivity to depict thalamic lesions in patients with vascular dementia.

**Methods:** We performed a review of T2-WI and FLAIR images in 73 patients fulfilling the radiological part of the NINDS-AIREN criteria (mean age = 71 years; range: 49 to 83). The sample was drawn from a large multicentre trial on vascular dementia and was expected to have a high prevalence of thalamic lesions. In a side-by-side review, including T1-weighted images as well, lesions were classified according to presumed underlying pathology.

**Results:** The total number of thalamic lesions was 214. Two hundred eight (97%) were detected on T2-WI, but only 117 (55%) were detected on FLAIR ($\chi^2 = 5.1; P < 0.05$). Although the mean size of lesions detected on T2-WI and not on FLAIR (4.4 mm) was significantly lower than the mean size of lesions detected on both sequences (6.7 mm; $P < 0.001$), 5 of the 29 lesions > 10mm on T2-WI were not visible on FLAIR. FLAIR depicted only 81 (51%) of the 158 ischaemic lesions and 30 (60%) of the 50 microbleeds detected on T2-WI.

**Conclusion:** FLAIR should not be used as the only T2-weighted sequence to detect thalamic lesions in patients suspected of having vascular dementia.
Introduction

In 1937, Papez described an anatomic circuit beginning and ending in the hippocampal formation possibly related to emotional experience. The projections of the Papez circuit involve the fornix, mammillary bodies, mamillothalamic tracts, anterior thalami, cingulate cortex, and the cingulate bundles. The early notion that Papez circuit subserves emotion has been abandoned and replaced by the proposal it is primarily involved in mnemonic functions. Lesions of the major components of this circuit have been shown to disrupt memory in humans, particularly those localized in the anterior group of thalamic nuclei. However, lesions affecting other thalamic components or connections not considered in the circuit, such as the mediodorsal (dorsomedial), intralaminar, and pulvinar nuclei or the thalamofrontal networks, may also cause cognitive deficits and marked behavioural changes.

Magnetic resonance imaging (MRI) and computed tomography (CT) are crucial for the diagnosis of cerebrovascular disease. The first studies using CT for the evaluation of brain lesions in patients with ischaemic stroke confirmed the importance of thalamic infarcts as a cause of dementia. Therefore, the criteria of the National Institute of Neurological Disorders and Stroke (NINDS) – Association Internationale pour la Recherche et l’ Enseignement en Neurosciences (AIREN) include radiological evidence of thalamic lesions for the diagnosis of probable vascular dementia. Moreover, one single thalamic infarct may induce vascular dementia.

It is generally believed that either T2-weighted images (T2-WI) or fluid-attenuated inversion recovery (FLAIR) images may depict supratentorial ischaemic abnormalities. However, to our knowledge no comparative study was performed to assess which of these MRI sequences yields the highest sensitivity to detect thalamic lesions. In this study we sought to compare their sensitivity to depict thalamic lesions in patients with vascular dementia.
Methods

Patients
The subjects were derived from the VantagE study, a multicentre, phase III, prospective, randomized, double blind clinical trial on the effects of rivastigmine in patients with vascular dementia. For the current study, we selected a sample of 73 patients (mean age = 71 years; range: 49 to 83) fulfilling the radiological part of the NINDS-AIREN criteria. On the basis of earlier central reading of the images for trial inclusion, we knew that approximately 75% of the current sample might be expected to have either unilateral or bilateral focal thalamic lesions. Apart from the diagnosis of vascular dementia, we were blinded to all clinical information of the patients.

Magnetic Resonance Imaging Protocol
The examinations were performed using scanners operating from 0.5 to 1.5 Tesla. Axial spin-echo T2-WI (echo time [TE]: 80 to 120ms, repetition time [TR]: 3000 to 4000ms, slice thickness = 5mm); axial FLAIR (TE: 110 to 150ms, TR: 9000 to 10000ms, inversion time [TI]: 2000 to 2200ms, slice thickness = 5mm); and axial, sagittal and coronal T1-weighted images (T1-WI; TE: 11 to 20ms, TR: 500 to 700ms, slice thickness = 5mm) were acquired. To maintain blinding, we were restricted from access to information about the type of scanner used for each particular patient, as well as to the location of the imaging centre.

Image Assessment
The initial assessment was performed in a blinded way, in which the T2-WI and FLAIR images were evaluated in pseudorandom order, with the use of 16-bit digital image files. All lesions were marked and numbered with digital overlays. We included only focal thalamic abnormalities > 1mm and excluded those suggestive of enlarged
perivascular (Virchow-Robin) spaces. Enlarged Virchow-Robin spaces were defined as sharply demarcated areas with a signal isointensity relative to cerebrospinal fluid (CSF), following the course of a perforating vessel on sagittal or coronal images. Care was also taken to avoid the inclusion of pulsation artifacts, recognizable by linear patterns of signal-intensity banding attributable to phase misregistration.

For further sub-typing and analysis, T2-WI, FLAIR and T1-WI were evaluated side-by-side. The greatest dimension of each focal abnormality was measured, and all were classified on each of the three imaging sequences into the following categories: hyperintense, hypointense, predominantly hypointense (hypointense with a small hyperintense component), and hypointense with a peripheral rim of hyperintensity. Lesions hyperintense on T2-WI and hypointense on T1-WI were classified as complete or lacunar infarcts. Lesions hyperintense on T2-WI and isointense on T1-WI were considered incomplete infarcts. Lesions hypointense on T2-WI were classified as haemorrhages. Complete infarcts hypointense on FLAIR were considered cystic infarcts.

**Statistical analysis**

Statistical analysis was performed with the use of SPSS 11.0 (SPSS for Windows, Chicago, Ill). We used chi-square statistics to compare categorical data, such as proportions of lesions depicted by each sequence. The independent sample Student’s t test was applied to compare continuous variables, because the data had an approximately normal distribution.


**Results**

The total number of focal thalamic lesions detected was 214. Most (86%) of the lesions measured < 10mm. One hundred nine (51%) were localized in the right thalamus, and 105 (49%) in the left.

Two hundred eight (97%) of the 214 lesions were identified on T2-WI, but only 117 (55%) were detected on FLAIR ($\chi^2 = 5.1; P < 0.05$; Table 1; Figure). Although the mean size of lesions detected on T2-WI and not on FLAIR (4.4 mm) was significantly lower than the mean size of lesions detected on both sequences (6.7 mm; $P < 0.001$), 5 of the 29 lesions > 10mm were not visible on FLAIR (Table 2).

**Table 1.** Thalamic lesions on T2-weighted images (T2-WI) and fluid-attenuated inversion recovery (FLAIR) images

<table>
<thead>
<tr>
<th>Signal on FLAIR</th>
<th>Not detected</th>
<th>Hyperintense</th>
<th>Hypointense</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not detected</td>
<td>0</td>
<td>77</td>
<td>20</td>
<td>97</td>
</tr>
<tr>
<td>Hyperintense</td>
<td>3</td>
<td>49</td>
<td>0</td>
<td>52</td>
</tr>
<tr>
<td>Hypointense</td>
<td>3</td>
<td>14</td>
<td>30</td>
<td>47</td>
</tr>
<tr>
<td>Predominantly hypointense</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Hypointense with hyperintense rim</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>158</td>
<td>50</td>
<td>214</td>
</tr>
</tbody>
</table>
Figure. a, c and e, Axial T2-weighted images of three different patients (aged 68, 52, and 79 years) showing a left tuberothalamic artery infarct, and two right-sided paramedian thalamic infarcts. b, d and f, Corresponding fluid-attenuated inversion recovery images do not reveal considerable thalamic abnormalities.
Table 2. Detection on FLAIR and size of lesions

<table>
<thead>
<tr>
<th>Size</th>
<th>Not detected</th>
<th>Detected</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1mm-5mm</td>
<td>66</td>
<td>58</td>
<td>124</td>
</tr>
<tr>
<td>5mm-10mm</td>
<td>26</td>
<td>35</td>
<td>61</td>
</tr>
<tr>
<td>&gt; 10mm</td>
<td>5</td>
<td>24</td>
<td>29</td>
</tr>
</tbody>
</table>

On the basis of the signal intensity on T2-WI and T1-WI, we found 108 lacunar infarcts, 50 incomplete infarcts, and 50 haemorrhages. FLAIR depicted 61 (56%) of the 108 lacunar infarcts, 20 (40%) of the 50 incomplete infarcts, and 30 (60%) of the 50 microbleeds. Thirty-two lacunar infarcts were hyperintense on FLAIR (noncystic infarcts), and 29 were totally or partially hypointense (cystic or partially cystic infarcts).

Most (79%) of the 97 lesions not detected on FLAIR were hyperintense on T2-WI, but no significant difference was found between the group of lesions detected on FLAIR and the group of lesions not detected on FLAIR with respect to the combination of signal intensities on T2-WI and T1-WI (Table 3).

Table 3. Detection on FLAIR and signal of lesions on T2-WI and T1-WI

<table>
<thead>
<tr>
<th>Detection on FLAIR</th>
<th>Detected on FLAIR</th>
<th>Not detected on FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperintense on T2-WI</td>
<td>Hypointense on T2-WI</td>
</tr>
<tr>
<td>Isointense on T1-WI</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Hypointense on T1-WI</td>
<td>61</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>81</td>
<td>30</td>
</tr>
</tbody>
</table>
Discussion

Our study shows that FLAIR images are not very sensitive to depict thalamic lesions in patients with vascular dementia. Therefore, FLAIR sequences are not well suited as stand-alone sequences for the evaluation of thalamic lesions in patients suspected of having vascular dementia.

FLAIR sequences use a long TI that suppresses the signal from CSF and a long TE that provides heavy T2 weighting. Therefore, major advantages of FLAIR images are to depict and help to characterize brain lesions around CSF spaces. FLAIR images also enable to identify CSF-like lesions.

Although most studies advocate superiority of FLAIR over conventional spin-echo imaging in a wide range of pathologies, some studies showed that FLAIR was more often associated with image artifacts or could not corroborate its aforementioned superiority. Disadvantages of FLAIR include a reduced sensitivity to depict infratentorial and spinal cord lesions. The reason for this is unknown but most likely reflects different relaxation characteristics in those regions, both in normal-appearing tissue and in lesions. For example, T1 and T2 relaxation times of infratentorial lesions in patients with multiple sclerosis were found to be closer to the relaxation times of the surrounding normal-appearing white matter than those of supratentorial lesions, which results in reduced contrast between infratentorial lesions and the background. Age-related increases in T1 relaxation times of the human brain have also been shown, particularly in the thalami, and may serve to explain the lack of sensitivity of FLAIR to show thalamic lesions in elderly patients with vascular dementia.
Alternatively, the occurrence of cystic changes in lacunar infarcts\textsuperscript{179} may lead to a prolongation of their T1 relaxation time, and the signal from these lesions may be suppressed on FLAIR, as occurs with the CSF spaces. The same happens with multiple sclerosis lesions severely hypointense on T1-WI.\textsuperscript{359}

MRI-pathological correlation studies performed to determine the background of age-related subcortical grey and white matter hyperintensities on T2-WI have found different types of pathology: infarcts, gliosis, myelin and axonal loss, breakdown of the ependymal lining, as well as enlarged Virchow-Robin spaces.\textsuperscript{186,187,192,360-362} Areas of myelin pallor can be hyperintense on T2-WI but isointense on T1-WI,\textsuperscript{186,187} and it is conceivable that differences in type of pathology can also influence the signal-intensity on FLAIR.

A proposed neuropathological classification of cerebral lacunae includes both ischaemic (type I) and haemorrhagic (type II) vascular abnormalities, as well as enlarged Virchow-Robin spaces (type III).\textsuperscript{179} Nevertheless, it seems important to differentiate vascular lesions from enlarged Virchow-Robin spaces. Most of enlarged Virchow-Robin spaces normally surround perforating arteries that enter the striatum in the anterior perforated substance, just above the internal carotid artery bifurcation, laterally to the anterior commissure. They are responsible for the so called “état criblé” of the basal ganglia,\textsuperscript{189,190,339,363-365} and are much less frequently located in the thalami.\textsuperscript{365} Therefore, it is unlikely that thalamic lesions classified as complete infarcts on the basis of MRI are in fact enlarged Virchow-Robin spaces, or that thalamic Virchow-Robin spaces could account for the greater number of lesions detected on T2-WI. Actually, FLAIR depicted more poorly all types of presumed thalamic pathology.
A limitation of our study is that we used images acquired on a wide range of scanners and sequences, which may have hampered the qualitative assessment of the abnormalities. On the other hand, this reflects the normal variability of vendor-supported sequences and illustrates that the image contrast mechanisms of FLAIR probably are less stable than those of spin-echo T2-weighted sequences. For the detection of type II haemorrhagic lacunae, both spin-echo and FLAIR sequences are insensitive when compared with gradient-echo T2*-weighted sequences, but these were not available in the context of this trial. Nevertheless, we detected a fair amount of probable microbleeds.

