Cognitive profiles of vascular and neurodegenerative MCI

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Abstract

The objective of the thesis was to investigate the cognitive profiles of different types of mild cognitive impairment (MCI) and follow their course over time. Would it be possible to differentiate between “benign” and “malign” forms of MCI, and identify different dementia disorders in their prodromal stages by means of cognitive profiles? In study I consecutive MCI subjects (N=112) were assessed with a neuropsyhological test battery of 21 tests. When compared to healthy controls (N=35) MCI subjects had impairments in all cognitive domains (speed/attention, memory and learning, visuospatial functions, language and executive functions), which contradicted the prevailing view of MCI typically being memory impairment, ”amnestic MCI”. In study II the subjects were grouped by cerebrovascular disease. Subjects with significant vascular disease (N=60) performed overall worse on the neuropsychological test battery than those without vascular disease (N=60). The most clear-cut differences were seen on speed/attention and executive tests, and the conclusion was that there were similarities in the cognitive profiles of MCI with vascular disease and vascular dementia. In study III MCI subjects without vascular disease were grouped by concentrations of the Alzheimer-typical biomarkers total-tau (T-tau) and beta-amyloid (Aß). Subjects with Alzheimer-typical concentrations of one or the other, or both biomakers in cerebrospinal fluid (N=73) performed worse on episodic memory and speed/attention tests than those with normal concentrations (N=73). When subjects were grouped into those with only high T-tau, only low Aß and both high T-tau and low Aß, those with both high T-tau and low Aß tended to perform slightly worse, while the other 2 groups performed quite similarly.
In study IV 175 subjects were followed up after 2 years. Forty-four converted to dementia, all with impairment in several cognitive domains at baseline, and all but 2 had either vascular disease or Alzheimer-typical biomarkers. Single domain MCI – regardless of vascular disease and biomarkers – had a benign prognosis over 2 years. The combination of multiple domain amnestic MCI and vascular disease was the best predictor of mixed and vascular dementia, while multiple domain amnestic MCI and biomarkers was the strongest predictor of Alzheimer’s disease.
MCI is a heterogeneous condition – the original purely amnestic MCI was very rare – with several aetiologies. The combination of cognitive profiles and aetiologies has the potential of making a crucial contribution in diagnosing dementia disorders at their earliest manifestations.

List of publications

The thesis is based on the following studies, referred to in the text by their Roman numerals:

I The Goteborg MCI study: mild cognitive impairment is a heterogeneous condition. *J Neurol Neurosurg Psychiatr*., 2005 76(11): 1485-1490.

II Cognitive profiles of mild cognitive impairment with and without vascular disease *Neuropsychology*. 2007 Nov;21(6):706-12..

III Episodic memory and speed/attention deficits are associated with Alzheimer-typical CSF abnormalities in MCI. In press *J International Neuropsychological Soc*

IV Two year outcome of MCI subtypes and aetiologies in the Goteborg MCI study. Manuscript

To my parents Martta and Elias

(tämä on teille, Äiti ja Isä)

I am not young enough to know everything…

Oscar Wilde

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Abbreviations

AD	Alzheimers disease
MD	mixed dementia
CVD	cerebrovascular disease
VaD	vascular dementia
ARCD	age related cognitive decline
AACD	aging-associated cognitive decline
AAMI	age-associated memory impairment
MCI	mild cognitive impairment
aMCI	amnestic = only memory impairment MCI
maMCI	amnestic MCI with multiple domains impaired
mdMCI	non-amnestic MCI with multiple domains impaired
sMCI	non-amnestic MCI with single domain impaired
DLB	dementia with Lewy bodies
FTD	frontotemporal dementia
VCI	vascular cognitive impairment
CSF	cerebrospinal fluid
T-tau	cerebrospinal fluid total tau protein
Aß42	cerebrospinal fluid amyloid-beta protein
STEP	stepwise comparative status analysis
EXIT	Executive interview
MMSE	mini-mental state examination
CDR	clinical dementia rating
MRI	magnetic resonance imaging
TIA	transient ischemic attack
ELISA	enzyme-linked immunosorbent assay
PLS-DA	Partial Least Squares Discriminant Analysis
VIP	variable influence on projection
ANOVA	analysis of variance
ANCOVA	analysis of co-variance
AAN	American Academy of Neurology
WAIS	Wechler's Adult Intelligence Scale
RAVLT	Rey Auditory Verbal Learning Test
WLM	Wechsler's Logical Memory
RCF	Rey Complex Figure
VOSP	Visual Object and Space Perception
ASLD	Assessment of Subtle Language Disorders
BNT	Boston Naming Test
WCST	Wisconsin Card Sorting Test
PaSMO	Parallel Serial Mental Operations
MCI-nov	MCI with no vascular disease
MCI-vas	MCI with vascular disease
MCI-norm	MCI with normal concentrations of T-tau and Aß42
MCI-dev	MCI with deviating concentrations of T-tau and Aß42

Introduction

Cognitive science, cognitive psychology and cognitive functions

A simple definition of cognitive science is the scientific study of the mind, or of thinking. It is an interdisciplinary science including the fields of psychology, philosophy, neuroscience, linguistics, anthropology, biology, and also computer science (Longuet-Higgins, 1987). There are several approaches to the study of cognitive science – symbolic, connectionist, and dynamic – of which cognitive psychology mainly uses the symbolic approach. Symbolic cognitive models are models intended to explain how some aspects of cognition are accomplished by sets of computational processes. A model is constructed for a specific cognitive task or class of tasks and constitutes a set of predictions that could be compared to data from human performance. Thus, the symbolic approach deals with models of mental – not brain regional – processes. The focus of this thesis will be on models of function and dysfunction within cognitive domains – speed and attention, memory and learning, visuospatial functions, language, and executive functions – rather than specific brain structures and locations of brain damage.

The scientific questions cognitive modeling seeks to answer belong to cognitive psychology. Cognitive psychology is a school of thought in psychology that examines internal mental processes such as those mentioned above. Cognitive psychologists are interested in how people understand, diagnose, and solve problems, thus concerning themselves with the mental processes which mediate between stimulus and response (Neisser, 1967). According to the definition in the Swedish national encyclopedia the thought processes that accomplish this – handle our sensory input and memories – are cognitive functions. Thus, cognitive functions are very generally the thought processes necessary to deal with the demands and solve the problems of our every day life. Ulrich Neisser, who presented the term ‘cognitive psychology’ in his book with that very title, published in 1967, provided a more elaborate definition. Neisser’s definition expands the concept beyond definitions such as “reasoning”, which often is found as a definition of cognition:

...the term "cognition" refers to all processes by which the sensory input is transformed, reduced, elaborated, stored, recovered, and used. It is concerned with these processes even when they operate in the absence of relevant stimulation, as in images and hallucinations... Given such a sweeping definition, it is apparent that cognition is involved in everything a human being might possibly do; that every psychological phenomenon is a cognitive phenomenon. Cognitive psychology is concerned with all human activity rather than some fraction of it.

This very exhaustive definition brings cognition beyond the focus and approach of this thesis, which is one of cognitive neuropsychology; the cognitive functions necessary to process and handle the every day life, and how to measure those functions with tests. Still the definition is relevant in order to understand the role of cognition in psychology. Although Neisser claims that cognitive psychology is concerned with all human activity, he adds that perspectives other than the cognitive are valuable. Psychodynamic psychology, for instance, deals with motives and drives rather than with sensory input and how it is processed. Instead of asking how a man's actions and experiences result from what he saw, remembered, or believed, the dynamic psychologists ask how they follow from his goals, needs, or instincts. The perspective of behavioral psychology is also different from that of cognitive psychology. While behaviorists are concerned with behaviour and how it is shaped by its consequences (i.e. conditioning), cognitive psychology acknowledges the existence of internal mental states, such as beliefs, wishes, desires and other motivating factors (Neisser, 1967). There are no absolute boundaries between the different traditions but their focuses certainly differ.

