Determinants of vascular cognitive impairment: White matter lesions, brain atrophy and their neuropsychological correlates

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ABSTRACT

The concept of vascular cognitive impairment (VCI) covers a wide spectrum of cognitive dysfunctions related to cerebrovascular disease. Among the pathophysiological determinants of VCI are cerebral stroke, white matter lesions and brain atrophy, which are known to be important risk factors for dementia. However, the specific mechanisms behind the brain abnormalities and cognitive decline are still poorly understood. The present study investigated the neuropsychological correlates of particular magnetic resonance imaging (MRI) findings, namely, medial temporal lobe atrophy (MTA), white matter hyperintensities (WMH), general cortical atrophy and corpus callosum (CC) atrophy in subjects with cerebrovascular disease. Furthermore, the cognitive profile of subcortical ischaemic vascular disease (SIVD) was examined.

This study was conducted as part of two large multidisciplinary study projects, the Helsinki Stroke Aging Memory (SAM) Study and the multinational Leukoaraiosis and Disability (LADIS) Study. The SAM cohort consisted of 486 patients, between 55 and 85 years old, with ischaemic stroke from the Helsinki University Hospital, Helsinki, Finland. The LADIS Study included a mixed sample of subjects (n=639) with age-related WMH, between 65 and 84 years old, gathered from 11 centres around Europe. Both studies included comprehensive clinical and neuropsychological assessments and detailed brain MRI. The relationships between the MRI findings and the neuropsychological test performance were analysed by controlling for relevant confounding factors such as age, education and other coexisting brain lesions.

The results revealed that in elderly patients with ischaemic stroke, moderate to severe MTA was specifically related to impairment of memory and visuospatial functions, but mild MTA had no clinical relevance. Instead, WMH were primarily associated with executive deficits and mental slowing. These deficits mediated the relationship between WMH and other, secondary cognitive deficits. Cognitive decline was best predicted by the overall degree of WMH, whereas the independent contribution of regional WMH measures was low. Executive deficits were the most prominent cognitive characteristic in SIVD. Compared to other stroke patients, the patients with SIVD also presented more severe memory deficits, which were related to MTA. The cognitive decline in SIVD occurred independently of depressive symptoms and, relative to healthy control subjects, it was substantial in severity. In stroke patients, general cortical atrophy also turned out to be a strong predictor of cognitive decline in a wide range of cognitive domains. Moreover, in elderly subjects with WMH, overall CC atrophy was related to reduction in mental speed, while anterior CC atrophy was independently associated with frontal lobe-mediated executive functions and attention.

The present study provides cross-sectional evidence for the involvement of WMH, MTA, general cortical atrophy and CC atrophy in VCI. The results suggest that there are multifaceted pathophysiological mechanisms behind VCI in the elderly, including both vascular ischaemic lesions and neurodegenerative changes. The different pathological changes are highly interrelated processes and together they may produce cumulative effects on cognitive decline.
TIIVISTELMÄ

Vaskulaarinen kognitiivinen heikentyminen sisältää käsittäen laajan kirjon aivot rentoheräiriöihin liittyviä kognitiivisia muutoksia. Sen taustalla vaikuttavia patofysiologisia tekijöitä ovat mm. aivot rentoheräiriöiden aiheuttamat kudosvauriot, valkean aineen muutokset sekä aivojen kudoskato (atrofia), joiden tiedetään olevan merkittäviä dementian riskitekijöitä. Kognitiivisten häiriöiden ja aivot renton taustalla vaikuttavia fysiologisia tekijöitä ovat mm. kudosvauriot, valkean aineen muutokset sekä aivojen kudoskato (atrofia), joiden tiedetään olevan merkittäviä dementian riskitekijöitä. Kognitiivisten häiriöiden ja aivot renton taustalla vaikuttavia fysiologisia tekijöitä ovat mm. kudosvauriot, valkean aineen muutokset sekä aivojen kudoskato (atrofia), joiden tiedetään olevan merkittäviä dementian riskitekijöitä. Kognitiivisten häiriöiden ja aivot renton taustalla vaikuttavia fysiologisia tekijöitä ovat mm. kudosvauriot, valkean aineen muutokset sekä aivojen kudoskato (atrofia), joiden tiedetään olevan merkittäviä dementian riskitekijöitä. Kognitiivisten häiriöiden ja aivot renton taustalla vaikuttavia fysiologisia tekijöitä ovat mm. kudosvauriot, valkean aineen muutokset sekä aivojen kudoskato (atrofia), joiden tiedetään olevan merkittäviä dementian riskitekijöitä. 

Tutkimuksen tarkoituksena oli tarkastella, millainen merkitys ohimolohkojen sisäosien ja aivot renton muutokset sekä aivojen rentoheräiriöiden aiheuttamien muutosten yhteydessä aivoverenkiertohäiriöiden kannalta. Lisäksi tutkittiin, millainen kognitiivinen suoritusprofiili liittyy ns. subkortikaaliseen iskeemiseen (engl. lyh. SIVD).


Tulokset osoittivat, että kohtalainen ja vaikea ohimolohkojen sisäosien rentovaihe oli yhteydessä erityisesti muistin ja visuospatiaalisten toimintojen heikentymiseen, mutta lievällä ohimolohkojen sisäosien rentovaiheilla ei ollut merkitystä kognitiivisten toimintojen kannalta. Sen sijaan valkean aineen rentovaihe sekä aivoinfarktipotilaiden vahvimman kliinisen ja neuropsykyologisen tunnistamisen sekä aivojen rentoheräiriöiden yhteydessä aivoverenkiertohäiriöiden kannalta. Lisäksi tutkittiin, millainen kognitiivinen suoritusprofiili liittyy ns. subkortikaaliseen iskeemiseen (engl. lyh. SIVD).

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LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original articles, referred to in the text by Roman numerals (I-IV).


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## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>CC</td>
<td>Corpus callosum</td>
</tr>
<tr>
<td>CC1-CC5</td>
<td>Corpus callosum subregions: rostrum and genu, rostral body, midbody, isthmus, splenium</td>
</tr>
<tr>
<td>DSM-III-R</td>
<td>Diagnostic and Statistical Manual of Mental Disorders III-revised</td>
</tr>
<tr>
<td>DWMH</td>
<td>White matter hyperintensities in deep, watershed and subcortical white matter areas</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Fluid attenuated inversion recovery</td>
</tr>
<tr>
<td>FOME</td>
<td>Fuld Object Memory Evaluation</td>
</tr>
<tr>
<td>LADIS</td>
<td>Leukoaraiosis and Disability Study</td>
</tr>
<tr>
<td>MANCOVA</td>
<td>Multivariate analysis of covariance</td>
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<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MTA</td>
<td>Medial temporal lobe atrophy</td>
</tr>
<tr>
<td>PVH</td>
<td>Periventricular white matter hyperintensity</td>
</tr>
<tr>
<td>PVH-B</td>
<td>White matter hyperintensities along the bodies of lateral ventricles</td>
</tr>
<tr>
<td>PVH-FH</td>
<td>White matter hyperintensities around frontal horns</td>
</tr>
<tr>
<td>PVH-OH</td>
<td>White matter hyperintensities around occipital horns</td>
</tr>
<tr>
<td>SAM</td>
<td>Helsinki Stroke Aging Memory Study</td>
</tr>
<tr>
<td>SIVD</td>
<td>Subcortical ischaemic vascular disease</td>
</tr>
<tr>
<td>UBO</td>
<td>Unidentified bright object</td>
</tr>
<tr>
<td>VADAS-cog</td>
<td>Vascular Dementia Assessment Scale-cognitive subtest</td>
</tr>
<tr>
<td>WAIS-R</td>
<td>Wechsler Adult Intelligence Scale-revised</td>
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<tr>
<td>VCI</td>
<td>Vascular cognitive impairment</td>
</tr>
<tr>
<td>WCST</td>
<td>Modified Wisconsin Card Sorting Test</td>
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<tr>
<td>WMH</td>
<td>White matter hyperintensities</td>
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<td>WMS</td>
<td>Wechsler Memory Scale</td>
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<td>WMS-R</td>
<td>Wechsler Memory Scale-revised</td>
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INTRODUCTION

As the population in the developed countries is growing older, age-related cognitive impairment and dementia are becoming an expanding challenge to public health care systems. It has been estimated that globally the number of people affected by dementia will double in every 20 years, reaching over 81 million by the year 2040 (Ferri et al. 2005). In Finland, it has been predicted that there will be 128 000 patients with moderate to severe dementia by 2030 (Viramo & Sulkava 2006). Currently, the estimates of prevalence of dementia in people over 65 years varies between 5 and 9 percent depending on study methods and population (Viramo & Sulkava 2006). Even a larger proportion of elderly individuals suffer from milder forms of cognitive impairment (see e.g. Hänninen et al. 1996, Purser et al. 2005). Consequently, both the humane burden and the economical costs related to cognitive disorders will be enormous in the forthcoming years.

The nature of cognitive impairment in the elderly has long been under scientific scrutiny, but there is still a lack of knowledge of the factors that contribute to it. In order to be able to develop effective strategies to prevent and treat cognitive disorders, it is important to understand the diverse underlying mechanisms behind cognitive decline. Cognitive functioning in the elderly can be seen as a continuum from ‘successful’ and ‘normal’ aging to mild cognitive impairment and dementia (Soininen & Hänninen 2006). Dementia is a heterogeneous group of syndromes, and its major subtypes are Alzheimer’s disease, vascular dementia, Lewy body dementia and frontotemporal dementias. As the knowledge of the risk factors and treatment of neurodegenerative and vascular diseases has increased, the focus of research has shifted from overt dementia to its preclinical stages. The goal is to recognise the ongoing process as early as possible, when the intervention opportunities are most favourable (Erkinjuntti 1999, Haan & Wallace 2004). A failure to perceive cognitive impairment that arises from vascular pathology, but does not fulfil the formal criteria of dementia, notably underestimates the prevalence and burden of the vascular disease (Rockwood et al. 2000).

Cerebrovascular diseases are one of the largest groups of neurological disorders. In Finland, some 16 000 people are affected by ischemic stroke each year (Kansanterveyslaitos 2006). The incidence of stroke is related to increasing age (Di Carlo et al. 2000), and it poses a considerable risk of poor outcome and prognosis (Schmidt et al. 2000). It has been estimated that 65-78% of the patients suffer from different degrees of cognitive deficits after stroke, and many of these deficits are a major cause of post-acute functional disability (Tatemichi et al. 1994, Pohjasvaara et al. 1998, Nyrkko 1999). Even more individuals are affected by less abrupt forms of vascular brain pathology, such as microangiopathy or small vessel disease, as manifested by white matter lesions and lacunar infarcts (Román et al. 2002, Launer 2003).