In conclusion, the sensitivity of T2-WI to depict thalamic lesions in patients with probable vascular dementia is far superior to FLAIR. Given the great clinical importance of these lesions, FLAIR should not be used as the only T2-weighted sequence in patients suspected of having vascular dementia.

In addition to the posterior fossa and spinal cord, the diencephalon seems to represent another region not suitable for evaluation by FLAIR MRI.
4.2

Infratentorial abnormalities in vascular dementia

António J. Bastos Leite, Wiesje M. van der Flier, Elisabeth C.W. van Straaten, Philip Scheltens, Frederik Barkhof

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Abstract

**Background and Purpose:** Infratentorial abnormalities may cause cognitive deficits, but current research criteria for vascular dementia do not consider them. Our purposes were to determine the prevalence of infratentorial abnormalities in vascular dementia, their relation with supratentorial abnormalities, and whether they influence cognitive functioning.

**Methods:** We examined 182 patients (120 men, mean age = 73 years, standard deviation = 8) with probable vascular dementia at inclusion into a multicentre clinical trial. Magnetic resonance imaging scans were evaluated for infratentorial vascular abnormalities, midbrain atrophy, cerebellar atrophy, basilar artery diameter and tortuosity, and supratentorial abnormalities. Cognitive testing included the mini-mental state examination (MMSE), and the vascular dementia assessment scale (VaDAS-cog).

**Results:** One hundred forty-one (77.5%) patients had infratentorial abnormalities: 119 (65.4%) had focal infratentorial vascular lesions, 65 (35.7%) had diffuse pontine vascular abnormalities hyperintense on T2-weighted images, 20 (11.0%) had midbrain atrophy, and 16 (8.8%) had cerebellar atrophy. Significant correlations were found between number of infratentorial vascular lesions and basilar artery diameter ($r = 0.26; P < 0.0001$), infratentorial and basal ganglia (including thalamus) vascular abnormalities ($r = 0.30; P < 0.0001$), as well as between midbrain atrophy and global supratentorial atrophy ($r = 0.27; P < 0.0001$). Infratentorial vascular abnormalities and cerebellar atrophy were not significantly associated with cognitive impairment. Patients with midbrain atrophy performed worse on cognitive tests than those without midbrain atrophy. After correction for sex, age, education, supratentorial abnormalities, and centre, midbrain atrophy remained significantly associated with lower MMSE scores ($P < 0.05$).

**Conclusions:** Infratentorial abnormalities often occur in patients with vascular dementia, but only midbrain atrophy was found to be associated with cognitive impairment.
Introduction

In the late eighties, it became accepted that besides motor function, the neocerebellum contributes to sensory, cognitive, linguistic, and emotional aspects of human behavior. In addition, animal studies provided evidence that the basilar pons and certain brain stem nuclei may also be involved in cognitive processes. Therefore, infratentorial abnormalities may be associated with cognitive deficits, and subjects with several pathologies restricted to the cerebellum were found to have a pattern of behavioural abnormalities characterized by disturbances in executive function, spatial cognition, language, and emotional regulation of behaviour, the so-called cerebellar cognitive affective syndrome. Furthermore, impairment of attention and visuospatial skills were found in patients with isolated infratentorial infarcts.

Although magnetic resonance imaging (MRI) studies have shown that midbrain atrophy is a main feature of progressive supranuclear palsy and that brain stem lesions occur in almost half of the patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), not much is known about the prevalence and relevance of infratentorial abnormalities in other types of dementia. Current research criteria for vascular dementia do not consider infratentorial involvement.

The purposes of this study were to describe the type, extent, and location of infratentorial abnormalities in patients with vascular dementia using MRI, to assess the possible associations between infratentorial and supratentorial abnormalities, and to determine whether infratentorial abnormalities may influence cognitive function.
Chapter 4

Materials and Methods

Patients

Baseline data of 182 patients (120 men, 62 women) were available for this study. The cases were the first batch involved in a large multicentre, phase III, prospective, randomized, double-blind clinical trial on the effects of rivastigmine in patients with vascular dementia – the VantagE study (Novartis International AG, Basel, Switzerland). Trial inclusion criteria included fulfilment of the clinical and radiological parts of the National Institute of Neurological Disorders and Stroke (NINDS) – Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) criteria for probable vascular dementia, with central assessment of the neuroimaging criteria at the Image Analysis Centre (VU University Medical Centre, Amsterdam, the Netherlands). Patients with space-occupying lesions or lobar haemorrhages were excluded.

To evaluate cognitive function, patients were submitted to a set of tests, which included the mini-mental state examination (MMSE) (possible range of scores: 0 to 30), and the vascular dementia assessment scale (VaDAS-cog), a battery of tests comprising a modified version of the Alzheimer’s disease assessment scale (ADAS-cog) (possible range of scores: 0 to 85) and five additional subtests covering neuropsychological domains (executive function, attention, working memory, and verbal fluency) frequently involved in vascular dementia: symbol digit modalities test (number of correct answers, possible range: 0 to 110), digits backwards test (number correct, possible range: 0 to 12), maze task (maximum time to completion = 240 seconds), digit cancellation task (number of targets hit), and verbal fluency tests (number of correct words). On the basis of the MMSE, patients were classified as having mild to moderate (MMSE scores ≥ 10) or severe (MMSE scores < 10) dementia.
**Magnetic Resonance Imaging Protocol**

All patients underwent an MRI examination before randomization. MRI scanners operating between 0.5 and 1.5 Tesla were used. Axial spin-echo T2-weighted images (T2-WI; echo time [TE]: 80 to 120 ms; repetition time [TR]: 3000 to 4000 ms; slice thickness = 5 mm); axial fluid-attenuated inversion recovery (FLAIR) images (TE: 110 to 150 ms; TR: 9000 to 10000 ms; inversion time: 2000 to 2200 ms; slice thickness = 5 mm); and axial, sagittal, and coronal spin-echo T1-weighted images (T1-WI; TE: 11 to 20 ms; TR: 500 to 700 ms; slice thickness = 5 mm) were acquired.

**Image assessment**

Image assessment was performed by a single reader blinded to clinical information, with the use of digital image files.

The assessment of vascular abnormalities included the items of the radiological NINDS-AIREN criteria for vascular dementia, according to operational definitions recently proposed. On the basis of these criteria, patients were classified as having large vessel vascular dementia, small vessel vascular dementia, or a combination of both.

The age-related white matter changes (ARWMC) scale was used to rate vascular abnormalities (including diffuse signal abnormalities hyperintense on T2-WI, as well as number and size of focal lesions: complete infarcts, incomplete infarcts, and haemorrhages) in the following five regions: frontal lobes, parietal and occipital lobes, temporal lobes, basal ganglia (including thalamus), and infratentorial structures (possible range of scores for each region: 0 to 6). Large vessel territorial infarcts were identified by means of templates based on imaging and anatomical studies. Lesions hyperintense on T2-WI and hypointense on T1-WI were
considered complete infarcts. Complete infarcts of deep small vessels were defined as ischaemic lacunae. Lesions hyperintense on T2-WI and isointense on T1-WI were considered incomplete infarcts. Lesions hypointense on T2-WI were considered haemorrhages and defined as microbleeds when measuring < 5 mm.

The location and side of each infratentorial vascular abnormality was registered according to anatomical location: mesencephalon, pons (basilar or tegmental), cerebellar peduncles, cerebellar hemispheres and vermis (cortical-subcortical or deep), and medulla oblongata. For each focal infratentorial lesion, the greatest dimension was determined on axial T2-WI.

We also measured the basilar artery diameter on axial T2-WI and rated the basilar artery tortuosity according to the following scale: non-tortuous basilar artery (score 0), tortuous basilar artery medial to the lateral border of pons (score 1), tortuous basilar artery reaching or going beyond the lateral border of pons (score 2), and dolichoectasia of the basilar artery (score 3).

In addition, we used visual rating scales to evaluate medial temporal lobe atrophy (MTA) (possible range of scores for each side: 0 to 4), and global cortical atrophy (GCA) (possible range of scores: 0 to 3). Midbrain and cerebellar atrophy were considered, respectively, when the anteroposterior diameter of the mesencephalon was < 15 mm, and the left/right average width of the largest cerebellar sulci, measured approximately at the midpoint of their longitudinal extension, was ≥ 2 mm.

Focal infratentorial abnormalities measuring < 2 mm were not included, nor were punctate and linear foci of abnormal signal (isointense with the cerebrospinal fluid) suggestive of enlarged perivascular (Virchow-Robin) spaces, regularly occurring
near the substantia nigra. Care was taken to avoid the inclusion of pulsation artifacts, recognizable by linear patterns of signal-intensity banding attributable to phase misregistration. Abnormalities suggestive of Wallerian degeneration of the corticospinal tract in the brain stem were excluded because they represent axonal degeneration secondary to supratentorial lesions.

**Statistical analysis**

Statistical analysis was performed by means of SPSS 11.0 (SPSS for Windows, Chicago, Ill). We used chi-squared tests to compare categorical variables and the Mann-Whitney U test to compare scores. For comparisons of continuous variables, the independent sample Student’s $t$ test and the Mann-Whitney U test were used, according to the distribution of data. Correlations were tested by using the Spearman rank correlation coefficient ($r$). We used stepwise multiple linear regression analyses to determine whether infratentorial abnormalities independently influenced cognitive function after correction for sex, age, education, duration of dementia, supratentorial ARWMC, MTA, and GCA. Because at least 50 different centres participated in the trial, centre of origin was additionally corrected for. Statistical significance was considered when $P$ values were < 0.05.

**Results**

**Patient sample**

Table 1 summarizes baseline characteristics of the patients. All patients had vascular dementia of mild to moderate severity.

On the basis of the operational definitions for the radiological part of the NINDS-AIREN criteria, 142 (78.0%) patients had small vessel vascular dementia, 22
(12.1%) had large vessel vascular dementia, and 18 (9.9%) had both small and large vessel vascular dementia. There was an overlap of findings suggestive of small vessel disease: 139 (76.4%) of the 182 patients had extensive supratentorial periventricular white matter lesions, which in 129 (70.9%) involved at least 25% of the white matter; 77 (42.3%) had multiple basal ganglia, thalamic, and frontal white matter lacunae; and 70 (38.5%) had bilateral thalamic lesions.

**Table 1.** Baseline characteristics of the patients (n = 182) including age and clinical data, age-related white matter changes (ARWMC) score, medial temporal lobe atrophy (MTA) score, and global cortical atrophy (GCA) score

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (standard deviation)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73.1 (7.5)</td>
<td>49 – 88</td>
</tr>
<tr>
<td>Education (years)</td>
<td>8.8 (4.1)</td>
<td>0 – 20</td>
</tr>
<tr>
<td>Duration of dementia (months)</td>
<td>35.7 (35.2)</td>
<td>1 – 325</td>
</tr>
<tr>
<td>Mini mental state examination¹</td>
<td>19.2° (3.9)</td>
<td>10 – 26</td>
</tr>
<tr>
<td>Alzheimer’s disease assessment scale²</td>
<td>32.5° (11.5)</td>
<td>11 – 80</td>
</tr>
<tr>
<td>Symbol digit modalities¹</td>
<td>9.5 (8.7)</td>
<td>0 – 43</td>
</tr>
<tr>
<td>Digits backwards¹</td>
<td>3.2 (1.8)</td>
<td>0 – 9</td>
</tr>
<tr>
<td>Maze (seconds)²</td>
<td>35.6 (42.3)</td>
<td>4 – 240</td>
</tr>
<tr>
<td>Digit cancellation¹</td>
<td>8.8 (5.4)</td>
<td>0 – 29</td>
</tr>
<tr>
<td>Verbal fluency¹</td>
<td>8.2 (4.6)</td>
<td>0 – 30</td>
</tr>
<tr>
<td>ARWMC frontal²</td>
<td>5.0° (1.4)</td>
<td>1 – 6</td>
</tr>
<tr>
<td>ARWMC parieto – occipital²</td>
<td>5.0° (1.5)</td>
<td>0 – 6</td>
</tr>
<tr>
<td>ARWMC basal ganglia (including thalamus)²</td>
<td>2.4° (1.7)</td>
<td>0 – 6</td>
</tr>
<tr>
<td>ARWMC temporal²</td>
<td>3.4° (1.8)</td>
<td>0 – 6</td>
</tr>
<tr>
<td>ARWMC infratentorial²</td>
<td>2.0° (1.8)</td>
<td>0 – 6</td>
</tr>
<tr>
<td>MTA (left/right average)²</td>
<td>2.1° (1.0)</td>
<td>0 – 4</td>
</tr>
<tr>
<td>GCA²</td>
<td>1.8° (0.7)</td>
<td>0 – 3</td>
</tr>
</tbody>
</table>

¹ Please note that means of scores are presented due to lack of variability in the medians;  
² Lower values indicate greater severity;  
² Higher values indicate greater severity. 
Infratentorial findings

One hundred forty-one (77.5%) of the patients with vascular dementia had infratentorial abnormalities: 119 (65.4%) had focal infratentorial vascular lesions (Figure 1), 65 (35.7%) had diffuse signal abnormalities occurring in the pons (Figure 2), 20 (11.0%) had midbrain atrophy (Figure 3), and 16 (8.8%) had cerebellar atrophy (Figure 4).