Cognitive impairment

Cognitive impairment has in the last decades got quite some attention. One conceivable reason for that is that we live in a society with increasing demands on cognitive functioning – faster and faster information exchange, rapid developments in technology, not least information processing – which could reveal even quite subtle cognitive deficits. Cognitive impairment is quite frequent in many states of ill-health, but often to some degree neglected and insufficiently surveyed, even though cognitive deficits may complicate treatment and follow-up. Significant cognitive impairment has been reported in Parkinson's disease (Caballol, Marti, & Tolosa, 2007; Riedel et al., 2008), multiple sclerosis (Roca et al., 2008), diabetes (Luchsinger et al., 2007), heart failure (Vogels et al., 2007), neuropsychiatric

disorders (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; Hale, Zaidel, McGough, Phillips, & McCracken, 2006; Loo, Hopfer, Teale, & Reite, 2004), chronic fatigue (Goshorn, 1998; Jason, Corradi, Torres-Harding, Taylor, & King, 2005), chronic stress or distress (Oei, Everaerd, Elzinga, van Well, & Bermond, 2006; Wilson et al., 2007), depression (Elderkin-Thompson et al., 2003; Thomas & O'Brien, 2008), schizophrenia (Joyce & Roiser, 2007; Keefe & Fenton, 2007), HIV (Vance & Struzick, 2007), cancer survivors who have undergone chemotherapy (Jansen, Miaskowski, Dodd, & Dowling, 2007; Vardy & Tannock, 2007), and even in sleep disorders (Massicotte-Marquez et al., 2008). These conditions may contribute or lead to more severe cognitive impairment and eventually promote the one condition that is characterized and defined by disabling cognitive impairment: dementia.

Dementia

Dementia is one of the most devastating and costly disorders affecting people. Dementia is a progressive decline in cognitive functions beyond what could be expected from normal aging, due to damage to, or disease in, the brain. Literally the Swedish word for dementia – demens – means out of one's mind; from Latin's **de-** "apart or away" and **mens** "mind". Dementia is not a disease per se but a term for a non-specific illness syndrome which is caused by many different disease processes. The general criteria for dementia in DSM-IV (*DSM-IV (Diagnostic and Statistical Manual of Mental Disorders)*, 1994), published by the American Psychiatric Association, is that there is impairment in several cognitive domains to such a degree that the person needs help or support in his or her everyday life. Thus, dementia does not affect only the patient, but also very much spouses, children and other close relations, whom the patient eventually will depend upon.

The single greatest risk factor for dementia is old age. About 6% of the population over the established retirement age of 65 in Sweden are affected. The prevalence increases strongly with age; 1% of 60-65 year olds, 6% of 75-79 year olds, and 45% of those aged 95 suffer from dementia (Wimo, Winblad, & Jonsson, 2007). According to some recent estimates, there are today about 30 million people in the world suffering from dementia, some 160.000 of them in Sweden (Ferri et al., 2005). Considering that especially the western population live longer and longer, and with a fast increasing number of people over 60 in the world, it has been estimated that the number

will roughly double every 20 years, resulting in more than 40 million affected by 2020 and over 80 million by 2040 (Ferri et al., 2005).

Dementia does not only cause the patient and the close relations serious suffering, but it is also an extremely costly condition. The direct costs of dementia have been estimated to 156 billion USD (about 1000 billion SEK) in 2003 (Wimo, Jonsson, & Winblad, 2006), an estimate that was doubled by 2005, to 315 billion USD (Wimo et al., 2007). Although highly developed countries spend over 90% of the money, they account for less than 40% the dementia cases (Wimo et al., 2006). Due to differences in culture, family patterns, economic strength, health care organization and financing, there is a great variability in how dementia care is provided, and thus the burden dementia causes the public finances. Nevertheless, there is no doubt that the burden is enormous and increases alarmingly, even in the less developed countries. Yet the indirect costs – production losses and premature mortality – are not included. Considering that the majority of persons with dementia are retired, those costs, however, can be expected to be relatively modest (Wimo et al., 2007).

Alzheimer's disease

The most common dementia disorder is Alzheimer's disease (AD), (Aggarwal & Decarli, 2007; Ferri et al., 2005) according to most reports it constitutes about 50% of all dementia cases (Ferri et al., 2005). This means that there are around 80.000 people suffering from AD in Sweden, a figure that has been estimated to increase to 100.000 by 2010 (Wimo et al., 2007). AD is an acquired neurodegenerative disease, the cause of which is unknown. Clinical signs of Alzheimer's disease include progressive cognitive deterioration, often beginning with memory impairment. Reports on symptoms in all cognitive domains in the earliest stages of the disease, however, exist according to an extensive review; attention, visuospatial, language and executive deficits (Twamley, Ropacki, & Bondi, 2006). The onset of AD is gradual, with subtle cognitive decline – known as mild cognitive impairment – for years before the disorder can be considered to represent manifest dementia (Maioli et al., 2007; Morris et al., 2001). The distinction between early and late onset AD is often made; whether the disease onset was before or after the age of 65. It is difficult to find reliable figures on the proportion of early onset AD. According to Mayo Clinic's information on internet, early onset makes up 5-10% of all AD cases, while the Swedish Alzheimer society estimates the proportion to be 10-15%. Thus,

a reasonable estimate would be about 10%, which means that there are about 8.000 AD patients under the age of 65 in Sweden. According to some reports the symptom profiles of early and late onset AD are different, with more "parietal" – language and visuospatial – symptoms and attention deficits in early onset, and a more generalized cognitive decline and confusion in late onset AD (Blennow & Wallin, 1992; Blennow, Wallin, & Gottfries, 1990; Reid et al., 1996). The duration of AD varies strongly depending on at which age the patient is diagnosed, with an average length of time from onset of symptoms to death in the range of 7 to 10 years for patients diagnosed in their 60s and 70s, to only about 3 years for patients diagnosed in their 90s (Brookmeyer, Corrada, Curriero, & Kawas, 2002) but it is not uncommon that patients live longer than that.

Mixed and vascular dementia

By definition, mixed dementia (MD) is a dementia syndrome caused by more than one disease process in the brain. The most common cause of MD is a combination of AD and vascular disease in the brain; cerebrovascular disease (CVD), compromising blood flow in the brain by small vessel disease, small infarctions or stroke (Langa, Foster, & Larson, 2004). MD can be diagnosed either on evidence of neurodegenerative dementia combined with CVD or a typical neurodegenerative symptomatology but also significant ischemic lesions on neuroimaging (Rockwood, 2003; Rockwood et al., 2000). There have been some discussion about the contribution of degenerative processes in vascular dementia (VaD), and vice versa, and the strict dichotomy between AD and VaD has been questioned. Recently, it has been suggested that "AD with CVD" or "mixed dementia" should be included in the clinical diagnosis of VaD (Nagata et al., 2007). There is no agreement about the prevalence and incidence of MD (Jellinger & Attems, 2007). According to some, MD is probably one of the most common forms of dementia, since the risks of both neurodegenerative dementia and CVD increase with age (Langa et al., 2004; Nagga, Radberg, & Marcusson, 2004; Zekry, Hauw, & Gold, 2002). On the other hand others state that the prevalence of MD and VaD is decreasing due to better medical care (Manton, Gu, & Ukraintseva, 2005).