Among stroke patients, in addition to infarct lesions, various other pathological features, such as white matter lesions, medial temporal lobe atrophy and global cerebral atrophy, are frequently observed as “side findings” in neuroimaging. They have been recognised as significant risk factors for post-stroke dementia (Tatemichi et al. 1990, Pasquier et al. 2000, Pohjasvaara et al. 2000, Prins et al. 2004, Leys et al. 2005). Despite the commonness of these findings, the role and mechanisms of cerebral stroke, small vessel disease and brain atrophy in cognitive functioning have been poorly understood.
The purpose of the present study was to identify the cognitive consequences of medial temporal lobe atrophy, white matter lesions and cerebral atrophy in an elderly population with ischaemic stroke. Furthermore, the contribution of corpus callosum atrophy to cognitive deficits was examined in subjects with age-related white matter lesions.

Cognitive functions and aging

Numerous cross-sectional and longitudinal studies have documented cognitive changes that are related to a normal aging process. These changes are thought to begin at the age of fifties (Schaie 1994), and they include subtle deterioration of memory (Korten et al. 1997, Ylikoski et al. 1998, Christensen 2001), verbal fluency (Ylikoski et al. 1998, Brickman et al. 2005), visuospatial and constructional ability (Ylikoski et al. 1998), attention and speed of behaviour (Korten et al. 1997, Ylikoski et al. 1998, Christensen 2001). The so-called fluid cognitive functions that require efficient and flexible processing and cognitive capacity (such as working memory and problem solving) are considered to be particularly susceptible to aging (see e.g. Hess 2005), whereas the crystallised functions, which rely on over-learned cognitive skills and knowledge, are better preserved (Christensen 2001). Generally, the cognitive changes in normal aging are mild in severity and do not cause marked deficits in everyday functional abilities. A more pronounced cognitive decline may indicate an ongoing pathological process in the brain. However, inter-individual variation in cognitive performance is high among the elderly, and therefore, making a difference between normal and pathological aging in clinical practice may be difficult (Christensen 2001, Fillit et al. 2002). In a population-based study (Ylikoski et al. 1999), several subgroups of cognitive aging have been identified. Based on distinct cognitive profiles, the subjects could be clustered into groups of individuals with successful aging or average aging and those with cognitive difficulties or risk for dementia. In order to be able to discriminate the preventable and treatable pathological conditions from healthy aging, it is important to gain knowledge of the determinants of age-related cognitive decline. Geriatric syndromes such as vascular dementia, mood disorders and motor disturbances are supposed to result from a combination of mechanisms related to aging and cardiovascular risk factors, together with cerebral grey and white matter degeneration, which lead to frontal-subcortical brain dysfunction (Cummings 1993, Pugh & Lipsitz 2002). The literature describing the age-related changes in some central cognitive domains is briefly reviewed in the subsequent sections.

1 Speed of mental processing

The concept of processing speed represents how quickly different types of cognitive processing operations can be carried out (Salthouse 1996a). Slowed mental processing is often an underlying factor behind other cognitive deficits such as attentional disorders (Salthouse 2000, Lezak et al. 2004, 349). The clinical test methods for assessing mental processing speed are typically either computer-aided reaction time tasks or paper-and-pencil tests that to some extent may also require psychomotor functioning. In these tests, the time scores are essential, whereas errors do not play an important role (van Zomeren & Spikman 2003). Tasks such as the simple parts of the Stroop test (word reading and colour naming) (MacLeod 1991) and the Trail Making test (part A) (Reitan 1958) do not specifically allow for separating between different subcomponents. Therefore these measures are here regarded as general (multidimensional) speed tests that also include the rates of reading, naming, and perceptual and visuomotor functions.
Mental speed is considered highly vulnerable to the effects of both normal aging and various pathological conditions. A central hypothesis is that increased age in adulthood is related to the deterioration of the speed with which many processing operations can be executed and that this decrement leads to decline in cognitive functions because of limited time and simultaneity mechanisms (Salthouse 1996a). A specific reduction of mental processing speed has been frequently reported as a result of brain damages such as traumatic brain injury (Mathias et al. 2004, Frencham et al. 2005), multiple sclerosis (Denney et al. 2005, Olivares et al. 2005) and vascular lesions (Rasquin et al. 2002, Almkvist 2003, Sachdev et al. 2004, Peters et al. 2005). Particularly, damage in subcortical brain structures is regarded critical for processing speed capacity (Lezak et al. 2004, 224).

2 Executive functions and attention

Executive functions refer to “a set of cognitive skills that are responsible for the planning, initiation, sequencing and monitoring of complex goal-directed behaviour” (Royall et al. 2002). According to the definition of the Diagnostic and Statistical Manual for Mental Disorders IV (APA 1994, 135), executive functioning involves the ability to think abstractly and to plan, initiate, sequence, monitor, and stop complex behaviour, to shift mental sets, generate novel verbal or non-verbal information, and to execute serial motor abilities. There is no unitary executive function, but rather the construct is an umbrella term encompassing a wide variety of functions related to cognitive control, attention and flexible strategic planning (Stuss & Alexander 2000). These skills are considered to be vital to human autonomy, and they are major determinants of disability in aging and in many neuropsychiatric disorders (Royall et al. 2002).

A large body of literature from brain lesion studies and functional neuroimaging has established that the primary structures mediating executive functions are the prefrontal cortex and its connecting pathways with the subcortical regions (see e.g. Royall et al. 2002, Elliott 2003, Buchsbaum et al. 2005). The frontal cortex can be divided into subsections, i.e. the dorsolateral prefrontal, orbitofrontal and anterior cingulate cortices, which, together with their related subcortical circuits, are suggested to be involved in distinct cognitive and behavioural responses and clinical syndromes (Royall et al. 2002, Tekin & Cummings 2002). The frontal-subcortical circuits prototypically originate from frontal lobes, project to striatal structures (caudate, putamen, ventral striatum), connect from striatum to globus pallidus and substantia nigra, then to specific thalamic nuclei and finally, link back to the frontal lobes (Cummings 1993) (Fig. 1). These frontal-subcortical structures are particularly susceptible to the effects of aging most commonly due to subcortical ischaemic microangiopathy (Pugh & Lipsitz 2002).

Figure 1. A prototype of the frontal-subcortical circuits (adapted from Cummings 1993, Tekin & Cummings 2002).
In a clinical setting, executive functions and attention are typically measured with tasks such as the Stroop (interference), Trail Making (part B), verbal fluency, Wisconsin Card Sorting and Tower of Hanoi tests that putatively assess response inhibition, set shifting, mental flexibility and problem solving (Royall et al. 2002, Lezak et al. 2004). The so-called executive tests are highly multi-factorial in nature, and therefore, although they are sensitive to frontal lobe damage, performance in them can be impaired also for other (non-frontal) reasons (Stuss & Alexander 2000). By using clinical test methods, it is problematic to clearly distinguish between various attentional and executive processes and, to date, there is no gold standard for any single executive measure (Royall et al. 2002).

3 Memory functions

The human memory functions can be classified into several categories and subcategories on the basis of their temporal scale (short-term vs. long-term) and the type of memory function (e.g. declarative vs. nondeclarative, episodic vs. semantic) (Squire & Zola-Morgan 1991, Squire 2004). Thus, memory is not a unitary function, but is composed of separate, yet interactive systems. According to present knowledge, some of the memory functions appear to be more vulnerable to the effects of aging than others. Nilsson et al. (2003) have investigated episodic, semantic and short-term memory as well as perceptual representation system (priming) and procedural memory across the life-span in a large longitudinal study. They found a steady age-related decline in episodic memory as measured with various free recall, cued recall, source recall, recognition and prospective memory tasks. In semantic memory, there was an increase in performance up to 55-60 years of age, and after that, a significant decrease. The other types of memory functions remained unchanged. Episodic memory, which refers to remembering past experiences in particular places at particular times (Tulving 2002), has been a central focus of research on cognitive aging. Specifically, the age-related decline in memory performance is found to be greatest in tasks that require efficient use of controlled processing mechanisms and involve effortful, self-initiated or strategic behaviour (Hess 2005).

Earlier studies of human amnesia and its animal models have proven that the medial temporal lobe, consisting of the hippocampus and the adjacent cortical areas (entorhinal, perirhinal and parahippocampal cortex), is the central anatomical basis for establishing long-term memory for facts and events (i.e. declarative memory) (Squire & Zola-Morgan 1991, Squire 2004). The integrity of the medial temporal lobe memory system is essential in the so-called consolidation process, binding together the distributed neocortical storage sites that represent a whole memory. The medial temporal lobe structures have strong reciprocal connections with each other as well as with widespread neocortical areas. However, their role in learning is only temporary as the memories stored in neocortex become independent (Squire & Zola-Morgan 1991). Recent studies have indicated that an integrated brain activity and cooperation between medial temporal and prefrontal areas is crucial for memory formation (Fernández & Tendolkar 2001). In fact, the hemispheric encoding/retrieval asymmetry (HERA) model suggests that the frontal lobes are heavily involved in episodic memory processes: encoding information to episodic memory is mediated by the left prefrontal cortex, while episodic memory retrieval is mediated by the right prefrontal cortex (Tulving 2002). These processes seem to be particularly susceptible to aging, since activations in prefrontal areas are reduced during various memory tasks (Hess 2005).
Cerebrovascular disease as a cause of cognitive disability

1 Ischaemic stroke

Stroke is defined as “an acute neurological dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of the focal areas in the brain” (WHO 1989). The two types of cerebral strokes are haemorrhages and infarcts, of which the latter refers to a temporary or permanent occlusion of a feeding artery. After stroke, cognitive impairment is highly frequent and, together with behavioural symptoms and motor deficits, it is a major cause of functional disability leading to an increased need for help and a decreased level of activity. In a sample from a stroke rehabilitation clinic, 65% of the patients had a specific neuropsychological deficit, 20% had anosognosia and 48% presented dysexecutive behaviour (Nyrkkö 1999). The cognitive domains most likely to be affected have been memory, orientation, language and attention (Tatemichi et al. 1994, see also Madureira et al. 2001). In the stroke cohort of the present study (Helsinki Stroke Aging Memory Study), 22% of the patients had deficits in attention, 23% in orientation, 34% in memory, 25% in executive functions, 37% in constructional and visuospatial abilities and 14% in speech (Pohjasvaara et al. 1997). Among survivors of ischaemic stroke, the prevalence of post-stroke dementia is about 30% (Pohjasvaara et al. 2000, Leys et al. 2005), and the risk of dementia is double-fold as compared to subjects who have not had stroke (Leys et al. 2005).