Figure 1. (a) Axial T2-weighted image of a 78 year-old patient showing multiple small vessel cerebellar infarcts, some involving the cerebellar cortex (arrows). (b), Coronal T1-weighted image of an 80 year-old patient showing multiple infratentorial lacunae in the basilar pons (large arrow), and supratentorial lacunae occurring in the right basal ganglia region and in both thalami (small arrows). (c, d) Axial T2-weighted images of a 66 year-old patient showing multiple deep cerebellar and pontine microbleeds (arrows).
Figure 2. Axial T2-weighted image showing diffuse hyperintensity occurring in the pons (round overlay) suggestive of small vessel ischaemic pathology.

Figure 3. Axial T2-weighted image showing midbrain atrophy (arrow) and the consequent dilatation of the cerebral aqueduct.
Focal infratentorial vascular lesions occurred more frequently among patients with small vessel vascular dementia (either isolated or associated with large vessel vascular dementia), than in patients with isolated large vessel vascular dementia (Pearson’s chi-square = 4.39; \( P < 0.05 \)). No significant differences between those groups were found for diffuse pontine signal abnormalities, midbrain atrophy, or cerebellar atrophy.

The total number of focal infratentorial vascular lesions detected, not including diffuse pontine abnormalities, was 399 (Table 2). The number of lesions per patient ranged from 0 to 25 (mean = 2.2; standard deviation [SD] = 3.1), but only 56 (30.8%) patients had > 2 lesions. The size of infratentorial vascular lesions ranged from 2 to 28 mm (mean = 6.2; SD = 4.8), but only 37 (20.3%) patients had lesions larger than 10 mm.
Table 2. Presumed pathology, number, location, and side of focal infratentorial lesions in patients with vascular dementia

<table>
<thead>
<tr>
<th>Side</th>
<th>Location</th>
<th>Large vessel complete infarcts</th>
<th>Small vessel complete infarcts</th>
<th>Small vessel incomplete infarcts</th>
<th>Haemorrhages</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>Mesencephalon</td>
<td>8 (2.0%)</td>
<td>1 (0.3%)</td>
<td>2 (0.5%)</td>
<td>11 (2.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basilar pons</td>
<td>42 (10.5%)</td>
<td>9 (2.3%)</td>
<td>26 (6.5%)</td>
<td>77 (19.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tegmental pons</td>
<td>5 (1.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>6 (1.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Middle cerebellar peduncles</td>
<td>2 (0.5%)</td>
<td>1 (0.3%)</td>
<td>3 (0.8%)</td>
<td>3 (0.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar hemispheres (cortical-subcortical)</td>
<td>69 (17.3%)</td>
<td>5 (1.3%)</td>
<td>3 (0.8%)</td>
<td>77 (19.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar vermis (cortical-subcortical)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar hemispheres (deep)</td>
<td>20 (5.0%)</td>
<td>7 (1.8%)</td>
<td>22 (5.5%)</td>
<td>49 (12.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medulla oblongata</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Subtotal left</strong></td>
<td>147 (36.8%)</td>
<td>24 (6.0%)</td>
<td>54 (13.5%)</td>
<td>225 (56.4%)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>Mesencephalon</td>
<td>2 (0.5%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>3 (0.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basilar pons</td>
<td>24 (6.0%)</td>
<td>13 (3.3%)</td>
<td>13 (3.3%)</td>
<td>50 (12.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tegmental pons</td>
<td>7 (1.8%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Middle cerebellar peduncles</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar hemispheres (cortical-subcortical)</td>
<td>57 (14.3%)</td>
<td>7 (1.8%)</td>
<td>5 (1.3%)</td>
<td>70 (17.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar hemispheres (deep)</td>
<td>17 (4.3%)</td>
<td>7 (1.8%)</td>
<td>19 (4.8%)</td>
<td>43 (10.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Subtotal right</strong></td>
<td>107 (26.8%)</td>
<td>27 (6.8%)</td>
<td>39 (9.8%)</td>
<td>174 (43.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td>1 (0.3%)</td>
<td>254 (63.7%)</td>
<td>49 (12.3%)</td>
<td>93 (23.3%)</td>
<td>399 (100%)</td>
</tr>
</tbody>
</table>

*Posteroinferior cerebellar artery infarct
Of the 399 focal lesions, 306 (76.7%) were ischaemic lesions and 93 (23.3%) were haemorrhages. Most (78.5%) of the haemorrhages were microbleeds. The majority (74.2%) of ischaemic lesions involved the cerebellar cortex or the basilar pons, and most (86.0%) of haemorrhages were deep cerebellar or basilar pontine (Figure 1). We found only one infratentorial large vessel infarct occurring in the right posteroinferior cerebellar artery territory.

The mean basilar artery diameter was 4.1 mm (SD = 0.8; range: 2 to 9 mm), and the mean basilar artery tortuosity score was 0.9 (SD = 0.8; range: 0 to 3). A significant correlation was found between basilar artery diameter and number of infratentorial vascular lesions \((r_s = 0.26; P < 0.0001)\), but not between basilar artery diameter and size of lesions. No significant correlations were found between basilar artery tortuosity and number or size of lesions, nor between basilar artery diameter or tortuosity and infratentorial ARWMC.

**Associations between infratentorial and supratentorial abnormalities**

A significant correlation was found between infratentorial and basal ganglia (including thalamus) ARWMC \((r_s = 0.30; P < 0.0001)\), but not between infratentorial and other supratentorial regions. With respect to atrophy, a significant correlation was found between midbrain atrophy and GCA \((r_s = 0.27; P < 0.0001)\), but not between midbrain atrophy and MTA, nor between cerebellar atrophy and GCA or MTA. No significant correlations were found between midbrain or cerebellar atrophy and ARWMC.

**Clinical-radiological associations of infratentorial abnormalities**

Neither focal infratentorial vascular lesions, nor diffuse pontine signal abnormalities or cerebellar atrophy were significantly associated with cognitive impairment.
Patients with midbrain atrophy performed worse on MMSE ($P < 0.01$), ADAS-cog ($P < 0.05$), digit cancellation ($P < 0.01$), and verbal fluency ($P < 0.05$) tests than patients without midbrain atrophy. No significant associations were found between midbrain atrophy and symbol digit modalities, digits backwards, or maze time to completion.

Stepwise multiple linear regression analyses revealed the following independent variables significantly associated with MMSE: MTA ($B = -0.97$; standard error [SE] = 0.28; $P < 0.01$), education ($B = 0.20$; SE = 0.06; $P < 0.01$), GCA ($B = -1.10$; SE = 0.42; $P < 0.05$), and midbrain atrophy ($B = -1.77$; SE = 0.88; $P < 0.05$). After additional correction for centre, midbrain atrophy remained significantly associated with MMSE ($B = -2.10$; SE = 0.99; $P < 0.05$). Stepwise multiple linear regression analyses also revealed that midbrain atrophy was significantly associated with digit cancellation ($B = -2.39$; SE = 1.19; $P < 0.05$), but this association no longer demonstrated statistical significance after correction for centre.

**Discussion**

Our study shows that infratentorial abnormalities often occur in patients fulfilling the NINDS-AIREN criteria for vascular dementia. Focal infratentorial vascular lesions are especially frequent among patients with small vessel type of vascular dementia, which is in agreement with the view that these patients have more widespread cerebrovascular pathology than those with isolated large vessel vascular dementia. In addition, patients with large basilar artery diameter were found to have more infratentorial vascular lesions, which may result from atheroembolic events associated with vascular ectasia. We also found diffuse signal abnormalities in the pons, probably representing diffuse ischaemic small vessel pathology.$^{386}$ Moreover,
we found that infratentorial vascular abnormalities are associated with basal ganglia and thalamic lesions. Since both infratentorial structures and the thalami are perfused by the vertebrobasilar system, this association may be partially explained. Furthermore, we found midbrain and cerebellar atrophy occurring in a minority of patients.

The observed infratentorial vascular lesions were mainly located in the cerebellum and basilar pons, structures currently considered relevant to cognitive processes, although the clinical scales that we used for vascular dementia, selected to test general cognitive and executive functions, did not confirm that such lesions indeed contribute to cognitive impairment. However, the amount of supratentorial vascular lesions occurring in our patients may have masked the cognitive relevance of infratentorial lesions, and it is also possible that more specific neuropsychological tests might have shown other subtle cognitive effects. Actually, neuropsychological batteries including tests for visuospatial skills showed abnormal results when used in subjects with predominant infratentorial pathology (e.g., large vessel cerebellar infarcts, Friedreich's ataxia, and olivopontocerebellar atrophy).

On the other hand, we found that patients with midbrain atrophy had worse general cognitive and executive functioning than the other patients with vascular dementia. Although midbrain atrophy was found to be related with GCA, most probably due to axonal degeneration secondary to supratentorial pathology, the association between midbrain atrophy and lower MMSE scores persisted even after correction for abnormalities representing degenerative and vascular supratentorial pathology. These findings suggest that the midbrain contributes to cognition independently of the supratentorial structures, and that assessment of midbrain atrophy should be included in the MRI evaluation of patients with dementia.
There is an increasing awareness that vascular and degenerative pathology may coexist. Additionally, neuropathological studies have reported involvement of the cerebellum and midbrain by Alzheimer’s pathology. Therefore, it is conceivable that cerebellar and midbrain atrophy observed in this sample of patients with vascular dementia may represent concomitant Alzheimer’s pathology, and that its occurrence in the periaqueductal grey matter may explain the association between midbrain atrophy and cognitive impairment by disruption of mesencephalic connections. More work is needed to determine whether midbrain atrophy actually represents degenerative pathology and whether its presence in patients fulfilling diagnostic criteria for vascular dementia is a marker for mixed dementia (Alzheimer and vascular).

Strong elements of the current study include the large sample of patients that were rigorously screened for their fulfilment of radiological criteria for probable vascular dementia by central assessment. Limitations include the fact that magnetic resonance images were acquired on a wide range of scanners and sequences, which may have hampered the qualitative assessment of the abnormalities; and that T2*-weighted images were not available, which may have underestimated the number of haemorrhages detected. In the present sample, we also lack information on neurological sequelae of the lesions.

Our study shows the high prevalence of infratentorial vascular lesions in patients with probable vascular dementia. Current neuroimaging criteria for vascular dementia do not include the occurrence of such lesions, and our results seem to support those criteria. However, apart from the relevance of midbrain atrophy, it is not ruled out that infratentorial vascular lesions may contribute to the clinical picture of vascular dementia, by interacting with strategic supratentorial (basal ganglia and thalamic) vascular lesions.
4.3

The contribution of medial temporal lobe atrophy and vascular pathology to cognitive impairment in vascular dementia

António J. Bastos-Leite, Wiesje M. van der Flier, Elisabeth C.W. van Straaten, Salka S. Staekenborg, Philip Scheltens, Frederik Barkhof

Stroke 2007; in press
Abstract

Background and Purpose: Besides cerebrovascular disease, medial temporal lobe atrophy (MTA), a neuroimaging finding suggestive of degenerative pathology, has been shown in vascular dementia. However, it is unknown to what extent MTA contributes to the pattern of cognitive impairment observed in vascular dementia. Therefore, our purpose was to investigate the relative contribution of cerebrovascular disease and MTA to cognitive impairment in patients fulfilling diagnostic criteria for vascular dementia.