Vascular dementia (VaD) is a heterogeneous clinical entity based on various expressions of vascular disease affecting the brain: small vessel disease as the primary vascular etiology, lacunar infarcts and ischaemic white matter lesions as the primary type of brain lesions (Erkinjuntti et al., 2000; Nagata

et al., 2007). VaD is, according to most studies, the second most common dementia disorder, but estimates on the prevalence of VaD vary – anything between 0.03% and 58% can be found in the autopsy literature (Jellinger, 2007). According to a recent review, between 1% and 4% of all of 65 year olds suffer from VaD, and the prevalence probably doubles every 5-10 years (McVeigh & Passmore, 2006). Although these figures also vary, a reasonable estimate would be that VaD constitutes about 20% of all dementias (Aggarwal & Decarli, 2007). VaD seems to be slightly more common in some Asian countries, such as Japan and Korea, constituting 25%-35% of all dementias (Jellinger, 2007). The perhaps most important distinction between different types of VaD made today is between poststroke dementia and subcortical VaD (Wallin, Milos, Sjogren, Pantoni, & Erkinjuntti, 2003). Poststroke dementia occurs with cognitive decline in close time relation to a transient ischemic attack. It has a sudden onset and stepwise course. The neuropsychological profile is diffuse, depending on the location of the brain insults. Subcortical VaD caused by small-vessel disease is probably the most common form of VaD, although the proportion figures vary between 37% and 67% (Roman, Erkinjuntti, Wallin, Pantoni, & Chui, 2002). Subcortical VaD has a more gradual onset and progressive course, with a clinical picture typically characterized by psycho-motor slowing and executive deficits (Roman et al., 2002; Roman & Royall, 1999). Since AD is the most common dementia disorder, it also generates the greatest burden on public finances, but according to several reports, VaD contributes most significantly to the costs, since the health care costs of a VaD patient are markedly higher than those of an AD patient – according to one report twice as high (Fillit & Hill, 2002; Hill, Fillit, Shah, del Valle, & Futterman, 2005).

Neuropsychology of the dementia disorders

According to many reports, there is considerable overlap between the neuropsychological profiles of AD, MD and VaD (Almkvist, Backman, Basun, & Wahlund, 1993; Fahlander, Wahlin, Almkvist, & Backman, 2002; Groves et al., 2000), but reports on distinctive differences have also been published (Baillon et al., 2003; Graham, Emery, & Hodges, 2004; Kertesz & Clydesdale, 1994; Matsuda, Saito, & Sugishita, 1998; Schmidtke & Hull, 2002). In summary, AD patients performed worse on memory and language tests, whereas VaD patients performed worse on motor, attention, visuospatial and executive tests. MD patients performed worse on a verbal executive test but performed otherwise similarly to AD patients.

Cognition and brain aging

Even though age is the sole greatest risk factor for dementia, far from all old people will be affected by cognitive impairment – in fact, there are data suggesting that the prevalence of dementia decreases after the age of 95 (Borjesson-Hanson, Edin, Gislason, & Skoog, 2004). In the last decades much effort has been put into developing concepts for describing how aging affects cognition. The concept of "successful aging" was first presented in The Gerontologist in 1961 (Havighurst, 1961) and has since been used to describe the 20% of all people who show practically no signs of cognitive decline and little somatic decline or ill-health with increased age. At about the same time the article "Senescent forgetfulness: benign and malignant" (Kral, 1962) was published, in which a distinction between normal forgetfulness and forgetfulness associated with brain disease was made. In the following decades cognitive decline associated with aging was mainly considered an expression of normal aging and explained by differences in general health and education (Anstey, Stankov, & Lord, 1993). Concepts such as age related cognitive decline (ARCD) (Craik & Salthouse, 1992) and aging-associated cognitive decline (AACD) (Levy, 1994) originally represented more benign forms of cognitive ageing. Eventually, however, in a number of studies individuals with the kind of cognitive decline these concepts were describing were found to be at a markedly increased risk for dementia (Celsis et al., 1997; Ritchie, Artero, & Touchon, 2001; Ritchie, Touchon, Ledesert, Leibovici, & Gorce, 1997). These findings led to the evolvement of diagnostic entities such as age-associated memory impairment (AAMI) (T. Crook, Bahar, & Sudilovsky, 1987; T. H. Crook, Larrabee, & Youngjohn, 1990) and mild cognitive impairment (MCI) (Petersen et al., 1997; Petersen et al., 1999), which were seen as potentially neurodegenerative conditions. MCI was even suggested to represent preliminary stages of dementia (Morris et al., 2001; Petersen, 2000). With symptomatic treatment available for AD – and potentially disease modifying treatments in clinical trials for both AD and VaD – the interest for identifying dementia disorders in their earliest manifestations has increased dramatically during the last decade.

Mild Cognitive Impairment (MCI)

In the second half of the last decade Mild Cognitive Impairment (MCI) (Petersen et al., 1997) emerged as the predominant target for studies on early signs and symptoms of dementia. MCI is conceptualized as a boundary or

transitional state between normal aging and dementia. In the original criteria MCI was defined as memory impairment with other cognitive domains relatively spared (Petersen et al., 1999). The memory impairment should be both subjective and objectively significant for age; confirmed by a significantly reduced memory test score. According to a number of studies, individuals with that kind of memory impairment, but with normal general cognitive function, converted to AD at a rate of 10-15% per year (Bowen et al., 1997; Guarch, Marcos, Salamero, & Blesa, 2004; Morris et al., 2001; Petersen et al., 1997; Petersen et al., 1999; Tierney et al., 1996). Although the focus of these studies was memory impairment, other cognitive impairments also were reported, for example naming deficits (Petersen et al., 1999), impaired concept formation (Guarch et al., 2004) and executive impairment (Chen et al., 2000; Guarch et al., 2004). Eventually it was suggested that the risk of dementia, including AD, was significantly increased when other cognitive impairment was present, and that isolated memory impairment was not the best predictor of dementia. According to some studies, subjects with memory impairment alone were very rare and rarely progressed to dementia (Ritchie et al., 2001).

These findings led to an amendment of the MCI criteria in 2001, the criteria were widened to encompass three MCI subgroups: amnestic (isolated memory impairment); multiple domains slightly impaired; single non-memory domain impaired (Petersen et al., 2001). This model with three subgroups was, however, soon replaced by new criteria and a model with four subgroups. In 2004 the International Working Group on Mild Cognitive Impairment published a consensus report in which the following criteria were proposed for MCI: (i) the person is neither normal nor demented; (ii) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired (Winblad et al., 2004). In accordance with the increasing heterogeneity of the concept, the MCI subgroups were increased with one; subjects could now be designated to one of four subgroups: amnestic; amnestic with multiple domains impaired: non- amnestic multiple domains impaired; non-amnestic single domain impaired.

The notion of different aetiologies causing MCI was also introduced: degenerative, vascular, psychiatric and traumatic (Petersen, 2004). A model with MCI subtypes of different aetiologies representing different prodromal

dementia disorders was put forward. Amnestic MCI (aMCI) of degenerative aetiology was suggested to represent prodromal AD; amnestic MCI with multiple domains impaired (maMCI) of degenerative aetiology would also represent prodromal AD; maMCI of vascular aetiology would represent vascular dementia (VaD); non- amnestic MCI with multiple domains impaired (mdMCI) of degenerative aetiology dementia was suggested to be prodromal dementia with Lewy bodies (DLB); mdMCI of vascular aetiology VaD; non-amnestic MCI with single domain impaired would be prodromal frontotemporal dementia (FTD) or DLB (Petersen, 2004). Thus, it was suggested that a combination of clinical subtypes and aetiologies would be useful in predicting the specific dementia disorder that a person with MCI would progress to.

There are numerous, discordant, reports on which MCI subtype constitutes the greatest risk of conversion to dementia. There is some agreement on that amnestic MCI – with or without other domains impaired – typically represents AD. Some studies report the risk of AD to be increased when domains other than memory also are impaired (Alexopoulos, Grimmer, Perneczky, Domes, & Kurz, 2006; Tabert et al., 2006) and conclude that pure aMCI has a more favourable prognosis than maMCI. Others report lower conversion rates for maMCI than aMCI and state that individuals with multiple domain or non-amnestic MCI ”include a substantial number of individuals who may not progress to dementia” and that neuropsychological variables other than memory are not instrumental to predict progression to dementia (Schmidtke & Hermeneit, 2008).