2 Vascular cognitive impairment

Traditionally, the diagnostic criteria for dementia have been constructed on the basis of Alzheimer’s disease, and therefore memory impairment has been strongly emphasised as a diagnostic feature (O’Brien et al. 2003, Román et al. 2004). However, the same definition may not be the most suitable one for other types of dementia. The ‘Alzheimerised’ criteria may particularly underestimate the prevalence of vascular dementia, in which executive dysfunction is considered to be the most prominent cognitive characteristic and the memory deficits may be only mild in severity (Looi & Sachdev 2000, Román 2003). In order to be able to recognise progressive vascular disease early enough for preventive therapies, a broader concept of ‘vascular cognitive impairment’ (VCI) has been adopted (Bowler 2002, O’Brien et al. 2003). VCI encompasses all causes of cerebrovascular disease and all levels of cognitive decline from subtle subclinical deficits to overt dementia. VCI without dementia has been observed to be the most prevalent form of VCI in the elderly (Rockwood et al. 2000), and thus a narrow focus on vascular dementia is considered to substantially overlook the cognitive consequences of vascular pathology (O’Brien et al. 2003). On the other hand, the concept of VCI has been criticised as being too vague and wide for a precise operative definition (Román 2003). A more limited terminology for vascular cognitive disorders has been proposed, in which VCI refers to mild vascular-related cognitive decline not fulfilling the criteria for vascular dementia (Román et al. 2004). Nevertheless, recent research indicates that executive dysfunction, including deficits in planning and sequencing, speed of mental processing, attention and performance in unstructured tasks, seems to be the essential cognitive feature that differentiates vascular pathology from Alzheimer’s disease (Desmond 2004).
3 Subtypes of vascular dementia

As vascular dementia and VCI are a highly heterogeneous group of conditions, several subtypes can be identified. The major subgroups of vascular dementia are cortical vascular or multi-infarct dementia, strategic infarct dementia and subcortical vascular dementia, which all have varying aetiological mechanisms and clinical characteristics (Erkinjuntti et al. 2000a, Román et al. 2002, O’Brien et al. 2003, Desmond 2004). The basic pathophysiological factors of VCI are illustrated in Figure 2. Cortical vascular dementia results mainly from large vessel disease or cardiac embolic events and presents cortical, cortico-subcortical arterial territorial and watershed infarcts. Strategic infarct dementia arises from focal, even small, ischaemic lesions in locations, e.g. hippocampus, angular gyrus, thalamus or basal ganglia structures, which are critical for higher cognitive functions. Subcortical vascular dementia is caused by small vessel disease and hypoperfusion and is characterised by lacunar infarcts, ischaemic white matter lesions and incomplete ischaemic injury. The clinical manifestations of both cortical and strategic infarct dementia are varied. However, subcortical vascular dementia is regarded as a more homogeneous subgroup with a more predictable outcome, thus making it more prone to clinical studies and treatment trials (Erkinjuntti et al. 2000a, Desmond 2004). It is also the most frequent form of vascular dementia (Bowler 2004). Research criteria for subcortical ischaemic vascular disease (SIVD) have been introduced on the basis of specific findings on magnetic resonance imaging (MRI) (Erkinjuntti et al. 2000b), but to date, empirical studies validating their clinical relevance have been few.

Figure 2. Pathophysiological mechanisms behind vascular cognitive impairment and dementia (modified from O’Brien et al. 2003). SIVD, subcortical ischaemic vascular disease.
Brain lesions potentially contributing to vascular cognitive impairment

1 White matter lesions

Cerebral white matter lesions are frequently found on brain imaging in the elderly. Their prevalence varies from one third to virtually all of the subjects in population-based studies depending on the used imaging techniques (Breteler et al. 1994, de Leeuw et al. 2001, Wen & Sachdev 2004). White matter lesions are more common in patients with ischaemic stroke, and they have also been associated with future strokes in subjects with atherosclerosis (Gerdes et al. 2006). Previously, white matter lesions were regarded as benign side findings in brain imaging, and their clinical relevance was not known. They were even called UBOs, ‘unidentified bright objects’. Since Hachinski proposed the term ‘leuko-araiosis’ (from Greek leuko=white, araiosis=rarefaction) in 1986 (Hachinski et al. 1986), white matter lesions have gradually received more and more attention in scientific research.

The cerebral white matter is composed of myelinated nerve fibres supported by neuroglia, whereas the grey matter consists of neuronal cell bodies. The glial cells (astrocytes, oligodendrocytes, ependymal cells, microglia) have an important role in the structural and nutritive support as well as in the repair and regeneration of the neurones (see e.g. Kandel 2000). White matter regions can be divided into periventricular (adjacent to the ventricular wall) and deep white matter areas, of which the latter includes subcortical (adjacent to cortex), watershed and deep white matter regions (Mäntylä et al. 1999). The periventricular and deep white matter areas receive their blood supply from the narrow penetrating end-arterioles that are vulnerable to small vessel disease and chronic hypoperfusion (Pantoni 1997, Haring 2002). The most important determinants of white matter lesions are increasing age and cardiovascular risk factors (Breteler et al. 1994, Longstreth et al. 1996, Launer 2003). The pathophysiological features are diffuse myelin pallor, astrocytic gliosis, widening of perivascular spaces and lacunes in the basal ganglia and pons; loss of oligodendrocytes leading to rarefaction, spongiosis and loss of myelin and axons without definite necrosis, which eventually result in white matter necrosis (Román et al. 2002). It has been suggested that the basic mechanism behind the structural changes is an alteration of cerebral blood flow autoregulation that exposes the white matter to brief and repeated episodes of hypotension and hypoperfusion (Pantoni 1997). Other possible mechanisms are related to the breakdown of the blood-brain barrier (Wardlaw et al. 2003) and Wallerian degeneration (Leys et al. 1991). It has been established that the age-related white matter lesions are ischaemic in origin (Pantoni 1997, Englund 2002) and that they can be reasonably distinguished from other causes of white matter alterations such as multiple sclerosis, vasculitis and infection (Barkhof & Scheltens 2002).

MRI is clearly superior to computed tomography in detecting white matter lesions. By using MRI, these changes appear hyperintense compared to normal white matter on proton-density and T2-weighted spin echo or fluid-attenuated inversion recovery (FLAIR) images, but they are hardly detectable as hypointensities on T1-weighted sequences (Mäntylä et al. 1999, Fazekas et al. 2002). Based on their appearance in MRI, these lesions are often called ‘white matter hyperintensities’ (WMH). WMH are typically evaluated by using rating scales that are based on visual inspection of the lesion type and size. However, there are several rating scales in use and their mutual agreement is only moderate (Mäntylä et al. 1997, Fazekas et al. 2002). Quantitative, semi-automated methods based on volumetric voxel-by-voxel analysis
of the lesions have recently become available, and they have proven to be more accurate and sensitive than the traditional rating scales that typically suffer from a ceiling effect (van Straaten et al. 2006). Furthermore, diffusion tensor magnetic imaging is a fairly novel technique providing promising opportunities to investigate the integrity of the structural organisation and neuronal networks of the brain (Fazekas et al. 2000). In clinical practice and with large patient samples, the conventional rating scales have still maintained their prominence because of their cost-effectiveness and relatively simple administration.

The age-related WMH have been associated with particular clinical characteristics such as motor and gait disturbance, urinary incontinence, depression and cognitive impairment (Inzitari et al. 2000, Kuo & Lipsitz 2004). Mental slowing, executive deficits, memory impairment and global cognitive decline have been the most common cognitive features related to WMH (Ylikoski et al. 1993, DeCarli et al. 1995, de Groot et al. 2000, Gunning-Dixon & Raz 2000, Inzitari et al. 2000, Mungas et al. 2001, Artero et al. 2004, Burton et al. 2004), which are postulated to result from a disconnection between the frontal-subcortical circuits (O'Sullivan et al. 2001, Pugh & Lipsitz 2002). However, negative findings have also been reported, showing no relationship between WMH and cognitive impairment (Bonnamo et al. 2000, Smith et al. 2000, Schmidt et al. 2002). The reason for the inconsistent findings has been suggested to lie in the differences of sampling methods, imaging techniques and neuropsychological assessment (Desmond 2002, Ferro & Madureira 2002). Moreover, the role of the severity (clinical threshold) and the location of WMH in cognitive impairment have not been well known.

2 Global cerebral atrophy

In addition to WMH, cortical and central atrophy (neuronal loss) are common structural brain changes related to aging. They are manifested in the enlargement of the sulcal and ventricular spaces and the loss of the whole brain volume. In healthy elderly, both cortical and central atrophy have been associated with deterioration of mental flexibility and abstract reasoning (Cook et al. 2002). Cortical grey matter volume has been a strong independent predictor of neuropsychological deficits in several domains also in a clinical sample with varying levels of cognitive functioning – exceeding the effects of white matter volume and subcortical lacunes (Mungas et al. 2001). In stroke survivors, global atrophy is an important determinant of post-stroke dementia (Tatemichi et al. 1990, Pasquier et al. 2000, Leys et al. 2005). Furthermore, among patients with vascular dementia, the whole brain volume has been strongly associated with overall cognitive ability (Cohen et al. 2002, Sachdev et al. 2004), while the volume of subcortical hyperintensities has been related to specific attention-executive impairment (Cohen et al. 2002). Yet, in a recent population-based study, only subcortical atrophy and periventricular WMH, but not cortical atrophy, independently predicted cognitive deficits (Söderlund et al. 2006). It should be noted that the periventricular WMH and central atrophy are likely to be causally related and reflect in part the same pathophysiological phenomenon. To some extent, also cortical atrophy may be linked to WMH through Wallerian degeneration or other related mechanisms, and thus they cannot be seen as fully independent processes in the aging brain.

3 Medial temporal lobe atrophy

Medial temporal lobe atrophy (MTA) in hippocampal formation and its adjacent cortical regions is a central feature in Alzheimer’s disease, and it becomes evident
already in the very early stages of the disease progress (Gómez-Isla et al. 1996). MTA detected on MRI can be used as a sensitive diagnostic marker of Alzheimer’s disease, even though its specificity to other neurodegenerative conditions is not as advantageous (Scheltens et al. 2002). Typically, MTA is evaluated on T1-weighted MRI scans by using visual rating scales with a relatively good reliability (Scheltens et al. 1992, Erkinjuntti et al. 1993, Scheltens et al. 2002). In experimental studies, more complicated volumetric techniques have also become available (Geuze et al. 2005a).


Thus far, the research has mainly focused on the consequences of MTA in dementia syndromes, even if MTA commonly occurs also in non-dementing neurological conditions such as in traumatic brain injury, cardiac arrest, epilepsy, neuropsychiatric disorders etc. (Grubb et al. 2000, Bigler et al. 2002, Geuze et al. 2005b). It has been recognised that in stroke patients MTA is a significant risk factor for dementia (Henon et al. 1998, Pohjasvaara et al. 2000, Barba et al. 2001, Leys et al. 2005). Nevertheless, its role in cognitive decline in non-demented subjects with cerebrovascular disease has been poorly known. Recently, MTA has been found to be associated with global cognitive impairment in combination with WMH among non-demented, non-disabled subjects (van der Flier et al. 2005a). Since to date, there are no means to unequivocally differentiate Alzheimer’s pathology from other diseases in vivo, it is unclear whether MTA reflects a coexisting Alzheimer pathology, or whether it is an independent phenomenon related to cerebrovascular disease.