Methods: We examined 590 patients (374 men, mean age = 73 years, standard deviation = 8) with probable vascular dementia, according to the National Institute of Neurological Disorders and Stroke (NINDS) – Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) criteria, at inclusion into a multicentre clinical trial. Cerebrovascular disease and the degree of MTA were evaluated by using magnetic resonance imaging. Cognitive testing included the mini-mental state examination (MMSE), and the vascular dementia assessment scale (VaDAS-cog).

Results: On the basis of the operational definitions for the neuroimaging part of the NINDS-AIREN criteria, 485 (82.2%) patients had small vessel vascular dementia, and 153 (25.9%) had large vessel vascular dementia. More than half (59.8%) of the patients had considerable MTA. Multiple linear regression analyses revealed that after correction for sex, age, education, and duration of dementia, neuropsychological tests showed that patients with higher grades of MTA or large vessel vascular dementia had significantly worse general cognitive and executive functioning, while associations with small vessel disease were restricted to worse executive functioning.

Conclusions: Both MTA and large vessel disease contribute to global cognitive impairment in vascular dementia. Small vessel disease contributes to executive dysfunction.
Introduction

Vascular dementia is the second most common type of dementia. Diagnostic criteria for vascular dementia, such as the National Institute of Neurological Disorders and Stroke (NINDS) – Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) criteria, emphasize the heterogeneity of both clinical syndromes and pathological subtypes of vascular dementia, as well as the importance of brain imaging to support clinical findings.

The main clinicopathological subtypes of vascular dementia are large vessel and small vessel disease, the later being more prevalent. Large vessel vascular dementia results from strategic large vessel strokes. Small vessel vascular dementia may either result from multiple subcortical lacunar infarcts, bilateral thalamic lesions, or from diffuse white matter lesions. Subcortical ischaemic small vessel vascular dementia is currently recognized as the most broad and homogeneous subtype of vascular dementia. On magnetic resonance imaging (MRI), subcortical ischaemic vascular dementia is characterized by the occurrence of extensive white matter hyperintensities (WMH) on T2-weighted images, which are generally considered as a surrogate marker for ischaemic small vessel disease in elderly subjects. According to the NINDS-AIREN criteria, WMH alone may be sufficient to cause dementia when at least 25% of the white matter is involved.

Medial temporal lobe atrophy (MTA), a neuroimaging finding suggestive of degenerative pathology, has been shown in vascular dementia, but it is unknown to what extent neurodegenerative disease, rather than cerebrovascular pathology, contributes to the pattern of cognitive impairment observed in vascular dementia. Therefore, our purpose was to investigate the contribution of large vessel disease, small vessel disease, MTA, and their interactions to cognitive impairment in a large sample of patients fulfilling diagnostic criteria for vascular dementia.
Materials and Methods

Patients

We examined the baseline data of 590 patients (374 men, 216 women) enrolled into the VantagE study (Novartis International AG, Basel, Switzerland), a multicentre, phase III, prospective, randomized, double-blind clinical trial on the effects of rivastigmine in patients with vascular dementia. Trial inclusion criteria included fulfilment of the clinical and radiological parts of the NINDS-AIREN criteria for probable vascular dementia, with central assessment of the neuroimaging criteria at the Image Analysis Centre (VU University Medical Centre, Amsterdam, the Netherlands). For the current study, all patients were required to have complete cognitive and MRI data. Patients with lobar haemorrhages or space occupying lesions were excluded.

To evaluate cognitive function, patients were submitted to a set of tests, which included the mini-mental state examination (MMSE) (possible range of scores: 0 to 30), and the vascular dementia assessment scale (VaDAS-cog), a battery of tests comprising the Alzheimer's disease assessment scale (ADAS-cog) (possible range of scores: 0 to 70) and five additional subtests covering neuropsychological domains (executive function, attention, working memory, and verbal fluency) frequently involved in vascular dementia: symbol digit modalities test (number of correct answers, possible range: 0 to 110), digits backwards test (number correct, possible range: 0 to 12), maze task (maximum time to completion = 240 seconds), digit cancellation task (number of targets hit), and verbal fluency tests (number of correct words).
Magnetic Resonance Imaging Protocol

All patients underwent an MRI examination before randomization. MRI scanners operating between 0.5 and 1.5 Tesla were used. Axial spin-echo T2-weighted images (T2-WI; echo time [TE]: 80 to 120 ms; repetition time [TR]: 3000 to 4000 ms; slice thickness = 5 mm); axial fluid-attenuated inversion recovery (FLAIR) images (TE: 110 to 150 ms; TR: 9000 to 10000 ms; inversion time: 2000 to 2200 ms; slice thickness = 5 mm); and axial, sagittal, and coronal spin-echo T1-weighted images (T1-WI; TE: 11 to 20 ms; TR: 500 to 700 ms; slice thickness =5 mm) were acquired.

Image assessment

Vascular abnormalities and MTA were evaluated by a single reader blinded to clinical information using the original digital image files. The assessment of vascular abnormalities included the items of the radiological NINDS-AIREN criteria for vascular dementia, according to published operational definitions, and patients either fulfilled criteria for large vessel vascular dementia, small vessel vascular dementia, or both. For the assessment of WMH, we used the age-related white matter changes (ARWMC) scale in the following five regions: frontal lobes, parietal and occipital lobes, temporal lobes, basal ganglia (including thalamus), and infratentorial structures (possible range of scores for each region: 0 to 6). MTA was evaluated by using a visual rating scale based on the choroidal fissure width, the temporal horn width, and the hippocampal height (possible range of scores for each side: 0 to 4).

Statistical analysis

Statistical analysis was done by means of SPSS 11.0 (SPSS for Windows, Chicago, Ill). Variables representing cerebrovascular disease were dichotomized as follows: large vessel vascular dementia absent or present, multiple subcortical lacunar infarcts
and bilateral thalamic lesions absent or present, and extensive WMH absent (total ARWMC score ≤ 12) or present (total ARWMC score > 12). Left/right average MTA scores ≥ 1.5 were regarded as representing considerable MTA. We used the Pearson’s chi-squared test to compare categorical variables, and the Mann-Whitney U test to compare scores. For comparisons of continuous variables, the independent sample Student’s t test or the Mann-Whitney U test were used, according to the distribution of data. Correlations were tested by using the Spearman rank correlation coefficient (r). To determine whether the occurrence of large vessel vascular dementia, small vessel disease, or MTA independently influenced cognitive function, we used multiple linear regression analyses with sex, age, education, and duration of dementia as covariates. We also tested interactions between the occurrence of large vessel vascular dementia, small vessel disease, and MTA by entering bivariate product-terms in the model. Statistical significance was considered when P values were < 0.05.

Results

Table 1 summarizes baseline characteristics of the patients. On the basis of the operational definitions for the radiological part of the NINDS-AIREN criteria, 437 (74.1%) patients had small vessel vascular dementia, 105 (17.8%) had large vessel vascular dementia, and 48 (8.1%) had both small and large vessel vascular dementia. Three hundred-ninety (66.1%) patients had extensive WMH (total ARWMC score > 12), and 103 (17.5%) had multiple subcortical lacunar infarcts in association with bilateral thalamic lesions. More than half (59.8%) of the patients had considerable MTA (left/right average MTA score ≥ 1.5).

A significant association was found between the occurrence of extensive WMH and the occurrence of multiple lacunar infarcts and thalamic lesions (P < 0.001). In
addition, a significant association was found between the occurrence of extensive WMH and MTA ($P < 0.05$). MTA scores in patients with large vessel vascular dementia were significantly lower than in patients with small vessel vascular dementia ($P < 0.01$), although the proportion of patients with considerable MTA did not significantly differ between those groups.

Table 1. Baseline characteristics of the patients ($n = 590$) including age and clinical data, age-related white matter changes (ARWMC) score, and medial temporal lobe atrophy (MTA) score

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (standard deviation)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72.5 (7.9)</td>
<td>44 – 89</td>
</tr>
<tr>
<td>Education (years)</td>
<td>9.5 (4.0)</td>
<td>0 – 25</td>
</tr>
<tr>
<td>Duration of dementia (months)</td>
<td>31.5 (29.1)</td>
<td>0 – 213</td>
</tr>
<tr>
<td>Mini mental state examination $^1$</td>
<td>19.4* (3.7)</td>
<td>9 – 26</td>
</tr>
<tr>
<td>Alzheimer’s disease assessment scale $^2$</td>
<td>22.1* (9.0)</td>
<td>4 – 51</td>
</tr>
<tr>
<td>Symbol digit modalities $^1$</td>
<td>12.6 (9.1)</td>
<td>0 – 60</td>
</tr>
<tr>
<td>Digits backwards $^1$</td>
<td>3.6 (1.9)</td>
<td>0 – 11</td>
</tr>
<tr>
<td>Maze (seconds) $^2$</td>
<td>32.1 (42.0)</td>
<td>3 – 240</td>
</tr>
<tr>
<td>Digit cancellation $^1$</td>
<td>10.1 (5.5)</td>
<td>0 – 35</td>
</tr>
<tr>
<td>Verbal fluency $^1$</td>
<td>8.9 (4.6)</td>
<td>0 – 43</td>
</tr>
<tr>
<td>ARWMC total $^2$</td>
<td>14.4* (6.2)</td>
<td>0 – 30</td>
</tr>
<tr>
<td>MTA (left/right average) $^2$</td>
<td>1.6* (0.9)</td>
<td>0 – 4</td>
</tr>
</tbody>
</table>

$^*$ Please note that means of scores are presented, whereas we used non-parametric tests to analyse data.
$^1$ Lower values indicate greater severity.
$^2$ Higher values indicate greater severity.

With the exception of the MMSE score, which was significantly lower ($P < 0.05$) in patients with large vessel vascular dementia, the results of the remaining neuropsychological tests almost did not differ between groups of patients with and without large vessel vascular dementia.
Table 2. Multiple linear regression analyses

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>Large vessel VaD and bilateral thalamic lesions</th>
<th>WMH</th>
<th>MTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-1.28 (0.35)***</td>
<td>0.26 (0.32)</td>
<td>-0.89 (0.31)**</td>
</tr>
<tr>
<td>2</td>
<td>-1.56 (0.41)***</td>
<td>0.48 (0.38)</td>
<td>-0.90 (0.31)**</td>
</tr>
<tr>
<td>ADAS-cog</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.33 (0.85)**</td>
<td>0.22 (0.79)</td>
<td>3.91 (0.75)***</td>
</tr>
<tr>
<td>2</td>
<td>3.44 (0.99)**</td>
<td>1.67 (0.91)</td>
<td>3.89 (0.75)***</td>
</tr>
<tr>
<td>Symbol digit modalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-0.03 (0.86)</td>
<td>-2.20 (0.79)**</td>
<td>-3.40 (0.77)***</td>
</tr>
<tr>
<td>2</td>
<td>-1.83 (1.00)</td>
<td>-2.71 (0.92)**</td>
<td>-3.23 (0.77)***</td>
</tr>
<tr>
<td>Digits backwards</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-0.39 (0.18)*</td>
<td>-0.02 (0.16)</td>
<td>-0.32 (0.16)</td>
</tr>
<tr>
<td>2</td>
<td>-0.56 (0.21)**</td>
<td>-0.29 (0.19)</td>
<td>-0.31 (0.16)</td>
</tr>
<tr>
<td>Maze</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8.64 (4.00)*</td>
<td>-2.70 (3.72)</td>
<td>2.94 (3.63)</td>
</tr>
<tr>
<td>2</td>
<td>9.34 (4.80)</td>
<td>2.47 (4.43)</td>
<td>2.99 (3.63)</td>
</tr>
<tr>
<td>Digit cancellation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-1.30 (0.51)*</td>
<td>-0.70 (0.47)</td>
<td>-1.84 (0.45)***</td>
</tr>
<tr>
<td>2</td>
<td>-2.51 (0.59)***</td>
<td>-1.67 (0.55)**</td>
<td>-1.81 (0.45)***</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-0.02 (0.44)</td>
<td>-0.63 (0.41)</td>
<td>-1.24 (0.40)**</td>
</tr>
<tr>
<td>2</td>
<td>-0.69 (0.52)</td>
<td>-0.68 (0.48)</td>
<td>-1.23 (0.40)**</td>
</tr>
</tbody>
</table>

WMH: white matter hyperintensities.
MTA: medial temporal lobe atrophy.
MMSE: mini-mental state examination.
ADAS-cog: Alzheimer’s disease assessment scale.
Model 1: single MRI measure (each MRI measure is a different model), corrected for age, sex, education, and duration of dementia.
Model 2: all three MRI measures simultaneously entered, corrected for age, sex, education, and duration of dementia.
Values represent unstandardized regression coefficients plus standard errors.
*P < 0.05; **P < 0.01; ***P < 0.001
Figure. Box plots displaying significant interactions between the occurrence of extensive white matter hyperintensities (WMH) and considerable medial temporal lobe atrophy (MTA). These interactions were found to influence results of the symbol digit modalities (SDM) and digit cancellation (DC) tests, and suggest that the contribution of WMH for executive dysfunction is specific for patients without considerable MTA.