MCI with vascular disease / Vascular Cognitive Impairment

Cognitive disorders associated with vascular disease have lately been paid increased attention, for instance by the International Society for Vascular Behavioural and Cognitive Disorders (VAS-COG) (Wallin, Skoog, Kalaria, & Roman, 2004). According to some studies, vascular risk factors increase the risk of AD in MCI. In one study – although the best predictors of conversion to AD were found to be neuropsychological tests – AD converters tended to be more affected by vascular risk factors. The authors concluded that some vascular risk factors seem to promote progression from MCI to AD (Sepe-Monti et al., 2007). In another study vascular risk factors were reported to increase the risk of dementia, independent of MCI subtype (Ravaglia et al., 2006). In yet another study, the authors found that signs of vascular disease in the form of white-matter hyperintensities on brain

imaging were significantly associated with cognitive decline in MCI (Debette et al., 2007). Also a differing conclusion has been reached: vascular disease does not contribute when predicting dementia in MCI (DeCarli et al., 2004).

Most studies on MCI have focused on MCI as prodromal AD, but studies on MCI preceding other possible dementia disorders, such as VaD, have also been conducted. In many studies the prodromal stage of VaD is called vascular cognitive impairment (VCI) (Frisoni, Galluzzi, Bresciani, Zanetti, & Geroldi, 2002; Meyer, Xu, Thornby, Chowdhury, & Quach, 2002; Ravaglia et al., 2006). VCI refers to cognitive impairment caused by cerebrovascular disease and covers a whole spectrum of disorders, from minimally objectively identifiable deficits to VaD (Moorhouse & Rockwood, 2008; O'Brien, 2006). There is very little agreement about the clinical picture of VCI. According to one study on VCI, VaD is preceded by a stage of mild impairment, with similar, but less severe, cognitive deficits as in VaD (Sachdev et al., 2004), whereas the conclusion of others has been that the preclinical phase in VCI differs from not only AD, but is not similar to VaD either (Ingles, Boulton, Fisk, & Rockwood, 2007). The conclusion in other studies has been that VaD caused by subcortical disease often is preceded by progressive cognitive impairment, similar to the form of MCI preceding AD (Frisoni et al., 2002; Meyer et al., 2002). In one study the cognitive profile of MCI patients with prodromal AD (MCI-AD) was compared to that of MCI patients with vascular disease (MCI-vascular). MCI-AD and MCI-vascular did not differ on measures of memory, language, visuospatial skills/praxis or executive function. The groups had similar cognitive profiles, with deficits both on memory and other tests (Loewenstein et al., 2006). In another recent study MCI subjects were classified with amnestic MCI (a-MCI) and with multiple impaired cognitive domains MCI (mcd-MCI). The authors found that the mcd-MCI mainly had executive deficits and also significantly more vascular comorbidity and signs of vascular disease on brain imaging. All subjects who after 3 years had progressed to AD had previously been classified as a-MCI, and all subjects who had progressed to VaD had been classified as mcd-MCI (Zanetti et al., 2006).

Biomarkers and MCI

Since 1995 two biochemical markers in the cerebrospinal fluid (CSF) for AD have emerged, total-tau (T-tau) and amyloid-ß42 (Aß42) (Andreasen,

Vanmechelen, Vanderstichele, Davidsson, & Blennow, 2003). Tau protein is located in the neuronal axons and the concentration of T-tau in the CSF is thought to reflect the intensity of neuronal degeneration in chronic neurodegenerative disorders (Blennow, 2004b). Aß42 is the major component of senile plaques and the decreased level of Aß42 in the CSF in AD may be caused by deposition of Aß42 in plaques, with lower levels being transported to CSF (Blennow, 2004a). Lately these biomarkers – increased levels of T-tau and decreased levels of Aß42 – have been used to predict AD in MCI subjects with some success (Andreasen et al., 2003; Hansson et al., 2006; Ivanoiu & Sindic, 2005). Recently the biomarkers have even been used to predict MCI in seemingly healthy individuals (Li et al., 2007). Some studies on MCI, examining the relation between CSF biomarkers and neuropsychological findings, have been conducted (Ivanoiu & Sindic, 2005; Schoonenboom et al., 2005). Both studies found elevated T-tau concentrations primarily to be associated with poor performance on episodic memory tests, whereas decreased Aß42 concentrations were associated with poorer general neuropsychological performance. In a recent study, both patients with amnestic MCI and MCI with a dysexecutive syndrome had abnormal biomarkers and progressed to AD to approximately the same extent, with T-tau as the biomarker with the strongest predictive power (Herukka et al., 2007).

Objectives of the thesis

Although there have been considerable efforts made to promote MCI as prodromal AD or dementia, it is to date rather a loosely defined concept, referring to cognitive impairment that can be caused by a multitude of conditions. The prognosis of the individual MCI patient is often quite unsure and the question about possible treatment difficult. Finding sensitive and specific markers for the most common dementia disorders is crucial in order to be able to answer the patient's rightfully worried questions about prognosis and possible treatment. This task is not only urgent for the individual patient but the society in large, considering the rapidly increasing strain on public finances cognitive ill-health cause, by for example stress and psychiatric ill-health, but especially dementia disorders.
The overall objective of the thesis was to investigate the cognitive profiles of different types of clinically defined MCI and follow their course over time. Would it be possible to differentiate between "benign" and "malign" forms of MCI, and identify different dementia disorders in their prodromal stages by means of cognitive profiles?

The specific objectives were

- To study which neuropsychological tests most clearly distinguish between a general population of clinically defined MCI subjects attending a memory clinic and healthy controls.
- To examine whether the cognitive profile of MCI subjects with vascular disease differ from that of MCI subjects with no vascular disease.
- To compare the neuropsychological profiles of MCI subjects with normal concentrations of total tau and Aß42 in CSF to MCI subjects with an AD-typical pattern, i.e. increased and decreased concentrations of these biomarkers.
- To investigate the predictive value of different MCI subtypes and aetiologies for conversion to AD, mixed dementia and VaD, and to study which neuropsychological tests strongest predicted conversion to dementia.

Materials and methods

Inclusion, exclusion criteria and MCI subgrouping

The subjects in the studies were recruited from patients attending a memory clinic at Sahlgrenska university hospital. The memory clinic started in 1992, and has since grown to be the major activity of the neuropsychiatric clinic, with 2400 new patients between 2000 and 2007. See table 1 for an overview of the studies and table 2 for demographic data for the participants. The diagnoses of MCI were made in diagnostic conferences by experienced clinicians, specifically for research purposes, following the 2004 MCI criteria (Winblad et al., 2004). The neuropsychological results were not used for diagnostic purposes; the diagnoses were based on information about medical history and a neuropsychiatric examination by means of checklists for cognitive symptoms: stepwise comparative status analysis (STEP) (Wallin et al., 1996), cognitive variables 13-20 (memory disturbance; disorientation; reduced abstract thinking; visuospatial disturbance; poverty of language; sensory aphasia; visual agnosia; apraxia) for basic dementia related cognitive symptoms; I-Flex, which is a short form of the Executive interview (EXIT) (Royall, Mahurin, & Gray, 1992) (items: number-letter task; word fluency; anomalous sentence repetition; interference task; Luria hand sequences; counting task) for frontal lobe symptoms; and mini-mental

state examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and clinical dementia rating (CDR) (Morris, 1997) as global measures of functioning. The information for CDR was gathered from both the subject and an informant. For the diagnosis of MCI, subjective and objective (verified by an informant) anamnestic evidence for progressive cognitive impairment for more than 6 months was required. A positive outcome on STEP, EXIT, MMSE or CDR was also required. Subjects without a positive outcome on the cognitive checklist were not included, since their cognitive impairment was considered merely subjective, neither were subjects with more than 2 positive outcomes on STEP or a score below 25 on MMSE – or both – as they were considered to fulfil criteria for dementia. Subjects with major depressive and other severe psychiatric disorders, and substance abuse were excluded. Minor depressive symptoms and mild anxiety were allowed.