4 Corpus callosum atrophy

The corpus callosum (CC) is a large band of commissural fibres that connects the two cerebral hemispheres. It is topographically organised so that the fibres from the frontal cortices traverse the anterior parts of the CC and the posterior cortices traverse the posterior parts. The CC can be structurally divided into five sections from the front to the back into rostrum and genu, rostral body, midbody, isthmus and splenium (Hampel et al. 2002, Ryberg et al. 2006). Recent advances with diffusion tensor tractography have augmented earlier neuroanatomical studies and revealed that the genu of the CC connects the lateral and medial frontal lobes, the rostrum connects the orbital frontal cortices and the body and splenium connect wide tempo-parietal and occipital homotopic regions (Abe et al. 2004, Hofer & Frahm 2006). Much of the knowledge of the role of the CC in cognitive functioning comes from patients with a surgical section of the CC (split-brain) or congenital agenesis of the CC. Despite the blockage of the interhemispheric transfer of information, the everyday functional consequences have typically been relatively mild. However,
disturbances such as slowed motor and cognitive performance (particularly in bimanual tasks) and impaired perception and language in tasks involving interhemispheric communication have been observed (Devinsky & Laff 2003, Lassonde et al. 2003, Zaidel & Iacoboni 2003, Gazzaniga 2005).

It has been noted that in neurodegenerative diseases, the size of the CC is significantly reduced on structural MRI, reflecting marked axonal loss and atrophy (Lyoo et al. 1997, Black et al. 2000, Yamauchi et al. 2000a, Hensel et al. 2002, Meguro et al. 2003, Wang et al. 2006). Yet the cause and the clinical significance of CC atrophy have been poorly understood. In Alzheimer’s disease, CC atrophy has been correlated with corresponding neuronal loss in neocortical regions (Pantel et al. 1999), also demonstrated independently of WMH (Hampel et al. 2002), and therefore CC atrophy is postulated to result from Wallerian degeneration originating from cortical damage. In patients with ischaemic cerebrovascular disease, however, the CC area has been related to subcortical white matter damage, suggesting a dissimilar mechanism to that of Alzheimer’s disease (Meguro et al. 2000, Tomimoto et al. 2004).

Previous studies have indicated that CC atrophy is associated with global cognitive decline as measured with simple dementia screening methods (Hanyu et al. 1999, Pantel et al. 1999, Black et al. 2000, Yamauchi et al. 2000b, Moretti et al. 2005, Ryberg et al. 2006). However, only a few studies have examined cognitive functions in detail (Giubilei et al. 1997, Meguro et al. 2003) and, as currently acknowledged, there are no studies investigating the contribution of regional CC measures to specific cognitive deficits in the elderly. Based on the topographical organisation of the CC, one could assume that the integrity of distinct CC regions is associated with differential neuropsychological deficits. Specifically, the role of the anterior CC could be related to attentional and executive deficits due to its interhemispheric connections with the prefrontal lobes and corresponding subcortical networks.
AIMS OF THE STUDY

The present study aimed to investigate how the vascular and degenerative brain imaging findings are related to cognitive decline in elderly subjects with cerebrovascular disease. The purposes of the study were to

1. examine the relationship between medial temporal lobe atrophy and cognitive deficits in elderly non-demented patients with ischaemic stroke (Study I)
2. explore how the severity and location of white matter hyperintensities predict neuropsychological test performance in elderly patients with ischaemic stroke (Study II)
3. describe the neuropsychological profile of the subcortical ischaemic vascular disease as compared to other stroke patients and neuropologically healthy control subjects (Study III)
4. investigate the contribution of overall and regional corpus callosum atrophy to deficits in mental speed, attention and executive functions (Study IV).
SUBJECTS AND METHODS

Studies I-III were conducted as part of the Helsinki Stroke Aging Memory (SAM) Study and Study IV as part of the Leukoaraiosis and Disability (LADIS) Study.

Helsinki Stroke Aging Memory (SAM) Study

1 Subjects and study protocol

The Helsinki SAM Study is a prospective cross-sectional study examining the cognitive, functional and emotional consequences of ischaemic stroke. The study focused on a sample of 486 stroke patients who were consecutively admitted to the emergency unit of the Helsinki University Central Hospital. The patients went through comprehensive clinical neurological, neuropsychological and psychiatric examinations and brain MRI three months after the index stroke. The patients were from 55 to 85 years of age and they lived in the city of Helsinki. The exclusion criteria were a condition other than ischaemic stroke (WHO 1989) and the patient’s poor knowledge of the Finnish language. From the present studies, patients who were not able to adequately complete the neuropsychological examination or the MRI were also excluded. Further, patients with dementia according to the DSM-III-R (APA 1987) and those with distinct speech deficits or visual neglect were excluded from Study I, because the aim was to evaluate memory impairment in its early stages. Aphasia and neglect syndrome were expected to excessively hamper memory performance. Consequently, the total number of patients was 260 in Study I and 323 in Studies II and III.

The control subjects for Study III (n=38) were derived from a population-based study that had been carried out earlier (Ylikoski et al. 1993). These subjects were clinically evaluated as neurologically healthy, and they participated in the neuropsychological examination and MRI according to the same protocol as the patients.

The study was approved by the Ethics committee of Department of Neurology, Helsinki University Central Hospital. The study was fully explained to all the subjects and those willing to participate gave an informed consent.

2 Neuropsychological assessment

The neuropsychological examination of the SAM Study was based on the diagnostic criteria of dementia and included several cognitive domains relevant for a post-stroke clinical judgment. The examination was conducted blindly to the radiological data. The neuropsychological tests were administered by following their standard instructions and scoring. The assessed cognitive domains and the methods are summarised in Table 1. Additionally, the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) was used as a measure of global cognitive status.


<table>
<thead>
<tr>
<th>Neuropsychological tests</th>
<th>Variables used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of mental processing</td>
<td></td>
</tr>
<tr>
<td>Trail Making A</td>
<td>Time</td>
</tr>
<tr>
<td>Stroop dots (colour naming)</td>
<td>Time</td>
</tr>
<tr>
<td>Attention and executive functions</td>
<td></td>
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<tr>
<td>Trail Making B</td>
<td>Time</td>
</tr>
<tr>
<td>Trail Making, difference</td>
<td>Subtraction score: B time–A time</td>
</tr>
<tr>
<td>Stroop words (interference)</td>
<td>Time</td>
</tr>
<tr>
<td>Stroop, difference</td>
<td>Subtraction score: words time–dots time</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test</td>
<td>Number of correct responses</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>Number of perseverative errors</td>
</tr>
<tr>
<td></td>
<td>Number of animal names (semantic)</td>
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<tr>
<td></td>
<td>Number of words beginning with K (phonemic)</td>
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<tr>
<td>Short-term memory</td>
<td></td>
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<tr>
<td>WMS Digit Span</td>
<td>Number of items correctly repeated forwards</td>
</tr>
<tr>
<td></td>
<td>Number of items correctly repeated backwards</td>
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<tr>
<td>Immediate memory recall</td>
<td></td>
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<tr>
<td>WMS-R Logical memory</td>
<td>Immediate total score</td>
</tr>
<tr>
<td>WMS-R Visual reproduction</td>
<td>Immediate total score</td>
</tr>
<tr>
<td>Fuld Object Memory Evaluation</td>
<td>Total retrieval in five learning trials</td>
</tr>
<tr>
<td>Delayed memory recall</td>
<td></td>
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<tr>
<td>WMS-R Logical memory</td>
<td>Delayed total score</td>
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<tr>
<td>WMS-R Visual reproduction</td>
<td>Delayed total score</td>
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<tr>
<td>Fuld Object Memory Evaluation</td>
<td>Delayed recall</td>
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<tr>
<td>Verbal intellectual functions</td>
<td></td>
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<tr>
<td>WAIS-R Similarities</td>
<td>Total score</td>
</tr>
<tr>
<td>WAIS-R Comprehension</td>
<td>Score in 4 items</td>
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<tr>
<td>WAIS-R Information</td>
<td>Score in 10 items</td>
</tr>
<tr>
<td>Visuospatial functions (construction)</td>
<td></td>
</tr>
<tr>
<td>WAIS-R Block design</td>
<td>Total score</td>
</tr>
</tbody>
</table>

WMS, Wechsler Memory Scale; WMS-R Wechsler Memory Scale-revised; WAIS-R, Wechsler Adult Intelligence Scale-revised.

Note: Neuropsychological raw scores were used in Study I. Both raw scores and composite scores were used in Studies II and III.

3 Magnetic resonance imaging

Brain MRI was carried out with a 1.0 T scanner. The protocol included transaxial T1, T2 and proton density-weighted images, which were obtained by using the spin echo technique. All images were analysed by the same neuroradiologist who was blind to the clinical data (for details, see Mäntylä et al. 2000). The lesions were recorded according to their number, location, side and type. The lesions close to the signal characteristics of the cerebrospinal fluid on T1-weighted images and measuring over 3 mm in diameter and wedge-shaped cortico-subcortical lesions were considered as infarcts. They were classified into four groups according to their size, and the average radii were used in volume estimation. Brain atrophy was rated visually on T1-weighted images from 0 to 3 (none, mild, moderate, severe), separately in cortical and subcortical regions in both hemispheres. MTA, in the left and right hippocampi and entorhinal cortices, was rated on three coronal slices (the slice showing the interpeduncular cistern ±1 slice) according to the same four-point scale (Erkinjuntti et al. 1993) through a comparison to standard images. The ratings of MTA are illustrated in Figure 3.
WMH were evaluated visually on the T2 and proton density-weighted images in periventricular areas (around frontal and posterior horns and along the bodies of lateral ventricles) and in deep, watershed and subcortical white matter. WMH in contact with the ventricular wall were regarded as periventricular hyperintensities (PVH), whereas the deep WMH (DWMH) were separated from the ventricular wall by a strip of normal-looking white matter. The PVH and DWMH ratings are illustrated in Figure 4. PVH around the frontal and occipital horns were classed on the basis of size and shape into small caps (≤5 mm), large caps (6-10 mm) and extending caps (>10 mm). PVH along the bodies of lateral ventricles were classed on the basis of thickness and shape into thin lining (≤5 mm), smooth halo (6-10 mm) and irregular halo (>10 mm). DWMH were classed based on size and shape into small focal (≤5 mm), large focal (6-10 mm), focal confluent (11-25 mm), diffusely confluent (>25 mm) and extensive (affecting the majority of white matter area) lesions. Furthermore, the extent of PVH was graded on a four-point scale: 0, absence; 1 small caps or thin lining; 2, large caps or smooth halo; 3, extending caps or irregular halo. The extent of DWMH was graded on a six-point scale: 0, absence; 1 only small focal lesions; 2, at least one large focal, no confluent lesions; 3, at least one focal confluent, no diffusely confluent lesions; 4, at least one diffusely confluent lesion; 5, extensive WMH.