A, patients without considerable MTA and without extensive WMH.
B, patients without considerable MTA, but with extensive WMH.
C, patients with considerable MTA, but without extensive WMH.
D, patients with considerable MTA and extensive WMH.
Multiple linear regression analyses revealed that after correction for sex, age, education, and duration of dementia, most of the neuropsychological tests showed that patients with higher grades of MTA or large vessel vascular dementia had worse general cognitive and executive functioning (table 2). The occurrence of multiple lacunar infarcts and thalamic lesions was found to be associated with worse verbal fluency. Extensive WMH were associated with worse performance in the following tests of executive functioning: symbol digit modalities and digit cancellation. In addition, significant interactions between MTA and WMH were found to influence the results of the symbol digit modalities \((P < 0.01)\) and digit cancellation \((P < 0.05)\) tests (Figure), suggesting that the effect of WMH was specific for patients without considerable MTA.

**Discussion**

Our study shows that both MTA and the occurrence of large vessel vascular dementia are independently associated with general cognitive and executive dysfunction in patients with vascular dementia. In addition, it shows that small vessel disease seems to be related to worse executive functioning, especially in patients without considerable MTA.

A large proportion of patients with dementia have a combination of degenerative and vascular pathology in the brain.\(^{308}\) From a radiological point of view, MTA is usually considered to be a surrogate marker of degenerative pathology, because neuropathological changes underlying Alzheimer’s disease first occur in the medial temporal lobe.\(^{59}\) Therefore, it is plausible that the occurrence of MTA in our patients, as well as its association with cognitive impairment, is attributable to concomitance of Alzheimer’s pathology. Alternatively, MTA may be secondary to vascular pathology,
more precisely to small vessel disease and ischaemia. Nevertheless, when there is neuroimaging evidence of mixed pathology (degenerative and vascular), atrophy seems to predict or correlate better with dementia than small vessel disease. Our results are in agreement with those findings, since we showed that, in a large sample of patients fulfilling diagnostic criteria for vascular dementia, WMH have a more restricted effect on cognitive function than MTA.

With respect to the causal relation between vascular lesions alone and dementia, it is currently considered that such a relation is only clear when patients are young and it is unlikely they have associated Alzheimer’s pathology; when cognitive functions are normal before stroke, impaired immediately after, and do not worsen over time; when vascular lesions are located in strategic regions; and when well-defined vasculopathies known to cause dementia are proven, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), or some types of cerebral amyloid angiopathies (CAA). In other circumstances, it is possible that both degenerative and vascular pathology may contribute to cognitive impairment. In our sample, we found a clear association between large vessel disease and cognitive impairment. However, the majority of our patients had small vessel vascular dementia and the contribution of MTA to cognitive dysfunction was more pronounced than the contribution of small vessel disease.

Executive dysfunction is usually considered to be a major characteristic of vascular dementia. Given that we found associations between small vessel disease and worse performance in tests of executive functioning, it is conceivable that the degree of such dysfunction may be justified, in part, by the severity of small vessel disease. Nevertheless, results from a recent neuropathological study indicate that the cognitive effects of small vessel cerebrovascular disease are variable and not especially distinct.
Strong elements of the current study include the large sample of patients that were rigorously screened for their fulfilment of radiological criteria for probable vascular dementia by central assessment. A limitation results from the selection bias secondary to the requirement that all the included patients had to fulfil the NINDS-AIREN criteria. Another limitation is the cross-sectional design of the current study, which precludes the assessment of causality.

In conclusion, both MTA and large vessel disease contribute to global cognitive impairment in vascular dementia, while the effect of small vessel disease contributes only to executive dysfunction, especially in patients without considerable MTA.
Chapter 5

White matter hyperintensities

5.1 Cerebral blood flow by using pulsed arterial spin labelling in elderly subjects with white matter hyperintensities


Submitted for publication
Abstract

Purpose: To prospectively determine whether there is an association between the degree of white matter hyperintensities (WMH) in elderly subjects and absolute cerebral blood flow (CBF) measurements obtained by means of quantitative imaging of perfusion using a single subtraction, second version, with thin-slice inversion time periodic saturation (Q2TIPS), a pulsed arterial spin labelling (PASL) magnetic resonance imaging (MRI) perfusion-weighted sequence.

Material and methods: MRI scans of 21 subjects (13 women, mean age = 76, standard deviation [SD] = 5), stratified for the degree of WMH, from a single centre within the multinational Leukoaraiosis and Disability (LADIS) study were investigated. The study was approved by both the local and the LADIS study institutional review boards, as well as by the LADIS study steering committee. All subjects gave written informed consent. Values of cortical grey matter (GM), subcortical (including white matter and deep GM), and global CBF were calculated by analyzing CBF images with a statistical parametric mapping program (SPM5). CBF measurements of subjects with diffuse confluent WMH (n = 7) were compared to those of subjects with punctiform or beginning confluent WMH (n = 14).

Results: Subjects with diffuse confluent WMH were found to have approximately 20% lower mean global CBF (43.5 ml/100 ml/min; SD = 6.3) than subjects with punctiform or beginning confluent WMH (57.9 ml/100 ml/min; SD = 8.6; P < 0.01); as well as approximately 20% lower mean subcortical (P < 0.01), and cortical GM CBF (P < 0.05).

Conclusion: PASL revealed a significant reduction of CBF measurements in elderly subjects with diffuse confluent WMH.
Introduction

On magnetic resonance imaging (MRI), white matter hyperintensities (WMH) on T2-weighted images, fluid-attenuated inversion recovery (FLAIR) images, and proton density-weighted images are generally considered as a surrogate marker for ischaemic small vessel disease in elderly subjects, but their significance is still under debate.

Arterial spin labelling (ASL) is a functional magnetic resonance (MR) technique that represents an alternative to both nuclear medicine and dynamic susceptibility contrast (DSC) echo-planar MR sequences for the evaluation of cerebral perfusion. By using water as a diffusible tracer, ASL does not need either ionizing radiation or an exogenous contrast bolus injection. After applying an appropriate series of radiofrequency pulses, water proton spins in the arterial blood can be inverted (magnetically labelled) before entering the capillary level. When these labelled water protons enter the capillary level, they alter the magnetization of the tissue in a way that can be measured quantitatively. Pulsed ASL (PASL) techniques generally label a large blood volume in a thick slab just below the planes of image acquisition, by inverting the magnetization of water protons with adiabatic hyperbolic secant radiofrequency pulses.

Because WMH most probably represent ischaemic small vessel disease, we hypothesized that higher grades of WMH would be associated with brain hypoperfusion. In fact, SPECT, PET, and DSC perfusion-weighted MRI studies have shown that WMH are associated with reduced cerebral perfusion, but most of them did not yield absolute quantification of cerebral blood flow (CBF), nor did they show a relation between different grades of WMH and CBF measurements. Therefore, our purpose was to determine the feasibility to demonstrate an association
between the degree of WMH in elderly subjects and absolute CBF measurements obtained by means of PASL.

Materials and Methods

Subjects
We included 21 subjects (8 men, 13 women) from a single centre within the Leukoaraiosis and Disability (LADIS) study. The current study was approved by both the local and the LADIS study institutional review boards, as well as by the LADIS study steering committee. All subjects gave written informed consent.

The LADIS study is a prospective, longitudinal, multicentre European study on the role of WMH as an independent predictor for transition to disability in non-demented elderly subjects. Inclusion criteria for the LADIS study were: age between 65 and 84 years old; WMH on MRI of any degree, according to the Fazekas scale; absence of disability; presence of a regularly contactable informant; and agreement to sign an informed consent. Exclusion criteria were: presence of severe illnesses; severe unrelated neurological diseases; leukoencephalopathy of non-vascular origin; severe psychiatric diseases; inability to give an informed consent; and inability or refusal to undergo cerebral MRI.

All subjects underwent an MRI examination at baseline. In our centre, follow-up MRI examinations were performed yearly, and the current report focuses on data obtained during the second or third year of follow-up.

On the basis of clinical findings at the time of undergoing MRI, the included subjects for the current study were classified as having: normal cognition, or
cognitive impairment. Concurrent medications and drugs possibly affecting CBF were also accounted for.

**Magnetic Resonance Imaging Protocol**

MRI examinations were acquired at 1.5 Tesla (Sonata, Siemens AG, Erlangen, Germany) and included axial FLAIR images (echo time [TE] = 84 ms; repetition time [TR] = 9000 ms; number of excitations [NEX] = 2; inversion time [TI] = 2200 ms; field of view [FOV] = 250 mm; slice thickness = 5 mm; number of slices = 24; acquisition matrix = 256x192, interpolated to image matrix = 512x384), and a high-resolution 3D T1-weighted inversion recovery sequence (TE = 5.17 ms; TR = 2700 ms; TI = 950 ms; flip angle = 8°; NEX = 1; FOV = 250 mm; slice thickness = 1 mm; number of slices = 160; acquisition matrix = 256x176 [69% FOV phase], interpolated to image matrix = 512x352). In addition, to obtain relative CBF (rCBF) images, we chose a quantitative imaging of perfusion using a single subtraction, second version, with thin-slice TI periodic saturation (Q2TIPS) PASL sequence with proximal inversion and control for off-resonance effects (PICORE). To convert the signal intensity of the rCBF images to absolute values of CBF, a single shot echo-planar imaging (EPI) sequence of the fully relaxed brain tissue was also acquired.

**Q2TIPS tailored to an elderly population**

ASL techniques rely on subtracting control images (acquired with blood and tissue water in identical magnetization states) from spin labelled images (acquired with blood and tissue water in different magnetization states). The Q2TIPS variant of PASL enables the acquisition of images in multiple slices, and aims to control for two major systematic errors of ASL: the variable transit time from the distal edge of the labelled region to the image slices, and the contamination by intravascular signal from labelled blood that flows through the image slices by applying thin-slice periodic saturation pulses at the distal end of the labelled region.
We used a 10 cm labelling region; a TE = 15 ms; a TI₁ = 700 ms (time between the inversion pulse and the beginning of periodic saturation pulses); a TI₁ stop time (TI₁s) = 1600 ms (time between the inversion pulse and the end of periodic saturation pulses); a TI₂ = 1800 ms (time between the inversion pulse and acquisition of the proximal image); and a TR = 2500 ms. By using a TI₂ = 1800 ms, one can obtain an appropriate brain tissue signal in elderly subjects, almost without intravascular signal. To further improve suppression of intravascular signal, we additionally used a bipolar crusher gradient. The sequence was repeated 200 times, alternating between acquisition of 100 labelled and 100 control images, and prospective motion correction was applied before subtracting each labelled-control pair. After subtraction, the difference images were averaged to obtain rCBF images in six slices (FOV = 224 mm; slice thickness = 6 mm; inter-slice gap = 1.5 mm; matrix = 64x64; ascending slice acquisition order).

**Quantification of CBF**

Quantification of CBF by means of ASL is based on the difference in longitudinal magnetization ($\Delta M$) between labelled and control images. For Q2TIPS, $\Delta M$ at time $t=TI₂$ is related to CBF by the following formula:

$$\Delta M (t=TI₂) = 2 f m₀ α TI₁ e^{TI₂/T₁b}$$

for $TI₁ < t_L$ and $TI₂ > TI₁ + t_T$ (1)

$TI₁$ and $TI₂$ are sequence parameters. $T₁b$ is the T1 value of arterial blood, $α$ is the degree of spin inversion, $m₀$ is the arterial blood longitudinal magnetization at equilibrium, $t_L$ is the labelling time, $t_T$ is the transit time from the distal edge of the labelled region to the image slices, and $f$ corresponds to absolute values of CBF. We assumed $T₁b = 1400$ ms and $α = 0.97$.401
To account for differences in proton density between blood and brain tissue, an average value (between grey and white matter) of 0.90 was assumed for the blood/brain partition coefficient ($\lambda$), which is defined by the following formula:

$$\lambda = \frac{M^0}{m^0_a}$$  \hspace{1cm} (2)

$M^0$ corresponds to the brain tissue longitudinal magnetization at equilibrium\(^{401}\) and is related to the magnitude of signal at equilibrium ($S^0$) by the scanner gain $G$:

$$S^0 = G M^0 = G \lambda m^0_a$$ \hspace{1cm} (3)

$S^0$ was determined by using a single shot EPI sequence of the fully relaxed brain tissue. This single shot EPI sequence is similar to the EPI readout in Q2TIPS, but does not have any presaturation, labelling, or periodic saturation pulses. In addition, a dead time of 10 seconds was inserted between adjustment pulses of the scanner and the acquisition of images.