The healthy controls were mainly recruited from senior citizen organisations and via information meetings on dementia. A few controls were spouses of subjects in the study.
Inclusion criteria for controls were that they should be physically and mentally healthy and not experience or exhibit any cognitive impairment or vascular disease. All controls were thoroughly interviewed about their somatic and mental health by a research nurse before being screened for the study. Before they were included, they underwent a thorough physical, neurological and neuropsychological examination as well as an MRI scan, in order to exclude cognitive impairment and cerebrovascular disease.

MCI with vascular disease

MCI subjects with vascular disease were identified as follows: occurrence of (i) symptoms of MCI, 2 (or more) expressions of vascular disease (arterial hypertension, cardiac insufficiency, angina pectoris, cardiac rhythm disturbance, cardiac infarction, TIA, stroke, hyperlipidemia, diabetes mellitus or peripheral vessel disease) *and* findings on MRI due to vascular disease: moderate white matter changes according to a 4 grade scale (Scheltens et al., 1998) *and/or* several lacunes (more than two) *and/or* signs of infarctions on MRI (ii) symptoms of MCI, TIA *and/or* stroke and moderate white matter changes/lacune formations, *and/or* signs of infarction on MRI.

Cerebrospinal fluid analysis

CSF samples were collected in polypropylene tubes, and were stored at –80º C pending biochemical analyses, without being thawed and re-frozen. CSF samples were taken at baseline in all MCI cases and controls. CSF T-tau was determined using a sandwich enzyme-linked immunosorbent assay (ELISA) constructed to measure total tau (Blennow et al., 1995). CSF Aß42 was determined using an ELISA constructed to measure Aß42 (Andreasen et al., 1999). For cut-off values, the CSF concentrations of the control group were used. The T-tau of the control group was 291 ± 102 pg/ml which was significantly lower than in the MCI group, 416 ± 328 pg/ml ($p<0.001$). The CSF Aß42 of the control group was 750 ± 224 pg/ml, which was significantly higher than in the MCI group, 622 ± 197 pg/ml ($p=0.001$). Using the 0.90 fractile of the control group values as a cut off, (Chemistry, 1987), the cut-off for T-tau was 405 pg/ml and for Aß42 465 pg/ml.

Statistical analyses

Several variables were found to be skewed and were rescaled as appropriate to approximate normality before being entered in the statistical calculations. The data are presented as means ± standard deviation of the raw data. In study I group comparisons were made with the t test and the Mann–Whitney U test (SPSS). Corrections for
multiple comparisons were made by the Bonferroni Holm method. In study II group comparisons were made with analysis of variance (ANOVA) and Pearson Chi-Square (SPSS). Multiple comparisons were adjusted for with Bonferroni correction.
Due to differences in age and education between the MCI groups in study III, those variables were entered as covariates in the statistical analyses of neuropsychological data, and group comparisons were made with ANCOVA (SPSS). Multiple comparisons were adjusted for with Sidak correction. In study I, II and III a principal components analysis (PCA; SIMCA-P 10.0) was performed on the data from the test battery, i.e including all test variables (Eriksson, Johansson, Kettaneh-Wold, Wikström, & Wold, 2002). Significance of the models was determined by cross validation. Each PCA resulted in one significant latent variable that summarized the constituent neuropsychological test variables. In study I, II and III we report Eta-squared (η^2) as an index of effect size in the parametric statistical tests, which can vary between 0 and 1. In study IV Partial Least Squares Discriminant Analysis (PLS-DA) was used to analyze the data (Eriksson, Johansson,

Kettaneh-Wold, & Wold, 2001), employing SIMCA-P 10.0 software (Umetrics AB, Umeå, Sweden). The PLS-DA, which can be regarded as a form of logistic regression, was used to separate subjects with or without dementia on the basis of their cognitive functioning in the multiple neuropsychological tests. The technique creates of a set of principal components, whose significance is determined by cross-validation, and which summarize the original cognitive variables on the basis of their covariances. The components are rotated in such a way as to separate the specified groups as much as possible. We present the parameter *variable influence on projection (VIP)* which succinctly summarizes the important independent variables. Predictors with a VIP ≥ 1 are very influential for the model as a whole (Eriksson et al., 2001).

Table 1 Overview of the data collection and subjects in the studies

Study	Period of data Collection	Number of Controls	Number of MCI	Group comparisons
I	Jan 2000-Oct 2002	35	112	Controls – MCI
II	June 2000-Dec 2003	60	120	Controls - MCI without vascular disease - MCI with vascular disease
III	May 2000-Dec 2005	50	146	Controls - MCI with AD biomarkers - MCI with normal biomarkers
IV	Mar 2000-Apr 2007	0	175	Stationary MCI - MCI converted to dementia

Table 2 Overview of demographic data in the studies

Study	Gender Male/female	Age	Education	MMSE	Main statistical Method
I	49/63	64 ± 8	11.6 ± 3.5	28.5 ± 1.5	Student's t-test
II	50/60	66 ± 7	11.5 ± 3.6	28.3 ± 1.5	ANOVA
III	66/80	63 ± 7	12.0 ± 3.2	28.5 ± 1.3	ANCOVA
IV	73/102	64 ± 8	12.0 ± 3.5	28.4 ± 1.5	Likelihood ratios, Sensitivities and specificities

Neuropsychological assessment

The cognitive profiles of MCI are defined by cognitive test scores – neuropsychology – which makes neuropsychology the central theme of this thesis. There is an overwhelming body of evidence that neuropsychological assessment is the most important tool for identifying neurocognitive disorders at their earliest manifestations (Marcos et al., 2006; Nelson & O'Connor, 2008; Tabert et al., 2006; Twamley et al., 2006). Although there is no real agreement on which specific tests should be used for different patient groups, the American Academy of Neurology (AAN), has published guidelines for what a neuropsychological assessment should comprise. According to AAN an assessment should cover the cognitive domains *speed and attention*, *learning and episodic memory*, *visuospatial functions*, *language and executive functions* and *intelligence/general cognitive capacity*. Within each cognitive domain several aspects of function should be assessed, in order to obtain as complete a picture as possible of the cognitive status of a subject. As described below, and presented in table 3, the neuropsychological battery used for this thesis is well in agreement with those guidelines.

Intelligence should not be considered a cognitive domain in the same sense of the concept as the other domains. According to AAN it is, however, important to obtain a measure of intelligence, or rather general cognitive capacity, as an initiating point for the neuropsychological examination. It is essential to have something to contrast the results against: is the present result what can be expected from this patient or is there reason to suspect that the result indicates impaired function for the patient, considering his or her general capacity? The most widespread measure of intelligence is Wechsler's Adult Intelligence Scale (WAIS) (Wechsler, 1981), which a few years ago was published in yet another revised edition, WAIS-III, in a number of languages, among them Swedish. WAIS is, however, quite extensive and thus time consuming to administer. Furthermore, WAIS may for subjects with MCI be misleading as a measure of general cognitive capacity, since performance on a number subtests will be influenced by impairment within any cognitive domain. Hence, simpler measures of general cognitive capacity have been developed for patients with cognitive impairment, so called resistant, or "hold", tests. One of the most frequently used nonverbal brief tests of intelligence, Raven's progressive matrices (Raven, 1965), was used. It exists in three versions and the shortest and easiest version, coloured matrices, which is intended for children, elderly

persons and persons with cognitive decline, was used in the studies in this thesis. Below, the other tests in the neuropsychological test battery are described.

Speed and attention

A definition of speed and attention would be the cognitive function by which a person concentrates on and processes some features of the environment to the relative exclusion of others. Basic psychomotor and processing speed, and being able to steer one's attention are most basic cognitive functions; much of all other cognitive functioning presupposes that we are able to process information and focus our attention as needed. If you are unable to focus your attention to the task at hand, you will fail the task, regardless of what the nature of the task is. Digit Span from WAIS (Wechsler, 1981) is a measure of attention span and working memory. In Digit Span the patient is to repeat series of digits, the span of which increases. First the digits are repeated forward and then backward. Digit Symbol is another of the WAIS subtest, which is quick and easy to administer – for 90 or 120 seconds (depending on which version is used) the patient is to enter symbols in boxes on a sheet of paper according to a symbol key – and provides a measure of focused attention and speed. The 2 other tests in this domain are Trailmaking A and B (Reitan, 1985). In the A version the patient is to draw lines between circles containing numbers 1 through 25 on a sheet of paper, as quickly as possible. Thus, the test provides a measure of survey ability and speed. In the B version the task has been made more complex: the patient is now given a sheet of paper with both numbers and letters. The patient is to alternate between numbers and letters; to draw a line from 1 to A, to 2 to B and so forth. Part B provides a measure of more complex, alternating, attention functions.