The reliability of the atrophy and WMH ratings was tested by reviewing 60 MRI scans independently by the same rater and by two other radiologists. Good intra-observer and inter-observer agreement was found for all the ratings (Mäntylä et al. 2000).
Figure 4. Exemplar ratings of the white matter hyper-intensities on magnetic resonance imaging (see arrows).

Periventricular lesions around frontal or occipital horns: A) small caps, B) large caps and C) extending caps. Periventricular lesions along the bodies of lateral ventricles: D) thin lining, E) smooth halo and F) irregular halo. Lesions in deep, watershed and subcortical white matter areas: G) small and large focal lesion, H) focal confluent lesion, I) diffusely confluent lesion and J) extensive white matter change. The Helsinki Stroke Aging Memory Study (modified from Mantylä et al. 1997, 1999).
Leukoaraiosis and Disability (LADIS) Study

1 Subjects and study protocol

The LADIS Study is a 3-year longitudinal, multinational and multidisciplinary study of the role of age-related WMH as a predictor of transition to disability (Pantoni et al. 2005). Eleven European centres (Amsterdam, Copenhagen, Florence, Graz, Gothenburg, Helsinki, Huddinge, Lisbon, Paris, Mannheim, Newcastle-upon-Tyne) participated in the study and gathered a sample of 639 elderly subjects with different degrees of WMH. The subjects, aged 65-84 years, were initially non-disabled in the activities of daily living, but presented complaints of mild cognitive or motor disturbances, mood alterations and other neurological problems. The study also included control subjects and volunteers from other studies as well as subjects in whom age-related WMH were incidentally found on brain imaging. Among the exclusion criteria were: severe unrelated neurological disease, leukoencephalopathy of non-vascular origin (immunological-demyelinating, metabolic, toxic, infectious or other) and severe psychiatric disorders. The study protocol consisted of detailed and structured clinical medical and neuropsychological evaluations carried out each year, and of brain MRI that was performed at baseline and at the last follow-up year. The present study (IV) focused on the baseline data. Cases with inadequate MRI data (n=72) were excluded (the dataset incomplete or of insufficient quality for quantitative analysis). The local ethics committee of each participating centre approved the study, and an informed written consent was received from all subjects.

2 Neuropsychological assessment

The neuropsychological test battery was constructed from methods that were regarded as sensitive to cognitive decline in the elderly, but not too strenuous, and that were suitable for multicentre use (Madureira et al. 2006). The tests were translated into each local language from the original English versions and the examiners were carefully instructed to assure the uniformity of the administration. The study included tests of global cognitive functions such as the MMSE (Folstein et al. 1975) and a modified version of the Vascular Dementia Assessment Scale-cognitive subtest (VADAS-cog) (Ferris 2003) as well as supplemental executive tests. The present study (IV) focused mainly on measures of mental speed, attention, executive functions and working memory (Table 2). Additionally, Constructional praxis (copying geometrical forms) and Object naming tasks of the VADAS-cog were used.
Table 2. The Leukoaraisis and Disability Study: cognitive domains and neuropsychological tests in Study IV

<table>
<thead>
<tr>
<th>Neuropsychological tests</th>
<th>Variables used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of mental processing</td>
<td></td>
</tr>
<tr>
<td>Trail Making A</td>
<td>Time</td>
</tr>
<tr>
<td>Stroop word reading, part I</td>
<td>Time</td>
</tr>
<tr>
<td>Stroop colour naming (dots), part II</td>
<td>Time</td>
</tr>
<tr>
<td>Attention and executive functions</td>
<td></td>
</tr>
<tr>
<td>Trail Making, difference</td>
<td>Subtraction score: B time – A time</td>
</tr>
<tr>
<td>Stroop, difference</td>
<td>Subtraction score: III (interference) time – II time</td>
</tr>
<tr>
<td>Symbol digit modalities</td>
<td>Number of correct responses</td>
</tr>
<tr>
<td>Digit cancellation</td>
<td>Number of correct responses</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>Number of animal names</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
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<tr>
<td>Digit span, backwards</td>
<td>Total score</td>
</tr>
<tr>
<td>Language</td>
<td></td>
</tr>
<tr>
<td>Object naming</td>
<td>Number of errors</td>
</tr>
<tr>
<td>Visuoconstruction</td>
<td></td>
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<tr>
<td>Constructional praxis</td>
<td>Number of errors</td>
</tr>
</tbody>
</table>

3 Magnetic resonance imaging

Brain MRI was performed for all subjects locally at the centre where they were recruited following a standard protocol with either a 0.5 T scanner (one centre) or a 1.5 T scanner (ten centres). The images were collected and analysed at the Image Analysis Centre of the Vrije Universiteit Medical Centre, Amsterdam. WMH were assessed on FLAIR images both visually with a modified version of the 3-point Fazekas scale (mild, moderate, severe) (Pantoni et al. 2005) and volumetrically by using a semiautomated technique (van Straaten et al. 2006). The corpus callosum area was analysed in the Danish Research Center for Magnetic Resonance, Copenhagen on the mid-sagittal slice so that the images were stereotactically normalised to a reference T1-weighted image positioned in Talairach orientation in order to correct for inter-individual variation in the brain size and orientation. The corpus callosum was localised automatically, after which an expert reviewer corrected any inaccuracies. Furthermore, the corpus callosum was divided into five subregions according to a coordinate system with radial dividers with equal angular spacing (Fig. 5) (Ryberg et al. 2006).
Data analysis

The main statistical methods in Studies I and III were multivariate and univariate analyses of covariance (MANCOVA, ANCOVA). In studies II and IV the principal method was multiple linear regression analysis. The confounding demographic and clinical factors and coexisting MRI findings were adjusted where appropriate. Prior to the analysis, the data was screened for outliers and non-normality and, if necessary, distribution transformations were applied (Tabachnick & Fidell 2001, 80-3). Missing values in the neuropsychological data were imputed with unweighted group means in Study I, and in the subsequent studies no replacement was used. Based on the number of analyses, p<0.01 was regarded as significant in Studies I, II and IV, and p<0.05 in Study III (with Bonferroni correction in pairwise comparisons).
RESULTS

The characteristics of the subject in Studies I-IV are presented in Table 3.

<table>
<thead>
<tr>
<th>Table 3. Characteristics of the subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
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<tr>
<td>--------</td>
</tr>
<tr>
<td><strong>SAM</strong> Study I</td>
</tr>
<tr>
<td>No MTA</td>
</tr>
<tr>
<td>Mild MTA</td>
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<tr>
<td>Moderate MTA</td>
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<tr>
<td>Study II</td>
</tr>
<tr>
<td>Study III</td>
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<tr>
<td>Other stroke</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td><strong>LADIS</strong> Study IV</td>
</tr>
</tbody>
</table>

Number, mean (standard deviation) or percentage. LADIS, Leukoaraiosis and Disability Study; MMSE, Mini-Mental State Examination; MTA, medial temporal lobe atrophy; SAM, Stroke Aging Memory Study; SIVD, subcortical ischaemic vascular disease

**Study I: Medial temporal lobe atrophy and memory deficits in elderly stroke patients**

The patients of the SAM cohort were divided into three study groups based on the severity of MTA (none, n=100; mild, n=106; moderate to severe, n=54). As analysed with one-way analysis of variance, there were significant differences between the groups in age (F=18.0, p<0.001), total volume of infarcts (F=4.1, p<0.05) and in the degree of general cortical atrophy (F=43.8, p<0.001) and WMH (F=7.5, p<0.001; F=8.3, p<0.001), but not in gender, education, handedness, number or side of infarcts, or depressive symptoms. The patients with more MTA were older and had more severe MRI findings. Consequently, age, infarct volume and cortical atrophy were considered as covariates when analysing MTA and cognitive functions. The analyses were also performed by controlling for WMH, but since it had no incremental effect on the results, the variable was not included in the final analysis.
Table 4. Neuropsychological test performance in subjects with different degrees of medial temporal lobe atrophy (The Helsinki Stroke Aging Memory Study)

<table>
<thead>
<tr>
<th>Medial temporal lobe atrophy</th>
<th>None</th>
<th>Mild</th>
<th>Moderate to severe</th>
<th>F</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>F</td>
</tr>
<tr>
<td>WMS-R Logical memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>12.1 (4.0)</td>
<td>12.1 (4.0)</td>
<td>10.1 (3.6)</td>
<td>4.9 **</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>10.2 (4.0)</td>
<td>9.9 (4.2)</td>
<td>7.7 (3.9)</td>
<td>7.1 ***</td>
</tr>
<tr>
<td>WMS-R Visual reproduction</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>30.5 (7.1)</td>
<td>28.8 (7.7)</td>
<td>21.9 (7.3)</td>
<td>13.9 ***</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>23.8 (9.8)</td>
<td>19.3 (11.3)</td>
<td>12.2 (8.9)</td>
<td>10.8 ***</td>
</tr>
<tr>
<td>FOME</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total retrieval</td>
<td>37.5 (6.2)</td>
<td>35.0 (7.6)</td>
<td>32.6 (6.9)</td>
<td>5.7 **</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>8.4 (1.5)</td>
<td>7.9 (1.6)</td>
<td>7.5 (1.6)</td>
<td>4.5 ns</td>
</tr>
<tr>
<td>Digit span</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward</td>
<td>5.5 (1.1)</td>
<td>5.3 (1.0)</td>
<td>5.3 (0.9)</td>
<td>0.6 ns</td>
</tr>
<tr>
<td>Backward</td>
<td>4.1 (0.9)</td>
<td>3.9 (0.8)</td>
<td>3.7 (0.7)</td>
<td>3.6 ns</td>
</tr>
<tr>
<td>WAIS-R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similarities</td>
<td>22.7 (5.2)</td>
<td>22.8 (6.2)</td>
<td>20.9 (5.6)</td>
<td>1.6 ns</td>
</tr>
<tr>
<td>Block design</td>
<td>22.1 (9.9)</td>
<td>18.6 (10.2)</td>
<td>13.0 (7.4)</td>
<td>7.2 ***</td>
</tr>
<tr>
<td>Information</td>
<td>7.6 (1.8)</td>
<td>7.8 (1.9)</td>
<td>7.2 (2.3)</td>
<td>1.8 ns</td>
</tr>
<tr>
<td>Trail Making</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A, time</td>
<td>65.6 (27.0)</td>
<td>74.1 (32.7)</td>
<td>107.7 (60.0)</td>
<td>9.7 ***</td>
</tr>
<tr>
<td>Part B, time</td>
<td>174.6 (73.4)</td>
<td>202.9 (82.5)</td>
<td>234.0 (83.4)</td>
<td>3.9 ns</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter</td>
<td>13.1 (5.3)</td>
<td>11.5 (5.2)</td>
<td>10.7 (5.1)</td>
<td>1.9 ns</td>
</tr>
<tr>
<td>Animals</td>
<td>19.0 (5.1)</td>
<td>17.3 (5.9)</td>
<td>15.0 (6.0)</td>
<td>3.3 ns</td>
</tr>
</tbody>
</table>

Analysis of covariance F (df = 2,254) adjusted for age, total volume of infarcts and cortical atrophy. FOME, Fuld Object Memory Evaluation; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised. ** p < 0.01, *** p < 0.001, ns = non-significant.