Finally, the difference in signal ($\Delta S$) between labelled and control images (signal of rCBF images) is also related to $\Delta M$ by the scanner gain $G$:

$$\Delta S = G \Delta M$$ \hspace{1cm} (4)

Combining equations (1), (3) and (4), and additionally accounting for T2* effects of blood and brain tissue, a scaling factor $C$ was calculated in order to determine absolute CBF measurements from $\Delta S$ and $S^0$:

$$f = \frac{\Delta S C}{S^0}$$ \hspace{1cm} (5)
Values for $T2^*$ of blood (40 ms) and brain tissue (100 ms, grey and white matter average) were taken from literature. Using these values and the values of $TE$, $TI_1$, $TI_2$, $T1_b$, $\alpha$, and $\lambda$ listed above, $C$ was calculated to be $11.5 \times 10^3$ ml/100ml/min for the proximal slice.

**Image Analysis**

A single reader, with more than five years of experience, visually rated the degree of WMH on axial FLAIR images. On the basis of the Fazekas scale, WMH were classified into the following categories: punctiform (score 1), beginning confluent (score 2), and diffuse confluent (score 3).

For all the included cases, the rCBF and $S^0$ image slices were uniformly positioned, parallel to the anterior commissure-posterior commissure line, in order to include the deep grey matter (GM) and most of the cerebral white matter (WM). To analyse rCBF and $S^0$ images, we used a statistical parametric mapping program (SPM5; Wellcome Department of Cognitive Neurosciences, London, United Kingdom). For each subject, rCBF and $S^0$ images were coregistered to the T1-weighted images (T1-WI) by using a stepwise coregistration involving first the coregistration of mean EPI images, obtained after averaging all labelled and control images, to the T1-WI. Additionally, a segmentation algorithm combining anatomic information and signal intensity was applied to the T1-WI to obtain probabilistic grey and white matter maps. After normalization to the standard T1-weighted template, grey and white matter probability maps (Figures 1C and 1D) were converted to binary masks.

Because most of WMH are isointense with GM on T1-WI, the corresponding voxels have higher probability values on the GM maps and lower probability values on the WM maps than voxels representing normal appearing WM. Therefore, to reduce
misclassification of WM lesions as GM after brain segmentation, we used a lower threshold to obtain WM binary masks than to obtain GM binary masks (i.e., voxels with values > 40% on the GM probability maps were assigned a value 1 on the GM binary masks; and voxels with values > 20% on the WM probability maps were assigned a value 1 on the WM binary masks; Figures 1E and 1F). The use of a 40% threshold to obtain GM binary masks was also planned to minimize partial volume effects of the cerebrospinal fluid occurring particularly in cases with cortical atrophy. On the obtained binary masks, we still created regions of interest either to correctly classify voxels representing lesions (e.g., voxels representing WM lesions misclassified as GM) or to exclude non-brain voxels (Figure 1E).

Because the Fazekas score reflects the severity of both WM and deep GM lesions, we decided to combine voxels classified as deep GM and voxels classified as WM into common subcortical binary masks (Figure 1H). Segmentation difficulties occurring in the putamen and thalamus (Figures 1C to 1F) due to lack of sufficient contrast between deep GM and the surrounding WM on T1-WI were, therefore, circumvented.

The cortical GM and subcortical binary masks were multiplied by the normalized rCBF images, as well as global binary masks obtained after combining all GM and WM. Global binary masks were also multiplied by normalized S⁰ images. Then, the average intensity of the product images (Figure 2) was taken and, on the basis of equation (5), values of cortical GM, subcortical (including WM and deep GM), and global CBF were calculated. For all CBF calculations, we used a global average (combining all GM and WM) S⁰ intensity measurement.
Figure 1. Axial magnetic resonance images, probability maps, and binary masks, at the level of basal ganglia and thalamus, from subject 14.

A, T1-weighted image (T1-WI); B, Fluid-attenuated inversion recovery (FLAIR) image showing beginning confluent white matter hyperintensities; C, Grey matter (GM) probability map; D, White matter (WM) probability map; E, GM binary mask thresholded at 40% with regions of interest (in grey) representing WM abnormalities misclassified as GM; F, WM binary mask thresholded at 20%; G, Cortical GM binary mask; H, Subcortical binary mask combining WM and deep GM.

Please note the existence of segmentation difficulties in the putamen and thalamus (C to F). Please also note that black voxels (with value 0) on the WM binary mask (F) corresponding to WMH on FLAIR (B) appear correctly classified (with value 1) on the subcortical binary
mask (H). Finally, note that voxels with value 1 on the WM binary mask (F) spatially corresponding to voxels with value 1 on the GM binary mask (E) were subtracted to the WM binary mask before obtaining the subcortical binary mask (H). Since the threshold to obtain GM binary masks doubled that to obtain WM binary masks, the subtraction was meant to avoid accounting voxels representing the cortical-subcortical transition both as cortical and subcortical in the process of CBF calculation.

**Statistical Analysis**

Statistical analysis was done by means of SPSS 11.0 (SPSS for Windows, Chicago, Ill). Given that the Shapiro-Wilk $W$ test demonstrated normality in the distribution of data, we used the independent-samples Student’s $t$ test to compare CBF measurements. Subjects with Fazekas score 3 were compared to those with Fazekas scores 1 or 2, because there were few subjects with Fazekas score 1 and the sample size was limited. We calculated the statistical power of the study on the basis of the standardized difference of global CBF between the two groups to ensure that the sample size was appropriate within an acceptable range of confidence. Statistical significance was considered when $P$ values were <0.05.
Figure 2. A, Axial fluid-attenuated inversion recovery (FLAIR) images, T1-weighted images (T1-WI), cortical grey matter (GM) cerebral blood flow (CBF) images, subcortical CBF images, and global CBF images combining all GM and WM at the level of basal ganglia and thalamus (above), and at the level of cerebral WM (below) from subject 4; B, Corresponding images from subject 18.

On the CBF images, please note that the cerebral cortex, the cortical-subcortical transition, and the thalamus are highly perfused structures. Please also note the perfusion differences between subject 18 (with diffuse confluent WMH on FLAIR images) and subject 4 (with punctiform WMH on FLAIR images). Finally, on the subcortical and global CBF images from subject 18, please note the relative hypoperfusion of the right thalamus, in which occurs a lacunar infarct (arrow).
Results

Table 1 summarizes clinical and radiological characteristics of the subjects and shows values of CBF. The mean age of the subjects was 76 years-old (SD = 5.1). At the time of undergoing MRI for this study, 18 (85.7%) of the 21 subjects had normal cognition. Of the three (14.3%) subjects with cognitive impairment, two fulfilled diagnostic criteria for Alzheimer’s disease, and one for subcortical ischaemic vascular dementia. Concurrent medications and drugs possibly affecting CBF are also displayed.

Table 2 shows comparisons of CBF measurements between subjects with Fazekas scores 1 or 2 (n = 14) and subjects with Fazekas score 3 (n = 7). Subjects with Fazekas score 3 were found to have approximately 20% lower mean global, subcortical (including WM and deep GM), and cortical GM CBF than subjects with Fazekas scores 1 or 2 (Figure 2). The differences were statistically significant, and on the basis of a standardized difference of 1.21 for global CBF, the statistical power was approximately 0.8 ($P = 0.05$).

No medications or drugs were found to have significant effects on the CBF measurements.
Table 1. Characteristics of subjects (n=21) including sex; age; clinical diagnosis; medications and drugs possibly affecting cerebral blood flow (CBF); cortical grey matter (GM), subcortical (including white matter and deep GM), and global CBF in ml/100 ml/min, and white matter hyperintensities (WMH) score

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Medication and drugs</th>
<th>Cortical CBF</th>
<th>Subcortical CBF</th>
<th>Global CBF</th>
<th>WMH(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>73</td>
<td>-</td>
<td>Diuretic</td>
<td>64.06</td>
<td>37.11</td>
<td>50.45</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>70</td>
<td>-</td>
<td>Diuretic</td>
<td>65.74</td>
<td>38.36</td>
<td>52.12</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>78</td>
<td>-</td>
<td>-</td>
<td>69.62</td>
<td>40.39</td>
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<td>1</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>79</td>
<td>-</td>
<td>Diuretic</td>
<td>68.45</td>
<td>48.63</td>
<td>58.02</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
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<td>76</td>
<td>AD</td>
<td>AA; nicotine</td>
<td>57.64</td>
<td>34.19</td>
<td>44.40</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>82</td>
<td>AD</td>
<td>β-Bl</td>
<td>61.58</td>
<td>34.39</td>
<td>46.19</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
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<td>-</td>
<td>-</td>
<td>62.06</td>
<td>37.07</td>
<td>47.87</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>78</td>
<td>-</td>
<td>-</td>
<td>55.46</td>
<td>41.43</td>
<td>47.93</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>75</td>
<td>-</td>
<td>Diuretic; CA</td>
<td>66.82</td>
<td>39.37</td>
<td>51.40</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>66</td>
<td>-</td>
<td>AA</td>
<td>70.73</td>
<td>51.54</td>
<td>59.99</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>73</td>
<td>-</td>
<td>-</td>
<td>72.50</td>
<td>47.79</td>
<td>60.42</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>70</td>
<td>-</td>
<td>α(2)-agonist</td>
<td>81.22</td>
<td>48.14</td>
<td>62.94</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>70</td>
<td>-</td>
<td>β-Bl; nitrate</td>
<td>77.07</td>
<td>53.27</td>
<td>64.36</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>72</td>
<td>-</td>
<td>CA; nitrate</td>
<td>106.10</td>
<td>60.18</td>
<td>78.88</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>80</td>
<td>-</td>
<td>β-Bl; CA</td>
<td>51.32</td>
<td>26.69</td>
<td>36.22</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>70</td>
<td>-</td>
<td>β-Bl; CA</td>
<td>48.71</td>
<td>26.89</td>
<td>37.77</td>
<td>3</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>84</td>
<td>-</td>
<td>Diuretic; β-Bl; AA; nitrate</td>
<td>47.56</td>
<td>34.98</td>
<td>40.63</td>
<td>3</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>76</td>
<td>VaD</td>
<td>Diuretic; ACE inhibitor</td>
<td>62.30</td>
<td>31.67</td>
<td>40.91</td>
<td>3</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>84</td>
<td>VaD</td>
<td>ACE inhibitor</td>
<td>60.64</td>
<td>35.18</td>
<td>46.28</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>71</td>
<td>-</td>
<td>Diuretic; β-Bl</td>
<td>65.32</td>
<td>37.04</td>
<td>49.39</td>
<td>3</td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>79</td>
<td>-</td>
<td>-</td>
<td>69.12</td>
<td>42.90</td>
<td>53.10</td>
<td>3</td>
</tr>
<tr>
<td>Mean (Standard Deviation)</td>
<td>-</td>
<td>75.5 (5.1)</td>
<td>-</td>
<td>-</td>
<td>65.9 (12.6)</td>
<td>40.3 (8.6)</td>
<td>51.6 (10.1)</td>
<td>2.1 (0.7)</td>
</tr>
</tbody>
</table>

\(^1\)Higher values indicate greater severity.

AD = Alzheimer disease.

tVaD = Vascular dementia.

AA = Angiotensin antagonist.

β-Bl = β-blocker.

CA = Calcium antagonist.