Memory and learning

Human memory consists of multiple, interacting, systems. In the 1970s, the grand old man of memory research, Endel Tulving, presented his model for memory, with the distinction between semantic and episodic memory (Tulving, 1987). These memory systems constitute the broader category of declarative memory: memory of factual information. Tulving described semantic memory as knowledge of grammar, vocabulary, and concepts. Semantic memory allows us to understand ideas, solve problems, and comprehend language. Episodic memory is the memory of events or

episodes that one has experienced personally, at a particular time and place. Later, procedural memory was added to the model. Procedural memory is the unconscious memory responsible for our ability to perform tasks, for example swimming or riding a bike, which are forms of procedural knowledge. Procedural memory differs from declarative memory in that declarative memory is a conscious memory of facts, while procedural memory is unconscious and responsible for skills and habits that become automatic.

The memory system that first and foremost is impaired in neurocognitive disorders – with the exception of some very rare conditions – is episodic memory. Semantic memory is often impaired in early AD, but not as markedly as episodic memory in the mild stages (Balthazar, Martinelli, Cendes, & Damasceno, 2007). There is a wide variety of episodic memory tests available, most of them verbal. One of the most frequently used tests in the world is Rey Auditory Verbal Learning Test (RAVLT) (Geffen, Butterworth, & Geffen, 1994). RAVLT consists of 15 high imagery nouns that are read to the patient five times. After each reading the patient is to repeat as many words as possible. Next, another 15 word distraction list is read to the patient, after which he/she is asked to repeat the first list once more. After another 30 minutes of distraction the patient is asked to try to recall the first word list once more. Lastly, the patient is asked to identify the words he/she is unable to recall from a recognition list. Thus, the test provides information about learning capacity – whether the patient is able to increase the number of words recalled as the word list is repeated – as well as recall and recognition. Another very widely used verbal memory test is Wechsler's Logical Memory (WLM) (Wechsler, 1987). Two short stories are read, which the patient is to repeat immediately and after 30 minutes of distraction. WLM is more about being able to recall and retell an event than learning capacity.

Rey Complex Figure (RCF) recall is a non-verbal memory test (Meyers, 1995). In RCF the patient is to copy a complex geometric figure, not knowing that he/she is performing a memory task. After a few minutes of distraction the patient is asked to draw the figure from memory. The memory task is repeated after yet 30 minutes of distraction. One disadvantage of RCF is that patients who have visuospatial deficits often have difficulty processing the figure in its entirety, which leads to memory performance not equivalent to their actual memory capacity. Face

recognition consists of 15 pictures of faces that the subject is to identify from 30 immediately after having seen the target faces.

Visuospatial functions

Visuospatial functions refer to thought processes involving visual and spatial awareness, which include comprehending and conceptualising visual representations and spatial relationships when performing a task. The most basic visuospatial function is spatial perception: to be able to distinguish an object from its background. A test battery, Visual Object and Space Perception (VOSP), has been developed for the purpose of measuring that very function (Binetti et al., 1998). In the Silhouettes subtest from the VOSP battery the patient is to identify 30 silhouettes representing animals and everyday objects. RCF copying measures spatial orientation; to perceive how the parts constitute the whole shape of what you see, and to interpret the parts based on how they contribute to the whole (Meyers, 1995). The third test in this domain is Block Design from WAIS (Wechsler, 1981), which is considered a measure of spatial construction. Block Design, however, is also sensitive to speed/attention and executive deficits and thus not as specifically visuospatial as the previously mentioned tests (Nordlund et al., 2007).

Language

The definition linguists use for language is symbolic representation; that a symbol – whether it is visual, auditory, or tactile – represents something other than itself, according to set rules. According to this definition language is uniquely human, and probably the most complex system that exists. Considering the complexity of language, several aspects need to be assessed: Token Test, part V, is a test of language comprehension. It consists of 22 commands that the patient is to follow using circles and squares in five different colours (Bandera, Capitani, Della Sala, & Spinnler, 1985). Token Test is very easy to use normatively, since a healthy adult is expected to manage all 22 commands. Assessment of Subtle Language Disorders (ASLD) Repetition is a test constructed to assess higher order language (Crosson, 1996). It consists of 10 sentences of increasing length that the subject is asked to repeat verbatim (Lezak, 1995). The ASLD logical grammar sub test is a test of complex language comprehension. It consists of 10 sentences of increasing complexity, in which the subject is to follow an

instruction or answer a question (Crosson, 1996). Boston Naming Test (BNT) is a naming test, which consists of 60 drawings of different objects, from some very high frequency (bed, tree) to some quite low frequency (sphinx, abacus) (Kaplan, 1983). Similarities from WAIS (Wechsler, 1981) is used for measuring abstract aspects of language. The patient is asked to explain the similarity between, for example, a seed and an egg, and an enemy and a friend. Word fluency FAS (or Controlled Oral Word Association Test as it is also called) is used for assessment of executive aspects of language (Crossley, D'Arcy, & Rawson, 1997). In FAS the patient is to try to produce as many words as possible beginning with F, A and S in one minute for each letter.

Executive functions

In short, executive function is goal directed behaviour; optimizing one's performance in order to reach a certain goal. This performance has by Lezak (2004) been described as having four components: (1) volition (2) planning (3) purposive action, and (4) effective performance. Thus, executive function is not so much about *what* you do, but *that* and *how* you do it. Dual task is a test of divided attention in which the subject is asked to draw crosses in boxes on a sheet of paper while simultaneously repeating series of digits (Della Sala, Baddeley, Papagno, & Spinnler, 1995). Wisconsin Card Sorting Test (WCST) is probably the best known and most frequently used executive test, also in dementia research (Paolo, Axelrod, Troster, Blackwell, & Koller, 1996). WCST consists of a number of cards with one to four symbols in different colours. The patient's task is to conclude the right principle for putting the cards in one of four piles. In Stroop Colour Word Test the patient is to name the colours a number of words are written with, and thus inhibit the automated response, which is to read the word. The short Victoria version, which is presented in Spreen & Strauss was used (Spreen & Strauss, 1998). Another test presented in Spreen & Strauss test that was constructed for assessing judgment – an essential aspect of executive function – is Cognitive Estimation Test. The test consists of ten questions about information that most people have a fair notion of, but probably do not know the exact answer to (how high is the Eiffel tower; how long is the spine of an average male). Thus, the patient is to make a reasonable estimate. A contribution of our clinic and the Institute of Neuroscience and Physiology at Sahlgrenska Academy to the battery is Parallel Serial Mental Operations (PaSMO), which is a measure of mental control. The patient is first asked to rattle off the alphabet as quickly as

possible. Next he or she is asked to rattle off the alphabet once more but this time also state the number of the letter, i.e. A-1, B-2, C-3 and so forth. Thus, it is a measure of mental control and tracking.