As studied with multivariate analysis of covariance, the groups differed significantly in cognitive performance (MANCOVA Wilks’ $\lambda$ F=2.0, p<0.001) (Table 4). The pairwise contrasts between the covariate-adjusted group means showed that, as compared to the no-MTA group, the patients with moderate to severe MTA performed significantly worse in tests of verbal and visual memory (WMS-R Logical memory and Visual reproduction) and learning (Fuld Object Memory Evaluation, FOME) as well as mental speed (Trail Making A) and visuospatial functions (WAIS-R Block design), whereas the mild MTA group showed similar levels of cognitive performance. The results for the visual memory test remained essentially unchanged after controlling for the performance in either the mental speed test or the visuospatial test.

Study II: White matter hyperintensities as a predictor of neuropsychological deficits post-stroke

The relationships between cognitive performance and the MRI predictors were further examined with 323 patients of the Helsinki SAM Study by using sequential (hierarchical) linear regression analyses. Neuropsychological test variables were handled as dependent variables one by one and the predictor variables were entered in the model in the following steps: 1) age and education, 2) total infarct volume, 3) WMH in the four target regions (periventricular lesions around frontal horns, PVH-FH; around occipital horns, PVH-OH and along the bodies of lateral
ventricles, PVH-B; and deep, watershed and subcortical white matter areas, DWMH) and 4) general cortical atrophy. In the sequential regression model, the variance accounted for in the previously entered steps is controlled, so that the independent contribution of the subsequent predictor(s) can be analysed. After controlling for the demographic factors, WMH and cortical atrophy were found to have the highest predictive values for cognitive performance, whereas the total infarct volume had only moderate explanatory power (Table 5). The WMH measures, as a whole, significantly predicted performance in tests of mental speed, executive functions, immediate and delayed memory and visuospatial functions. However, the independent contributions of the separate white matter regions were low. Only PVH-B had independent predictive value for Trail Making A time (standardised β 0.25, p<0.01) and Wisconsin Cart Sorting Test (WCST) correct responses (standardised β -0.24, p<0.01).

Table 5. The relationship between test performance and predictor variables (The Helsinki Stroke Aging Memory Study)

<table>
<thead>
<tr>
<th>Predictor variables</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age and education</td>
<td>Total infarct volume</td>
<td>WMH in four target regions</td>
<td>Cortical atrophy</td>
</tr>
<tr>
<td>Trail Making</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A, time</td>
<td>.179 ***</td>
<td>.254 ***</td>
<td>.313 ***</td>
<td>.350 ***</td>
</tr>
<tr>
<td>Part B, time</td>
<td>.111 ***</td>
<td>.120</td>
<td>.202 ***</td>
<td>.211</td>
</tr>
<tr>
<td>Part B, correct</td>
<td>.107 ***</td>
<td>.155 ***</td>
<td>.185</td>
<td>.207 **</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colour naming, time</td>
<td>.173 ***</td>
<td>.202 ***</td>
<td>.237 **</td>
<td>.264 ***</td>
</tr>
<tr>
<td>Interference, time</td>
<td>.056 ***</td>
<td>.066</td>
<td>.124 ***</td>
<td>.137</td>
</tr>
<tr>
<td>Interference, correct</td>
<td>.142 ***</td>
<td>.150</td>
<td>.200 **</td>
<td>.247 ***</td>
</tr>
<tr>
<td>WCST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct responses</td>
<td>.123 ***</td>
<td>.139</td>
<td>.187 **</td>
<td>.201</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter</td>
<td>.073 ***</td>
<td>.083</td>
<td>.117</td>
<td>.127</td>
</tr>
<tr>
<td>Animals</td>
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<td>.110 **</td>
<td>.175 ***</td>
<td>.214 ***</td>
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<tr>
<td>WMS Digit Span</td>
<td>.065 ***</td>
<td>.080</td>
<td>.100</td>
<td>.114</td>
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<tr>
<td>WMS-R Logical Memory</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Immediate</td>
<td>.049 ***</td>
<td>.052</td>
<td>.061</td>
<td>.075</td>
</tr>
<tr>
<td>Delayed</td>
<td>.068 ***</td>
<td>.069</td>
<td>.084</td>
<td>.113 **</td>
</tr>
<tr>
<td>WMS-R Visual Reproduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>.193 ***</td>
<td>.262 ***</td>
<td>.323 ***</td>
<td>.368 ***</td>
</tr>
<tr>
<td>Delayed</td>
<td>.188 ***</td>
<td>.229 ***</td>
<td>.274 ***</td>
<td>.317 ***</td>
</tr>
<tr>
<td>FOME</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total retrieval</td>
<td>.090 ***</td>
<td>.090</td>
<td>.130</td>
<td>.169 ***</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>.053 ***</td>
<td>.058</td>
<td>.107 **</td>
<td>.141 ***</td>
</tr>
<tr>
<td>WAIS-R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block Design</td>
<td>.181 ***</td>
<td>.267 ***</td>
<td>.304 **</td>
<td>.332 ***</td>
</tr>
<tr>
<td>Similarities</td>
<td>.154 ***</td>
<td>.155</td>
<td>.178</td>
<td>.186</td>
</tr>
</tbody>
</table>

Sequential linear regression analyses with neuropsychological tests handled individually as dependent variables. The results are expressed as proportions of total variance (R²) explained by the regression models (cumulative in subsequent steps). Statistical significance represents the incremental explanatory power produced by each step (significance of R²change). ** p < 0.01, *** p < 0.001.

FOME, Fuld Object Memory Evaluation; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WCST, Modified Wisconsin Card Sorting Test; WMH, white matter hyperintensity; WMS, Wechsler Memory Scale; WMS-R, Wechsler Memory Scale-Revised.
The mediating relationships between WMH and cognitive functions were analysed by using a sum score of the four regional white matter variables and standardised composite scores of the cognitive domains (memory, mental speed, executive functions). As analysed with linear regression, the direct relationship between WMH and memory performance was highly significant (Fig. 6A), but when executive functions were added to the model as a mediator, this relationship dropped below the significance level (Fig. 6B), indicating a complete mediating relationship. Instead, when mental speed was considered as a possible mediator, the relationship decreased, but still remained significant, indicating a partial mediation (Fig. 6C). The indirect pathways were confirmed by the Sobel test (see e.g. Kenny 2006). Similar analyses were performed to study the mediating effects of executive functions and mental speed to visuospatial deficits. Identical results were found, i.e., executive functions acted as a complete mediator and mental speed as a partial mediator between WMH and visuospatial deficits.

**Figure 6.** Executive functions and mental speed as mediators between white matter hyperintensities (WMH) and memory impairment. A) The direct association between WMH and memory performance, B) Executive functions as a complete mediator, C) Mental speed as a partial mediator. The values are standardised β coefficients of linear regression. **p<0.01; *** p<0.001; ns, non-significant.
Study III: Cognitive profile of subcortical ischaemic vascular disease

In the Helsinki SAM cohort, the neuropsychological test performance of patients fulfilling the MRI-based criteria of SIVD (Erkinjuntti et al. 2000b) (n=85) was compared to that of other stroke patients (n=238) and healthy controls (n=38) by using standardised composite scores for seven cognitive domains (summarised in Table 1). Typical MRI findings of patients with SIVD are illustrated in Figure 7 showing a case with predominant WMH and a case with multiple lacunar infarcts.

Figure 7. Exemplar magnetic resonance images of patients with subcortical ischaemic vascular disease. A case with predominantly white matter lesions on the left and a case with predominantly lacunar infarcts on the right. The Helsinki Stroke Aging Memory Study.

Since the patients with SIVD were significantly older (F=4.6, p<0.05) and had less years of education (F=4.2, p<0.05), these demographic variables were taken into account as covariates. As analysed with multivariate analysis of covariance with the cognitive composite scores as dependent variables, the main effect for the study groups was significant (MANCOVA Wilks’ λ F=4.1, p<0.0001). The groups differed significantly in all of the cognitive composite scores, namely mental speed (F=3.6, p<0.05), executive functions (F=14.9, p<0.001), short-term memory (F=3.9, p<0.05), immediate (F=17.3, p<0.001) and delayed memory recall (F=19.3, p<0.001), verbal intellectual functions (F=10.1, p<0.001) and visuospatial functions (F=15.5, p<0.001). In pairwise comparisons, the SIVD group was inferior to the healthy control group in all domains. As compared to the other stroke patients, the patients with SIVD were inferior in executive functions and delayed memory performance. The results of the two patient groups standardised according to the healthy control group are illustrated in Figure 8.
Because there were significant differences between the patient groups also in depressive symptoms as assessed with the Beck Depression Inventory (Beck et al. 1961) and in the severity of MTA, the results were also analysed by controlling for these factors. After adjusting for depression, the results of the patient groups remained unchanged. However, after adjusting for MTA, the patient groups still differed from each other in executive functions, but not in delayed memory. Additional analyses by using the raw scores of the neuropsychological tests revealed that, after controlling for age and education, the patients with SIVD performed worse than the other stroke patients in FOME delayed recall, verbal fluency test (both semantic and phonemic tasks) and the Trail Making and Stroop tests (subtraction scores).

**Study IV: Corpus callosum atrophy is associated with mental slowing and executive deficits in subjects with age-related white matter hyperintensities**

The relationships between CC atrophy and cognitive deficits were studied within the LADIS sample (n=567) by using mainly multiple linear regression in two sets of models. In the first model set, the explanatory variables were the total CC area together with age, education, history of stroke and WMH volume as covariates. In the second model set, the five regional CC measures (Fig. 5) were examined using the same covariate variables. All explanatory variables were entered simultaneously. The neuropsychological test scores were set as dependent variables one by one. The results showed that the total CC area was related to poor performance in Trail Making A, Stroop parts I (word reading) and II (colour naming) and verbal fluency test (Table 6, Model I). Of the regional CC measures, the most
anterior part (rostrum and genu, CC1) was associated with poor performance in the subtraction scores of the Trail Making (B time – A time) and Stroop (III time – II time) test as well as in Symbol digit modalities and Digit cancellation tests. Furthermore, the midposterior CC area (isthmus, CC4) predicted verbal fluency performance (Table 6, Model II).