ACE inhibitor = Angiotensin-converting enzyme inhibitor.
Table 2. Comparisons of cerebral blood flow (CBF) in ml/100 ml/min between groups of subjects with different grades of white matter hyperintensities (WMH)

<table>
<thead>
<tr>
<th></th>
<th>Mean CBF (Standard deviation)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMH scores 1 or 2 (n = 14)</td>
<td>WMH score 3 (n = 7)</td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>55.7 (9.2)</td>
<td>43.5 (6.3)</td>
</tr>
<tr>
<td>Subcortical</td>
<td>43.7 (7.9)</td>
<td>33.6 (5.8)</td>
</tr>
<tr>
<td>Cortical</td>
<td>69.9 (12.6)</td>
<td>57.9 (8.6)</td>
</tr>
</tbody>
</table>

Discussion

In this study, we determined absolute values of CBF in subjects with WMH by means of Q2TIPS, a PASL magnetic resonance perfusion-weighted sequence. Our study indicates that elderly subjects with diffuse confluent WMH have approximately 20% lower CBF measurements than subjects with punctiform or beginning confluent WMH.

So far, few ASL studies presented absolute values of CBF in elderly subjects, or analysed CBF measurements in healthy adult subjects accounting for the effect of age. Considering that CBF quantification by means of ASL techniques is reliable, we found, as in other studies, high variation of CBF measurements between subjects.

Although there is no previous report of subcortical CBF values combining WM and deep GM to compare with, the mean global and cortical GM CBF measurements in cases with punctiform or beginning confluent WMH are in agreement with those previously reported for subjects without evidence of WMH. Actually, they are even slightly higher than expected. Therefore, subjects with punctiform or
beginning confluent WMH do not seem to have considerable brain hypoperfusion, perhaps because their mechanisms of cerebrovascular autoregulation play a role in the maintenance of CBF. On the contrary, subjects with diffuse confluent WMH have global and cortical GM CBF values falling below or in the lower range of those previously reported,\textsuperscript{399,408} which leads us to consider them as abnormally low.

The existence of an association between low CBF measurements and diffuse confluent WMH adds support to the concept that brain hypoperfusion is a key factor to explain the occurrence of WM lesions in the elderly, most probably because of ischaemic small vessel disease.\textsuperscript{130,197} The existence of histological evidence of decreased afferent vascular density in WMH, normal-appearing WM and cortical GM in patients with leukoaraiosis\textsuperscript{409} supports both that concept and our findings. The loss of cerebrovascular autoregulation in subjects with diffuse confluent abnormalities serves also as an explanation.\textsuperscript{410} However, the cross-sectional design of the current study precludes inferring causality, as the relation may also be reverse, with hypoperfusion being secondary to the existence of lesions.

WMH are often associated with Alzheimer’s disease\textsuperscript{130} and other studies already demonstrated hypoperfusion in patients with Alzheimer’s disease and mild cognitive impairment by means of ASL.\textsuperscript{261,411,412} In our sample, only three patients had the diagnosis of dementia and, because of insufficient statistical power, it was not appropriate to compare their CBF measurements with those of the remaining subjects. Nevertheless, to our knowledge, no previous ASL study accounted for the effect of WMH in patients with dementia. Therefore, WMH should perhaps be a factor to take into account in future studies of brain perfusion involving those patients.
Given that our sample was taken from the LADIS study, which only recruited subjects with WMH, we were unable to determine values of CBF from age-matched controls without WMH. However, as previously mentioned, cases with punctiform or beginning confluent WMH seem to have comparable values of CBF to those previously reported for subjects without evidence of WMH\textsuperscript{399,408} and may, therefore, serve as controls to compare the CBF measurements from subjects with diffuse confluent WMH. Moreover, according to large population-based and community-dwelling studies on the prevalence of WMH, subjects without WMH represent no more than approximately 5% of the elderly people.\textsuperscript{197,413}

Limitations of the current study are the small sample size and the relatively poor signal-to-noise ratio (SNR) of the acquired rCBF and $S^0$ images. Because of their low SNR, we decided to analyse rCBF and $S^0$ images globally, by using a statistical parametric mapping program, instead of taking CBF measurements from regions of interest, such as from regions representing the WM lesions or normal appearing white matter. In future studies, the acquisition of images with higher SNR, by means of higher-field strengths, may allow to further investigate this issue. Nevertheless, since we found a significant reduction of subcortical (including white matter and deep GM), cortical GM, and global CBF values in subjects with diffuse confluent WMH, it seems that such subjects have indeed a generalized cerebrovascular disease process rather than one confined to lesions.\textsuperscript{409}

In conclusion, PASL enabled us to demonstrate a significant association between brain hypoperfusion and the occurrence of diffuse confluent WMH in elderly subjects, and can be used in future studies with larger sample sizes. Longitudinal studies may help to clarify the contribution of brain hypoperfusion as a cause of occurrence or increased severity of WMH.
Chapter 6

Summary, general discussion, and future perspectives
This thesis presented a neuroimaging perspective of pathological ageing and focused on the contributions of magnetic resonance (MR) imaging to study patients with Alzheimer’s disease, vascular dementia, and elderly subjects with white matter hyperintensities (WMH).

In chapter 2, various disorders causing dementia were discussed, as well as the usefulness of several neuroimaging modalities for their diagnosis. It was stressed that a large proportion of patients may have a combination of degenerative and vascular pathology in the brain. New functional MR and molecular imaging techniques were also discussed, as well as future perspectives concerning their potential benefit.

Chapter 3 focused on medial temporal lobe atrophy (MTA), a structural neuroimaging feature suggestive of Alzheimer’s pathology. A new linear measurement to assess MTA on magnified coronal high-resolution T1-weighted images was proposed, the fimbriosubicular distance. By using this measurement, it was possible to evaluate the hippocampal sulcus width, whose enlargement is associated with MTA in Alzheimer’s disease. It is also plausible that the assessment of the hippocampal sulcus width may become useful in clinical practice, because it complements the currently used visual rating scale for MTA.

In chapter 4, three studies on vascular dementia were presented. These studies were derived from baseline data of patients fulfilling the clinical and neuroimaging parts of the National Institute of Neurological Disorders and Stroke (NINDS) – Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) criteria for probable vascular dementia, with central assessment of the neuroimaging criteria at the Image Analysis Centre (VU University Medical Centre, Amsterdam, the Netherlands) according to published operational definitions.
Chapter 4.1 corresponds to a study comparing the sensitivity of T2-weighted images (T2-WI) with fluid-attenuated inversion recovery (FLAIR) images to depict thalamic lesions. The study showed that the sensitivity of T2-WI to depict thalamic lesions is far superior to FLAIR images and, for this reason, FLAIR should not be used as the only T2-weighted sequence to detect thalamic lesions in patients suspected of having vascular dementia.\textsuperscript{415} The reason for this is unknown but may reflect different relaxation properties in the thalamus. In addition, MR-pathological correlation studies should be performed to determine how the underlying pathology of thalamic lesions may influence their detection on FLAIR. Furthermore, the clinical relevance of the potential concealment of thalamic lesions on FLAIR should be determined. Additional studies to determine how the thalamic topography of lesions and their underlying pathology may influence cognitive function in vascular dementia are also warranted.

Chapter 4.2 corresponds to a study about the prevalence and clinical relevance of infratentorial abnormalities in vascular dementia.\textsuperscript{416} Focal infratentorial vascular lesions were found to be especially frequent among patients with small vessel disease and were associated with basal ganglia and thalamic lesions. Midbrain and cerebellar atrophy were also present in a minority of patients. Only midbrain atrophy was found to be associated with cognitive impairment, and the association persisted after correction for abnormalities representing degenerative and vascular supratentorial pathology. These findings suggested that the midbrain may contribute to cognition independently of the supratentorial structures, and that assessment of midbrain atrophy should perhaps be a factor to take into account in future studies on brain ageing and dementia. It is conceivable that midbrain atrophy may represent concomitant Alzheimer’s pathology, and that its occurrence in the periaqueductal grey matter may explain the association between midbrain atrophy and cognitive impairment by disruption of mesencephalic connections,\textsuperscript{391} but more work is
needed to establish the actual contribution of midbrain pathology to cognitive impairment.

A study designed to investigate the relative contribution of cerebrovascular disease and MTA to cognitive impairment in a large sample of patients with vascular dementia was presented in chapter 4.3. The study showed that both MTA and the occurrence of large vessel vascular dementia were independently associated with general cognitive and executive dysfunction, while small vessel disease seemed to be related to worse executive functioning, especially in patients without considerable MTA. Again, the results of this study point to the possibility that both the occurrence of MTA in patients fulfilling diagnostic criteria for vascular dementia and its association with cognitive impairment are attributable to concomitance of Alzheimer’s pathology. Alternatively, MTA may be secondary to vascular pathology, more precisely to small vessel disease and ischaemia. Nevertheless, it may be useful to consider the occurrence of substantial MTA as a neuroimaging marker of cognitive impairment in patients fulfilling diagnostic criteria for vascular dementia.

Finally, chapter 5 corresponds to a study of a sub-sample of the Leukoaraiosis and Disability (LADIS) study. The LADIS study is a prospective, longitudinal, multicentre European study on the role of WMH as an independent predictor for transition to disability in nondemented elderly subjects. The study presented in the thesis explored the relation between cerebral blood flow (CBF) and the amount of WMH by means of pulsed arterial spin labelling (PASL), a new functional MR perfusion-weighted technique. In this study, absolute values of CBF were determined and an association was found between lower CBF measurements and higher grades of WMH, indicating that subjects with diffuse confluent white matter lesions have approximately 20% lower CBF than subjects with punctiform or beginning confluent lesions. The existence of an association between lower CBF measurements and higher grades of WMH adds support to the concept that hypoperfusion is a
key factor to explain the occurrence of white matter lesions in the elderly, most probably because of ischaemic small vessel disease. Very recently, follow-up results from the entire sample of the LADIS study were published. These results indicate that functionally independent elderly subjects with diffuse confluent WMH are at a considerable risk of becoming dependent in a short period, mostly owing to motor and cognitive deterioration. The demonstration of a considerable hypoperfusion in subjects with diffuse confluent WMH by means of PASL helps to explain the high risk of cognitive deterioration in such subjects. Furthermore, PASL may help to clarify the contribution of brain hypoperfusion to cognitive impairment in subjects with or at risk of developing dementia.

As discussed in the last section of chapter 2, the big future challenge of neuroimaging techniques in the diagnosis of dementia will be to demonstrate pathologic processes occurring at a microscopic level, and therefore help to recognize subjects at risk of developing dementia before the occurrence of atrophy as an indicator of substantial tissue loss. New functional MR techniques and serial volumetric imaging studies to identify subtle brain abnormalities may provide surrogate markers for pathologic processes occurring in diseases causing dementia. Molecular imaging techniques possibly will target specific abnormal proteins that represent biological markers of neurodegenerative diseases. Moreover, those techniques may allow monitoring the effects of new therapies aimed at modifying the course of these diseases.

In conclusion, most of the work presented in this thesis reflects that brain atrophy and cerebrovascular disease currently are the two most important characteristics in the evaluation of dementia by means of neuroimaging. In the future, it is expected that neuroimaging techniques will detect neuropathology and its morphofunctional consequences even before the occurrence of substantial brain atrophy, which in conjunction with clinical evaluation, will enable to do earlier diagnoses, as well as to better monitor the potential benefit of treatment.
Chapter 7

Summary in Dutch / Nederlandse Samenvatting
In dit proefschrift wordt met behulp van radiologische technieken de veroudering van de hersenen bestudeerd. Hierbij wordt in het bijzonder aandacht besteed aan veranderingen die het gevolg zijn van ziekten van de bloedvaten.

In hoofdstuk 2 worden diverse aandoeningen besproken die dementie kunnen veroorzaken en de waarde van beeldvormende technieken zoals computertomografie en magneet resonantie (MR) bij het diagnosticeren van deze aandoeningen. In dit hoofdstuk wordt benadrukt dat een groot deel van de patiënten met dementie een combinatie van vaatziekten en degeneratieve ziekten kan hebben. Nieuwe functionele MR technieken (hierbij worden afbeeldingen gemaakt terwijl de proefpersonen taken uitvoeren) en moleculaire beeldvormende technieken worden ook besproken, alsmede hun mogelijke toevoegende waarde in de toekomst.

Hoofdstuk 3 besteedt aandacht aan mediale temporale kwab atrofie (MTA), een bevinding bij afbeelding van de hersenen die past bij de ziekte van Alzheimer. Een nieuwe techniek om dit vast te stellen, namelijk het meten van de fimbriosubiculaire afstand op vergrootte T1-gewogen hoge resolutie afbeeldingen, wordt geïntroduceerd. Met deze techniek wordt lineair gemeten en is het mogelijk een maat te verkrijgen voor de hippocampale sulcus. Verwijding van deze sulcus is geassocieerd met de ziekte van Alzheimer.