Table 3 Cognitive domain *Specific functions* and neuropsychological tests

Speed and attention	Digit Symbol (WAIS-R), Trail making A and B, *Attention span/working memory*: Digit Span (WAIS-R)
Learning and memory	*Verbal episodic memory*: RAVLT, Wechsler's Logical Memory (WMS-R), *Non-verbal episodic memory*: Rey Complex Figure
Visuospatial functions	*Perception*: Silhouettes (VOSP), *Spatial organisation*: Rey Complex Figure copy, *Construction*: Block Design (WAIS-R)
Language	*Comprehension*: Token Test, subtest V, *Comprehension and repetition*: ASLD repetition, *Confrontation naming*: Boston Naming Test, *Abstraction*: Similarities (WAIS-R) *Word Fluency*: FAS
Executive functions	*Divided attention*: Dual Task, *Planning and inference*: WCST-CV64, *Distractibility*: Stroop Test, Victoria version, *Judgement and calculation:* Cognitive Estimation Test, *Mental control*: PaSMO

WAIS-R=Wechsler's Adult Intelligence Scale-Revised, RAVLT=Rey Auditory Verbal Learning Test, WMS-R=Wechsler's Memory Scale-Revised, VOSP=Visual Object and Space Perception, ASLD=Assessment of Subtle Language Deficits, PaSMO=Parallel Serial Mental Operations, WCST-CV64=Wisconsin Card Sorting Test-Computer Version 64 (short version)

Results

Study I

The objective of the study was to find out which neuropsychological tests most clearly distinguish between MCI and healthy controls. The participants consisted of 35 healthy controls with a mean age of 68 ± 5 years and 112 consecutive MCI subjects with a mean age of 65 ± 8 years. The results showed that MCI is a heterogeneous condition, the MCI subjects were impaired in all cognitive domains, when compared to the controls. The original,"traditional" amnestic MCI with isolated memory impairment was very rare, only 2/112 subjects (1.7%) had such a cognitive profile. The cognitive domains in which most MCI subjects had significantly impaired results were language and executive function, episodic memory being the third domain. About one out of six (17%) subjects did not show any impaired results, as compared to their age norms. These subjects were younger, better educated and performed better on test of general cognitive capacity than the other subjects.

Study II

The objective of the study was to find out whether the cognitive profile of MCI subjects with vascular disease differ from that of MCI subjects with no vascular disease. The participants consisted of 60 healthy controls, mean age 66 ± 5 years, and 120 age matched MCI subjects: 60 without vascular disease (MCI-nov), mean age 66 ± 7 years, and 60 with vascular disease (MCI-vas), mean age 67 ± 7 years.
The healthy controls performed better than the 2 MCI groups on the cognitive test battery. Cognitively, controls, MCI-nov and MCI-vas constituted three distinct groups, both in terms of overall performance, according to the Principal Components Analysis (PCA) and cognitive profiles. The most clear-cut differences between MCI-nov and MCI-vas were seen on tests of speed/attention and executive functions, as illustrated in table Study II, in which the significant test results and the memory tests are presented.

Study II Means and significance levels for the test battery

	Controls	MCI-nov	MCI-vas	η^2	Controls vs MCI-nov adjusted p value	MCI-nov vs MCI-vas adjusted p value
Speed and attention						
Trail Making B (sec)	85.9 ± 25.9	107.4 ± 52.4	130.5±60.5	0.14	0.019	0.027
Digit Span backward	4.8 ± 1.1	4.8 ± 1.2	4.2 ± 1.2	0.05	ns	0.047
Memory and learning						
RAVLT learning	45.0 ± 7.5	39.9 ± 11.2	36.1 ± 11.7	0.12	0.023	ns
RAVLT delayed	9.0 ± 3.1	6.8 ± 3.8	6.1 ± 4.1	0.11	0.004	ns
Visuospatial functions						
Block Design	28.4 ± 8.2	27.9 ± 9.1	23.0 ± 8.2	0.06	ns	0.005
Language						
Token Test	21.0 ± 1.2	19.4 ± 2.7	17.8 ± 3.7	0.19	<0.001	0.040
ASLD Logical gram	23.3 ± 3.5	22.2 ± 3.4	20.0 ± 4.4	0.12	ns	0.045
Executive functions						
PaSMO (seconds)	67.2 ± 24.4	80.1 ± 33.0	98.8 ± 44.3	0.16	0.050	0.008
Weighted average (PCA)	1.97 ± 2.18	-0.36 ± 3.49	-1.98 ±3.56	0.21	<0.001	0.016

p value=ANOVA, Adjusted p value=adjustment for multiple comparisons (Bonferroni), RAVLT=Rey Auditory Verbal Learning Test, ASLD=Assessment of Subtle Language Deficits, PaSMO=Parallel Serial Mental Operations,

There were also significant differences concerning MCI subtype between the groups. A larger proportion of MCI-vas belonged to the multiple domains non-amnestic group and a larger proportion of MCI-nov showed no significant impairment as compared to their age norm.

Study III

The objective of the study was to compare the neuropsychological profiles of MCI subjects with normal concentrations of total tau and Aß42 in cerebrospinal fluid (CSF) to MCI subjects with a deviating, AD-typical pattern, i.e. increased and decreased concentrations of the biomarkers. The participants consisted of 50 healthy controls, mean age 65 ± 6 years, 73 MCI subjects with normal concentrations of T-tau and Aß42 (MCI-norm), mean age 61 ± 7 years and 73 MCI subjects with deviating concentrations of the biomarkers (MCI-dev), mean age 65 ± 7 years. Controls performed overall significantly better on the neuropsychological battery than the MCI groups. As to overall performance, MCI-norm and MCI-dev also differed significantly according to the PCA. The most clear-cut differences were seen on tests of speed/attention and episodic memory, as seen in table study III. When the MCI-dev subjects were grouped according to type of deviation in CSF into only high T-tau (N=35), only low Aß42 (N=15) and both high T-tau and low Aß42 (N=23), the group with both high T-tau and low Aß42 had a tendency to perform slightly worse, whereas the other 2 groups performed quite similarly.

Study III Means and significance levels for neuropsychology

Neuropsychological data	Controls	MCI-norm	MCI-dev	Eta2	Controls vs MCI-norm adjusted p	Controls vs MCI-dev adjusted p	MCI-norm vs MCI-dev adjusted p
Weighted average	1.56	0.88	-2.13	0.22	0.006	<0.001	<0.001
Speed and attention							
Digit Symbol	47.5 ± 9.8	46.5 ± 11.0	39.2 ± 10.9	0.11	0.204	<0.001*	0.012*
Trail Making A	35.6 ± 11.3	38.4 ± 13.3	46.4 ± 17.7	0.12	0.016*	<0.001*	0.054
Trail Making B	81.8 ± 27.5	87.8 ± 34..9	114.5±48.6	0.12	0.102	<0.001*	0.012*
Memory and learning							
RAVLT learning	44.5 ± 7.9	45.8 ± 8.6	37.2 ± 11.5	0.12	0.995	<0.001*	<0.001*
RAVLT delayed recall	8.8 ± 3.0	8.7 ± 2.9	6.2 ± 4.0	0.10	0.858	<0.001*	0.001*
WLM delayed recall	21.1 ± 6.0	21.1 ± 7.0	16.2 ± 10.3	0.04	0.978	0.090	0.173
RCF delayed recall	16.6 ± 6.0	16.5 ± 7.5	10.3 ± 7.1	0.14	0.488	<0.001*	<0.001*
RAVLT recognition	14.7 ± 0.5	14.6 ± 0.8	13.9 ± 1.8	0.08	0.851	0.001*	0.007*
Language							
Token Test	21.1 ± 1.2	20.1 ± 1.7	18.8 ± 2.9	0.16	0.001*	<0.001*	0.060
Boston Naming Test	55.3 ± 2.9	53.5 ± 5.2	50.2 ± 6.9	0.14	0.007*	<0.001*	0.050*

MCI-norm=MCI with normal concentrations of CSF T-tau and Aß42, MCI-dev= MCI with deviating concentrations of CSF T-tau and/or Aß42, *=mean difference is significant on 0.05 level, RAVLT=Rey Auditory Verbal Learning Test, WLM=Wechler's Logical Memory, RCF=Rey Complex Figure

When all 146 MCI subjects were subclassified into the 4 MCI subtypes, the majority of the 2 multidomain MCI groups, 59%, had high T-tau and/or low Aß42 concentrations, whereas only 33% of the amnestic and 28% of the single domain non-memory groups had deviating concentrations.