Table 6. Relationship between corpus callosum atrophy and cognitive functioning

<table>
<thead>
<tr>
<th></th>
<th>Corpus callosum area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model I</td>
</tr>
<tr>
<td></td>
<td>CC total</td>
</tr>
<tr>
<td>Trail Making A, time</td>
<td>-0.13**</td>
</tr>
<tr>
<td>Trail Making B-A, time</td>
<td>-0.03</td>
</tr>
<tr>
<td>Stroop part I, time</td>
<td>-0.13**</td>
</tr>
<tr>
<td>Stroop part II, time</td>
<td>-0.13**</td>
</tr>
<tr>
<td>Stroop part III-II, time</td>
<td>-0.03</td>
</tr>
<tr>
<td>Symbol digit modalities</td>
<td>0.09</td>
</tr>
<tr>
<td>Digit cancellation</td>
<td>0.05</td>
</tr>
<tr>
<td>Digit span backwards</td>
<td>0.07</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>0.14***</td>
</tr>
</tbody>
</table>

Standardised β coefficients of linear regression models expressing the independent predictive values of CC measures for neuropsychological test performance after adjusting for age, education, history of stroke, and WMH volume. Model I includes the total CC area and Model II includes the five CC subregions. CC, corpus callosum; CC1, rostrum and genu; CC2, rostral body; CC3, midbody; CC4, isthmus; CC5, splenium. ** p<0.01, *** p<0.001.

The Object naming and Constructional praxis tasks of the VADAS-cog were analysed in order to cover cognitive functions mediated by the more posterior brain areas. However, due to substantial skewness of the distributions, these variables were coded dichotomous (errors vs. no errors) and logistic regression was applied by using the same explanatory variables and model sets as in the previously described linear regression analyses. The results revealed no significant relationships between either of these tasks and the CC measures (odds ratios between 0.99 and 1.01).
DISCUSSION

Medial temporal lobe atrophy and cognitive deficits

In a sample of elderly non-demented patients with ischaemic stroke, it was found that after controlling for age, total infarct volume and cortical atrophy, MTA was associated with poor episodic memory performance in tasks covering both immediate and delayed recall as well as learning. The memory decline was not specific to a particular test material, since visual, verbal and multimodal memory performances were equally affected. In addition, MTA was also found to be related to a decrease in visuospatial abilities and speed. These, however, did not explain the observed relationship between MTA and visual memory deficits. Moreover, no significant associations were found between MTA and short-term storage (working memory), established semantic memory, verbal fluency, conceptualisation or mental flexibility. It is notable that MTA seemed to affect cognitive functions only when it was at least moderate in severity. Mild MTA had no significant contribution in cognitive performance, which suggests that a certain threshold must be surpassed before MTA has clinical relevance.

The findings are in accordance with previous results from studies with Alzheimer’s patients (Deweer et al. 1995, Mori et al. 1997, O’Brien et al. 1997, Pantel et al. 2004, van der Flier et al. 2005b) and other dementias (Laakso et al. 1996, Barber et al. 1999, Tam et al. 2005), in which MTA has specifically correlated with memory functions. Furthermore, neuronal loss in the medial temporal lobe structures has been associated with memory deficits also in patients with traumatic brain injury (Bigler et al. 2002) and temporal lobe epilepsy (Sass et al. 1990, Lencz et al. 1992, Miller et al. 1993). In patients with cerebrovascular disease, MTA significantly increases the risk of dementia (Henon et al. 1998, Pohjasvaara et al. 2000, Barba et al. 2001, Leys et al. 2005). However, the present study is the first to demonstrate the role of MTA in VCI in non-demented patients. Later on, another recent study has proved that MTA contributes to global cognitive decline in non-demented subjects with age-related ischaemic WMH (van der Flier et al. 2005a). It is concluded that MTA is not a specific phenomenon for Alzheimer’s disease, and it poses a notable risk for cognitive impairment also in non-demented subjects with cerebrovascular disease. In stroke patients, MTA is related to specific cognitive disturbances such as long-term memory deficits and visuospatial deficits. Notably, cerebrovascular disease and Alzheimer’s disease occur together more often than by chance, and they have several common vascular risk factors (Kalaria 2000). Thus, the cognitive impairment observed in stroke patients with MTA can be partly explained by preclinical Alzheimer’s disease, since MTA occurs already in the very early stages of the disease.

White matter hyperintensities, cortical atrophy and cognitive decline

Previous studies have indicated that WMH are frequent in elderly stroke patients (Mäntylä et al. 1999). Nevertheless, the role of WMH in cognitive functions in these patients has been poorly understood. The present study examined the MRI predictors of cognitive decline post-stroke. The results revealed that after controlling for the relevant demographic factors and total infarct volume, the overall degree of WMH was significantly associated with cognitive decline, particularly in tests assessing mental speed and executive deficits. Findings from various patient
samples and healthy elderly have suggested that WMH have a role in mental or psychomotor slowing (Junqué et al. 1990, Ylikoski et al. 1993, Fukui et al. 1994, de Groot et al. 2000, Cohen et al. 2002, Burton et al. 2003, 2004, Prins et al. 2005, van der Flier et al. 2005b, van den Heuvel et al. 2006). Executive functions have also been frequently affected (DeCarli et al. 1995, Mungas et al. 2001, Cohen et al. 2002, Cook et al. 2002, Burton et al. 2003, Price et al. 2005, Prins et al. 2005), but not in all of the studies (Burton et al. 2004, van der Flier et al. 2005b). In the present study, WMH were additionally associated with memory performance in tasks of visual memory and delayed recall of object learning. However, there were no significant associations between WMH and short-term storage or story recall. Some of the earlier studies have found correlations with visual (DeCarli et al. 1995, Cohen et al. 2002) and other (Mungas et al. 2001, Burton et al. 2004) memory functions, but also with working memory (Cohen et al. 2002, Burton et al. 2003, 2004). WMH were also related to visuospatial and constructive performance as assessed by the WAIS-R Block Design subtest. A parallel finding has been reported earlier with healthy elderly subjects (Garde et al. 2000).

An important novel finding of the present study was that the relationships between WMH and memory functions as well as visuospatial functions were completely mediated by executive deficits. A similar, but only partial, mediating effect was produced by mental speed. The finding suggests that executive dysfunction and mental slowing are the primary cognitive consequences associated with WMH, and they seem to be responsible for the secondary deficits in the other cognitive domains. A conceivable explanation is that patients with executive deficits and slowed mental processing are unable to fully utilise their memory capacity because of inefficient encoding and retrieval strategies. In visuoconstructive tasks, they likewise may have secondary difficulties due to poor planning and monitoring of the performance. To the current knowledge, similar results have not been published before. Instead, related findings have been observed in cognitive aging studies, whereby processing speed has been suggested to explain individual age differences in memory performance and other cognitive tasks (Salthouse 1996b, Sliwinski & Buschke 1997, Salthouse 2000).

In the present study, the independent predictive values of the lesions in the single white matter regions were relatively low as compared to the overall effect of WMH measures. Only the PVH along the bodies of the ventricles were independently associated with speed and problem solving tasks, whereas PVH around frontal or occipital horns and DWMH had no specific relevance. Some other studies have reported regional differences, i.e. in temporal vs. frontal white matter (Burton et al. 2004) and periventricular vs. deep white matter (Ylikoski et al. 1993, Fukui et al. 1994, de Groot et al. 2000, Prins et al. 2005, van den Heuvel et al. 2006). However, in many of these studies, only bivariate relationships have been analysed without controlling for the confounding WMH in other regions. In the present sample, the regional WMH measures were strongly correlated with each other, which could have reduced their individual explanatory powers. Due to the diffuse nature of the ischaemic pathophysiology, WMH unlikely appear in isolated white matter regions, therefore making it difficult to evaluate the relative contributions of the specific locations. On the other hand, Tullberg et al. (2004) have observed that WMH are associated with frontal lobe hypometabolism and executive dysfunction regardless of their location. This, in accordance with the present results, suggests that the site of WMH is less relevant for cognitive functions than the overall degree and severity.

General cortical atrophy turned out to be a strong predictor of post-stroke cognitive performance even after adjusting for demographic factors, infarct volume and WMH. It was associated with a wide variety of cognitive domains and hence may reflect
global cognitive decline. Previously, both WMH and global atrophy have proven to be strong determinants of dementia in stroke survivors (Tatemichi et al. 1990, Pasquier et al. 2000, Leys et al. 2005). Moreover, atrophy has significantly contributed to various cognitive deficits in patients with cerebrovascular disease also in earlier studies (Cohen et al. 2002, Sachdev et al. 2004).

Neuropsychological characteristics of subcortical ischaemic vascular disease

After controlling for age and education, the patients with MRI-defined SIVD, other patients with ischaemic stroke and the healthy control subjects differed from each other as groups in cognitive performance both quantitatively and qualitatively. The patients with SIVD performed considerably inferior to the healthy control subjects in all of the assessed cognitive domains. Compared to the other stroke patients, the patients with SIVD had comparable levels of global cognitive status as reflected by the MMSE, but they were significantly inferior in tests assessing executive functions (mental flexibility, response inhibition, verbal fluency) and delayed memory. The two patient groups did not differ from each other in mental speed, short-term memory, immediate memory or verbal intellectual and visuospatial performance.

Earlier studies have suggested that the pattern of cognitive deficits in SIVD is dissimilar to that of Alzheimer’s disease, in which recognition memory and spatial cognition have been poorer, but verbal fluency better (Tierney et al. 2001, Schmidtke & Hüll 2002). The cognitive profile in SIVD has been proposed to be closer to Parkinson’s disease with considerable impairment in executive functioning (Libon et al. 2001). As compared to healthy elderly, the patients with SIVD have in fact presented subtle deficits in executive functions and visual memory (Kramer et al. 2002). In the present study, the cognitive deficits in SIVD were substantial in severity in relation to normal aging. Subtle, but significant, differences were also demonstrated as the patients with SIVD were contrasted to other stroke patients, even if the latter group had a larger mean infarct volume. Interestingly, verbal fluency performance seems to differentiate patients with SIVD not only from patients with Alzheimer’s disease (Tierney et al. 2001), but also from patients with ischaemic stroke. Yet it is important to note that the earlier studies have used varying definitions for SIVD and the present study is one of the first to implement the formal MRI-based research criteria (Erkinjuntti et al. 2000b).

In this study, the delayed memory deficits associated with SIVD were explained in part by MTA. Earlier, Kramer et al. (2004) have suggested that rapid forgetting in SIVD implies concomitant Alzheimer’s disease, while dementia with good retention may originate from pure vascular aetiology. This might be the case also in the present study. As we cannot entirely exclude patients with early Alzheimer’s disease in vivo, the memory deficits in patients with SIVD may reflect mixed pathology with both neurodegenerative and vascular mechanisms. On the other hand, MTA has been observed also as a post-mortem characteristic of small vessel disease in a similar pattern and degree as in Alzheimer’s disease (Kril et al. 2002). The memory deficits may also occur as a secondary consequence of WMH-related executive dysfunction as was shown in Study II.