In hoofdstuk 4 worden drie onderzoeken beschreven die betrekking hebben op vasculaire dementie. Voor deze onderzoeken werden gegevens gebruikt patiënten met een waarschijnlijke vasculaire dementie. De diagnose werd vastgesteld met behulp van criteria van het National Institute of Neurological Disorders and Stroke (NINDS) – Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN). De classificatie van de MR afbeeldingen vond centraal plaats bij het Image Analysis Center van het VU medisch centrum in Amsterdam.
In de eerste studie (hoofdstuk 4.1) wordt de gevoeligheid van T2-gewogen afbeeldingen met fluid-attenuated inversion recovery (FLAIR) afbeeldingen beschreven met betrekking tot het ontdekken van afwijkingen in de thalamus, een van de kernen van de hersenen die een rol kan spelen bij het ontstaan van vasculaire dementie. Dit onderzoek toont aan dat met behulp van T2-gewogen afbeeldingen veel vaker afwijkingen worden gezien in de thalamus dan met de FLAIR afbeeldingen. Op grond van de resultaten van deze studie wordt aanbevolen naast de FLAIR techniek ook de T2-gewogen techniek toe te passen bij de diagnostiek patiënten waarbij een vasculaire dementie wordt vermoed.

**Hoofdstuk 4.2** beschrijft een onderzoek met betrekking tot het voorkomen van afwijkingen in de kleine hersenen en het mesencephalon (letterlijk middenhersenen) en de betekenis ervan bij vasculaire dementie. Kleine vasculaire afwijkingen in deze gebieden werden met name gevonden bij patiënten waarbij gedacht werd aan aandoeningen van de kleine hersenvaten. Bij deze patiënten werden ook vaker afwijkingen gezien in de basale kernen van de hersenen en in het bijzonder in de thalamus. Atrofie van het mesencefalon en de kleine hersenen werd bij een minderheid van de patiënten gezien. Bij patiënten met atrofie van het mesencefalon werden meer cognitieve problemen vastgesteld, ook als rekening werd gehouden met de invloed van degeneratieve ziekte en afwijkingen in de grote hersenen. Dit is een aanwijzing dat het mesencefalon onafhankelijk van de conditie van de grote hersenen invloed heeft op de cognitie. Het lijkt belangrijk bij toekomstig onderzoek met betrekking tot de veroudering van de hersenen en het ontstaan van dementie hieraan aandacht te besteden. Het is voorstelbaar dat atrofie van het mesencefalon gepaard gaat met pathologische veranderingen zoals die ook bij de ziekte van Alzheimer worden gezien. De onderbreking van verbindingen in het mesencefalon door atrofie in de grijze stof rondom de zogenaamde aquaduct, zou een verklaring kunnen vormen voor het verband tussen atrofie van het mesencefalon en het ontstaan van cognitieve stoornissen.
De invloed van vaataandoeningen van de hersenen en atrofie van de mediale temporale kwab op verval van de cognitie werd in een grotere groep patiënten onderzocht in hoofdstuk 4.3. Deze studie toonde aan dat zowel atrofie van de mediale temporale kwab als de aanwezigheid van herseninfarcten in de stroomgebieden van de grote hersenvaten onafhankelijk van elkaar een negatieve invloed hadden op cognitie en uitvoerende taken. De aanwezigheid van afwijkingen in de kleinere bloedvaten had vooral een negatieve invloed op de uitvoerende taken, met name bij patiënten met aanzienlijke atrofie van de mediale temporale kwab. De resultaten van deze studie vormen opnieuw een aanwijzing dat atrofie van de mediale temporale kwab voorkomt bij personen met vasculaire dementie en dat bij deze patiënten ook sprake kan zijn van veranderingen in het hersenweefsel, zoals die gezien worden bij de ziekte van Alzheimer.

In hoofdstuk 5 tenslotte wordt een aantal patiënten onderzocht, die deelnamen aan de Leukoaraiosis and Disability (LADIS) studie. In het LADIS onderzoek wordt een groot aantal patiënten gevolgd in verschillende Europese landen. Al deze patiënten hebben afwijkingen in de witte stof van de hersenen ten gevolge van aandoeningen van de kleine bloedvaten. Bij aanvang van het onderzoek functioneerden alle patiënten onafhankelijk. In het kader van deze studie wordt gekeken in hoeverre de ernst van deze wittestofafwijkingen invloed heeft op het ontwikkelen van afhankelijkheid. Het in dit proefschrift beschreven deelonderzoek van LADIS onderzoekt de relatie tussen de bloeddoorstroming van de hersenen (cerebral blood flow, CBF) en de ernst van de wittestofafwijkingen met behulp van de pulsed arterial spin labelling (PASL) techniek, een nieuwe MR perfusie-gewogen techniek. In dit onderzoek werd de CBF bepaald. Er was een relatie te zien tussen een lagere CBF en dus een minder grote doorstroming van de hersenen en een ernstigere mate van wittestofafwijkingen. Bij personen met ernstige wittestofafwijkingen, waarbij een groot deel van de witte stof is aangedaan en de lesies met elkaar vervloeien was de CBF ongeveer 20% lager dan bij personen met puntvormige of nog nauwelijks vervloeien dere wittestofafwijkingen.
Samenvattend ondersteunt het onderzoek beschreven in dit proefschrift de hypothese dat atrofie van de hersenen en afwijkingen in de hersenen die wijzen op het doorgemaakt hebben van vaatziekten twee zeer belangrijke elementen zijn om te bestuderen met behulp van beeldvormende technieken bij de analyse van patiënten met dementie. In de toekomst zouden moderne beeldvormende technieken aanwijzingen kunnen vinden voor neuropathologische en anatomische veranderingen in de hersenen voordat evidente atrofie van de hersenen optreedt. Dit kan, in combinatie met de klinische presentatie leiden tot een diagnostiek in een eerder stadium en de mogelijkheid bieden het effect van een behandeling nauwkeuriger te vervolgen.
Chapter 8

Summary in Portuguese / Sumário em Português
O objectivo da tese foi apresentar uma perspectiva imagiológica do envelhecimento cerebral patológico, especialmente sobre aspectos vasculares.

No capítulo 2, foram discutidas várias doenças que causam demência, bem como a utilidade de várias técnicas imagiológicas para o seu diagnóstico. Foi salientado que uma grande proporção de doentes pode ter uma combinação de patologias degenerativa e vascular. Foram também discutidas novas técnicas de ressonância magnética (RM) funcional e de imagem molecular, bem como perspectivas do seu potencial interesse no futuro.

O capítulo 3 incidiu sobre a atrofia da porção medial do lobo temporal, uma característica sugestiva de patologia tipo Alzheimer. Foi proposta a distância fimbriosubicular como um novo tipo de medição linear para avaliar a atrofia temporal em imagens coronais de alta resolução ponderadas em T1. Através desta medição, foi possível avaliar a largura do sulco hipocampal, cujo alargamento se associa à atrofia do lobo temporal na doença de Alzheimer.

No capítulo 4, foram apresentados três estudos sobre demência vascular. Os dados foram provenientes de um ensaio clínico multicêntrico em doentes com critérios clínicos e radiológicos de provável demência vascular segundo o National Institute of Neurological Disorders and Stroke (NINDS) – Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN). A avaliação dos critérios radiológicos foi realizada, para todos os doentes, no Image Analysis Centre (VU University Medical Centre, Amesterdão, Holanda).

No capítulo 4.1, foi comparada a sensibilidade para detectar lesões talâmicas usando imagens de RM ponderadas em T2 versus imagens ponderadas na sequência fluid-attenuated inversion recovery (FLAIR). O estudo mostrou que a sensibilidade das
imagens ponderadas em T2 para mostrar lesões talâmicas é bastante superior à das imagens FLAIR e, por essa razão, a sequência FLAIR não deve ser a única a ser usada para detectar lesões talâmicas em doentes com suspeita clínica de demência vascular.

No capítulo 4.2, foi apresentado um estudo acerca da prevalência e relevância clínica das lesões infratentoriais na demência vascular. Foram encontradas lesões vasculares focais infratentoriais, principalmente em doentes com lesões supratentoriais de pequenos vasos e, particularmente, nos que apresentavam lesões dos núcleos da base e tálamos. Nalguns doentes, também foi encontrada atrofia do mesencéfalo e do cerebelo. Apenas a atrofia do mesencéfalo se associou a perturbações cognitivas, mesmo após correção estatística para a ocorrência de alterações supratentoriais sugestivas de patologia degenerativa e vascular. Estes resultados sugerem que o mesencéfalo possa contribuir para funções cognitivas independentemente das estruturas supratentoriais e que a avaliação da atrofia mesencefálica deva ser um factor a considerar em estudos futuros sobre envelhecimento cerebral e demência. É possível que a atrofia mesencefálica represente coexistência de patologia tipo Alzheimer, e que a sua ocorrência na substância cinzenta periaqueductal possa explicar a associação da atrofia mesencefálica com perturbações cognitivas devido a lesão de conexões mesencefálicas.

No capítulo 4.3, foi apresentado um estudo com o objectivo de investigar a contribuição relativa da doença cerebrovascular e da atrofia da porção medial do lobo temporal numa grande amostra de doentes com demência vascular. O estudo mostrou que a atrofia temporal e a ocorrência de lesões de grandes vasos em localizações estratégicas se associavam, independentemente, a perturbação cognitiva global e a disfunção executiva, enquanto que a doença de pequenos vasos se associava apenas a disfunção executiva, especialmente em doentes sem considerável atrofia temporal.
Novamente, os resultados deste estudo apontam para a possibilidade das patologias degenerativa e vascular coexistirem, mesmo em doentes rigorosamente seleccionados com critérios clínicos e radiológicos de demência vascular.

Finalmente, no capítulo 5, foi apresentado um estudo do centro de Amsterdão no contexto do estudo Europeu Leukoaraiosis and Disability (LADIS), um estudo prospectivo, longitudinal, multicêntrico, sobre o papel das alterações da substância branca relacionadas com a idade como factor predictivo de incapacidade em indivíduos idosos não dementes. O trabalho apresentado nesta tese teve como objectivo investigar a relação entre a severidade das alterações da substância branca e o fluxo sanguíneo cerebral avaliado através de pulsed arterial spin labelling, uma nova técnica de RM funcional ponderada em perfusão. Foram determinados valores absolutos de fluxo sanguíneo cerebral e foi encontrada uma associação entre valores mais baixos de fluxo sanguíneo e maiores graus de severidade das alterações da substância branca. Indivíduos com alterações da substância branca difusas e confluentes têm, aproximadamente, um valor de fluxo sanguíneo cerebral 20% menor que o dos indivíduos com alterações da substância branca punctiformes ou em início de confluência.

Como conclusão, a maior parte do trabalho apresentado nesta tese reflecte que a atrofia cerebral e a doença cerebrovascular são, actualmente, as duas características mais importantes na avaliação da demência do ponto de vista imagiológico. No futuro, espera-se que as técnicas de neuroimagem venham a detectar a neuropatologia e as suas consequências morfo-funcionais mesmo antes da ocorrência de atrofia, o que, em conjunto com a avaliação clínica, permitirá alcançar diagnósticos mais precoces, bem como monitorizar o potencial benefício do tratamento.
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Curriculum Vitae
António José de Bastos Leite was born on June the 3rd, 1971, in Oporto, Portugal. He attended primary school at S. Cristóvão de Nogueira (Cinfães, Portugal) and secondary school at Colégio de Lamego (Lamego, Portugal). Since 1988, he studied medicine at the Faculty of Medicine, University of Oporto (Oporto, Portugal), where he graduated in 1994. From 1992 to 1997, he worked as an invited teaching assistant at the Institute of Anatomy J.A. Pires de Lima (Oporto, Portugal) under supervision of Prof. Dr. Manuel Paula-Barbosa. Since 1999, he worked as a resident doctor in neuroradiology at the Hospital Geral de Santo António (Oporto, Portugal) under supervision of Prof. Dr. José Almeida-Pinto, Dr. Romeu Cruz, Dr. João Xavier, and Dr. Alfredo Stocker. He obtained the degree of neuroradiologist in February 2004. Then, he started working on the current thesis as a PhD student at the VU University Medical Centre (Amsterdam, the Netherlands) under supervision of Prof. Dr. Frederik Barkhof and Prof. Dr. Philip Scheltens. Since February 2007, he also works as an invited teaching assistant at the Department of Medical Imaging, Faculty of Medicine, University of Oporto (Oporto, Portugal) under supervision of Prof. Dr. Isabel Ramos.
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168 Reference list


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