Depression has been repeatedly observed to be related to subcortical ischaemic damage in the elderly (Vataja et al. 2001, Pohjasvaara et al. 2003, Krishnan et al. 2004). According to the vascular depression hypothesis, cerebrovascular disease can predispose and exacerbate depressive symptoms in the elderly (Alexopoulos et
However, the results indicated that cognitive deficits associated with SIVD were not accounted for by depressive symptoms, which therefore suggested that the mood and cognitive changes are parallel, but independent processes related to SIVD.

**Corpus callosum atrophy and cognitive deficits**

The relationship between regional CC atrophy and cognitive performance was investigated in elderly non-demented and functionally independent subjects with different degrees of age-related WMH by controlling for age, education, history of stroke and WMH volume. The CC measures were corrected for brain size by means of a spatial normalisation procedure adjusting also for major global atrophic changes. The results revealed that the total CC area, reflecting overall CC atrophy, was related to performance in cognitive tests assessing psychomotor and mental speed (Stroop parts I and II, Trail Making A). Of the regional measures, the most anterior CC area (rostrum and genu) was independently associated with performance in the executive tests assessing mental flexibility, response inhibition and selective attention (subtraction scores of the Trail Making and Stroop test, Symbol digit modalities, Digit cancellation). In addition, the total CC area and the midposterior CC region (isthmus) were associated with semantic verbal fluency. Based on these results, it is concluded that anterior CC atrophy seems to reflect a relatively focal dysfunction possibly resulting from an interhemispheric disconnection of the prefrontal cortices and their related subcortical circuits leading to specific attentional-executive deficits. Instead, the overall CC atrophy appears to be involved in a diffuse subcortical damage and disconnection affecting general speed of mental processing. Moreover, the relationship of isthmus area to verbal fluency could be explained by the posterior connections between temporo-parietal cortices involved in semantic processing and language.

Earlier studies have examined the role of CC atrophy in relation to global cognitive decline in aging, but specific regional relationships to cognitive processes have not been investigated. Based on the split-brain research, it has been postulated that complex tasks require more efficient interhemispheric cooperation as compared to simpler tasks (Gazzaniga 2005). The anterior region of the CC is thought to be involved in the transfer of attentional resources and higher cognitive information, and posterior regions in transfer of basic sensory information (Gazzaniga 2005). The functional imaging studies provide further evidence for bilateral frontal lobe involvement in executive processing (Buchsbaum et al. 2005). One of the few studies investigating specific executive functions in the elderly found that subjects with a higher overall CC atrophy rating had lower scores in Trail Making B test, Digit Symbol test and a phonemic fluency task (Meguro et al. 2003). The present study partly parallels these results, since the affected cognitive processes are congruent, but in addition, considerable regional specificity was now observed.

To conclude, CC atrophy seems to have a specific contribution to cognitive decline in the elderly, not only as an indirect manifestation of white matter damage and global atrophy, but as an indicator of reduced functional connectivity between cortical areas.

**Methodological considerations**

Certain methodological issues should be addressed when evaluating the results of these studies. The studies were conducted as part of two extensive multidisciplinary
study projects, the Helsinki SAM Study and the LADIS Study. Both of the subject samples were eminently large and well-defined providing a representative picture of elderly subjects with cerebrovascular disease. The SAM Study consisted of a consecutive series of elderly patients with ischaemic stroke admitted to the Helsinki University Hospital in a given time period, and therefore the sample accurately represents clinical stroke population. The LADIS Study, in turn, included a mixed population of elderly subjects with a wide range of WMH (from mild to severe) gathered from several European centres on the basis of varying referral reasons. The sample reflects well the clinical diversity of elderly population with various neurological complaints. Neither of the studies, however, was based on a random sample from community, and thus the results may not be completely applicable to general population. It is conceivable that the relationships between cognitive performance and MRI findings are more pronounced in these clinical samples of subjects with marked neurological symptoms as compared to the healthy elderly.

The heterogeneous clinical characteristics of elderly subjects with cerebrovascular disease should be kept in mind when evaluating the results. A careful attempt was made to control the numerous confounding factors between the MRI findings and their cognitive correlates by using specific exclusion/inclusion criteria and multivariate statistical methods. The intervening variables were the demographic factors, such as age and education, clinical risk factors as well as other concomitant MRI findings. In the elderly population, the MRI findings, such as cerebral infarcts, focal and global atrophy and WMH, are strongly correlated with each other and also with increasing age. Statistical adjusting procedures can effectively remove the hampering effects of the covariate variables, but a possible drawback is multicollinearity when multiple intercorrelated variables are analysed. Even though the multicollinearity indices in these analyses were tolerable, it should be noted that when several explanatory variables are analysed simultaneously in the multivariate models, their individual contributions may be underestimated due to the mutual correlations. On the other hand, the multivariate analyses are much more reliable than the commonly used bivariate correlations, in which the possibility of overestimating the results is substantial.

Among the strengths of these studies are the extensive and clinically relevant neuropsychological test batteries. The SAM Study included a particularly comprehensive and detailed neuropsychological assessment that gave a full picture of the cognitive spectrum. The flip side of using numerous and demanding neuropsychological tests is the increase of missing data. In the SAM Study, the
amount of missing values in the neuropsychological tests varied between 0 and 14%, and they most frequently occurred in some of the executive and memory tests (WCST, Trail Making B test and FOME). In additional analyses, it was found that the patients with missing values in the above mentioned three tests were older, had less education and more cortical atrophy and WMH (unpublished data). This implies that these factors contribute to the patient’s inability to complete the test (floor effect). Thus, in clinical studies, missing data does not necessarily occur in a random fashion, but can be affected by various patient characteristics. Instead of regarding it merely as a source of error, it can also be used as valuable information.

The amount of missing values was low in the Ladis Study, in which the neuropsychological test battery was designed to be less demanding. Study IV focused on the measures of mental speed, attention, executive functions as well as naming and visuoconstructive skills. Although the results pointed at specific associations between atrophy of particular CC regions and cognitive deficits, no inferences can yet be made regarding other cognitive domains such as memory functions.

The neuropsychological tests variables were grouped into composite scores in Studies II and III on the basis of clinical experience and prior knowledge. These cognitive domains are multidimensional and partly overlapping constructs. They reflect general, but clinically relevant, aspects of cognitive functioning. Statistical factor modelling was not used, because it is not well applicable to a clinical sample of patients with versatile neuropsychological syndromes. The individual test variables included in the composite scores had sufficient internal coherence according to the reliability analysis. Furthermore, the raw scores were analysed along with the composite scores in order to ascertain the results.

A methodological advantage of these studies is the sophisticated MRI analyses that give an extensive picture of the different types of brain lesions. In the SAM Study, WMH and MTA were visually rated by a single neuroradiologist according to formal rating scales through a comparison to previously collected standard images. The reliability analysis by three independent raters revealed good intra-observer and inter-observer agreement for all the ratings (Mäntylä et al. 2000). In the LADIS Study, CC atrophy and WMH were evaluated with semiautomated volumetric techniques providing highly accurate measures of the CC morphology and WMH load. A volumetric analysis of WMH has turned out to be more sensitive compared to the visual rating scales with a potential ceiling effect (van Straaten et al. 2006). On the other hand, the rating scales are much less time-consuming and simpler to use, and they have proved to be sufficient when analysing the relationships of WMH to clinical parameters in a clinical setting (Gouw et al. 2006). It has also been shown that the visual rating of MTA is as accurate as the volumetric analysis of these vaguely outlined structures both in distinguishing patients with Alzheimer’s disease from normal controls (Desmond et al. 1994, Wahlund et al. 2000, Bresciani et al. 2005) and in predicting memory performance in normal aging (Lye et al. 2006).

**General discussion**

In the recent few years, a keen interest in VCI and its determinants has arisen. Contrary to earlier conceptions, WMH are no longer regarded as benign incidental features of aging, but rather they are considered to be an important factor contributing to cognitive decline. WMH are associated with vascular risk factors and increasing age (Breteler et al. 1994, Longstreth et al. 1996, Launer 2003), and they are frequently found in patients with cerebrovascular disease (Mäntylä et al. 1999).
The relevance of the so-called vascular burden, referring to the versatile brain pathologies caused by cerebrovascular disease, for cognitive deficits has been established, but the specific mechanisms are still under scrutiny. These underlying mechanisms behind cognitive decline are now perceived to be much more complex than was previously assumed. It has been noted that the risk factors for vascular disease and Alzheimer’s disease are strikingly similar, and considerable overlap has been observed in their pathophysiological characteristics (Kalaria 2000).

Taken together, the results of the present studies indicate that there are multifaceted brain mechanisms behind VCI. They include periventricular and deep WMH, global and focal atrophy as well as cerebral infarcts. The age-related WMH are associated with decline in executive functions and mental processing speed, and these deficits may cause secondary impairment in other cognitive domains. Anterior CC atrophy is independently related to executive and attentional deficits, which implies the involvement of specific interhemispheric frontal-subcortical disconnections. Impairment in the frontal lobe-mediated executive functions is the most prominent cognitive feature in SIVD that is caused by small-vessel disease and characterised by extensive WMH and lacunar infarcts. However, the memory deficits in these patients seem to be explained by MTA.

In elderly subjects with cerebrovascular disease, the different pathological changes are more or less interrelated processes, and together they seem to produce cumulative effects on cognitive decline. The results support the view that complex interactions of both vascular and degenerative changes contribute to cognitive impairment in the elderly. The present studies provide strong cross-sectional evidence for the involvement of WMH, MTA and CC atrophy in VCI. Future studies with longitudinal design are necessary to establish the clinical significance of the progression of these changes.
CONCLUSIONS

1. Moderate to severe MTA is associated with specific cognitive deficits in non-demented elderly patients with ischaemic stroke. Long-term memory and visuospatial skills are the most vulnerable cognitive domains, whereas verbal and executive functions are insensitive to MTA.

2. The overall degree of WMH is related to post-stroke cognitive decline. Instead, the independent contribution of the separate white matter regions is low. WMH are primarily associated with executive deficits and slowed mental processing. These deficits seem to lead to secondary impairment in other cognitive domains such as memory and visuospatial functions.

3. Together with WMH, general cortical atrophy is a strong predictor of post-stroke cognitive decline, even exceeding the contribution of the total infarct volume.

4. Cognitive deficits in SIVD can be qualitatively differentiated from those of other stroke patients three months post-stroke. As compared to healthy controls, these deficits are notable in severity. Executive dysfunction is the most prominent cognitive characteristic. The patients with SIVD also exhibit impairment of delayed memory recall, which is explained in part by MTA.

5. Cognitive deficits and depressive symptoms are parallel, but independent consequences of SIVD.

6. CC atrophy seems to contribute to cognitive decline in the elderly as an indicator of reduced functional connectivity between cortical areas, independently of the concomitant white matter damage and global atrophy. Anterior CC atrophy appears to have an impact on the frontal lobe-mediated executive functions and attention, whereas overall CC atrophy is associated with the slowing of processing speed.
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ORIGINAL PUBLICATIONS