Study IV

Two years after baseline assessment, 34 subjects out of 209 were lost to follow up. Thus 175 subjects (84%) underwent follow-up examinations. The subjects lost to follow up did not differ on demographic variables from the others. Out of the 175 MCI subjects, 44 (25%) were diagnosed with dementia at follow-up, and 8 (4,5%) returned to normal function. The subjects who converted to dementia were significantly older, had shorter educations and scored lower on MMSE than the stable MCI group and those who returned to normal function.

Aetiology and MCI subgroups

The MCI subjects were classified into different aetiologies: vascular (N=56), neurodegenerative, based on Alzheimer-typical biomarkers (N=58), and no known aetiology (N=61). Out of the 44 dementias, 21 were AD, 12 MD, 8 VaD, 2 non ultra descriptum (NUD) and one primary progressive aphasia (PPA), as seen in table study IV. The distribution of dementias and aetiologies in the different MCI subtypes are also presented.

Study IV Specific dementia diagnoses and distribution among MCI subtypes

MCI subtype	Vascular	Degenerative	AD	Mixed	VaD	NUD	PPA
aMCI (N=8)	1	3	0	0	0	0	0
maMCI (N=62)	27	29	18	7	6	2	1
mdMCI (N=30)	9	11	3	5	2	0	0
sMCI (N=47)	10	10	0	0	0	0	0
No impairment (N=28)	7	7	0	0	0	0	0

As seen in the table, only the multiple domain MCI subjects converted to dementia. The MCI subtype with the highest proportion of converters was maMCI (56%), followed by mdMCI (30%). When classified by aetiology, the MCI group with AD biomarkers had the highest proportion of converters, 38%, while vascular disease had 34%. The MCI subtype with the highest proportion of subjects returning to normal function after 2 years was purely amnestic MCI.

Likelihood ratios, sensitivities and specificities

In order to find out which variables best predicted conversion to dementia, we calculated Likelihood Ratios (LR), sensitivities and specificities. The Likelihood Ratio (LR) is the likelihood that a patient with dementia – AD or MD/VaD – belongs to the specific MCI group, compared to the likelihood that the patient would belong to any of the other groups. Sensitivity and specificity are measures of accuracy. Sensitivity is the proportion of dementia patients who belong to the specific MCI group; specificity is the proportion of subjects without dementia who belong to another group. The highest LRs, sensitivities and specificities, for dementia in general, AD and MD/VaD were as follows:

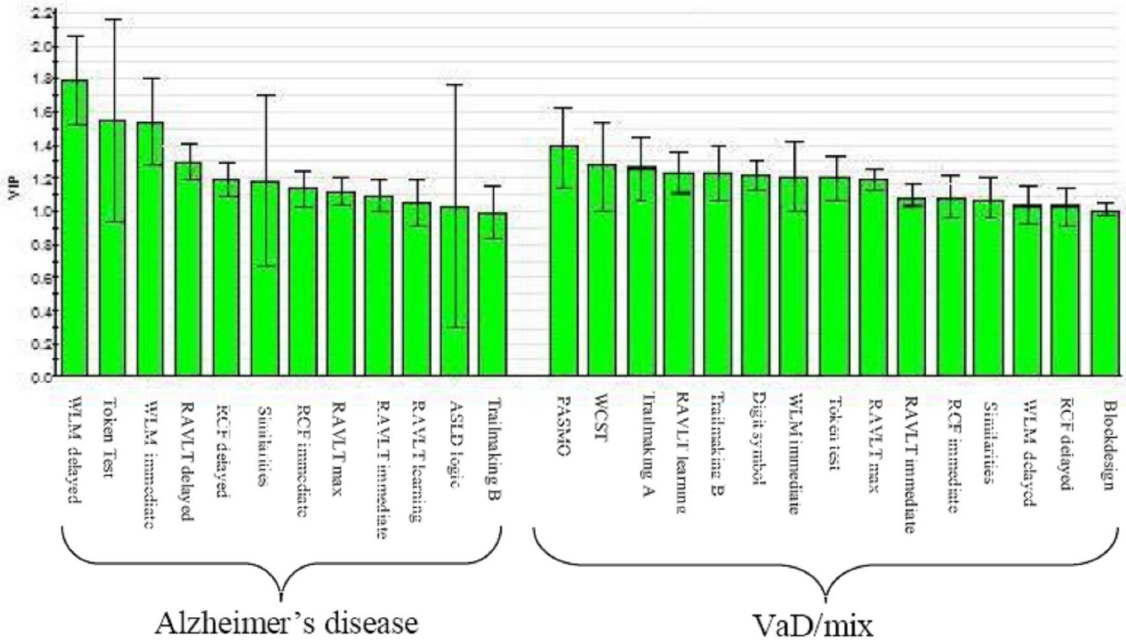
- Dementia: maMCI: LR=49.6 ($p<0.001$), sensitivity 80%, specificity 79%
- AD: maMCI: LR=26.0 ($p<0.001$), sensitivity 86%, specificity 71%
- AD: maMCI/biomarkers: LR=30.0 ($p<0.001$), sensitivity 62%, specificity 92%
- MD/VaD: vascular MCI: LR=22.4 ($p<0.001$), sensitivity 80% specificity 74%
- MD/VaD: vas MCI/maMCI: LR=30.6 ($p<0.001$), sensitivity 65%, specificity 91%

Thus, the highest LRs for both AD and MD/VaD were obtained by combining MCI subtype and aetiology.

Neuropsychological variables

We used a very basic evaluation method for the neuropsychological test battery: we reviewed the impaired results (<1.5 sd below mean of age appropriate controls) of the subjects who converted to dementia. Out of the 21 AD patients, 18 had memory impairment at baseline. The 2 other cognitive domains with frequently impaired results were the visuospatial and language. Fourteen AD patients had both visuospatial and language impairment at baseline, 3 had only visuospatial impairment, and another 3 only language impairment. For MD/VaD the executive and visuospatial were the domains with the highest proportion of impaired results, 14 out of 20 subjects had impaired results in both, followed by speed/attention, 13 subjects with impaired results.

In order to identify the neuropsychological tests that were the strongest predictors of dementia in general and the specific dementia disorders (AD and Mixed/VaD), a Partial Least Squares Discriminant Analysis (PLS-DA) was performed on the data. According to the variable importance scores, no single test, or combination of tests, stood out for dementia in general, the most important variables being a number of memory and speed/attention variables (no figure shown). For AD, Wechsler's Logical Memory, both immediate and delayed recall, together with the language comprehension test Token Test stood out. For MD/VaD, the executive test PaSMO tended to stand out, followed by some other executive, speed/attention, and learning and immediate – not delayed – recall variables.



The figure shows that the strongest predictor of AD was the episodic memory test WLM delayed recall, followed by the language comprehension test Token Test. Also the memory variables RAVLT and RCF delayed recall contributed very significantly to the model.
For MD/VaD the executive tests PaSMO and WCST were the best predictors, followed by the speed/attention tests Trailmaking A and B, Digit Symbol and RAVLT learning. Also WLM immediate recall and Token Test contributed significantly to the model.

Discussion

The objective of the thesis was to investigate the cognitive profiles of different types of MCI and follow their course over time. The results of the studies show that MCI is a very heterogeneous condition with significant impairment in all cognitive domains. One of the central findings of all 4 studies was the importance of impairment other than memory in MCI. Memory impairment was not the most common kind of impairment, and only subjects who had additional impairment to memory, or other impairment than memory, converted to dementia. This finding contradicts the general views in the MCI literature, according to which memory impairment is the primary and most predictive symptom of MCI preceding dementia (DeCarli et al., 2004; Modrego, 2006; Petersen, 2000; Schmidtke & Hermeneit, 2008). Findings similar to ours have, however, lately been

reported (Alexopoulos et al., 2006; Herukka et al., 2007). The purely amnestic MCI (aMCI) has been quite rare throughout the studies and has also proved to have rather a benign prognosis, indeed more so than other single domain MCI types. Slightly less than half the MCI subjects in the studies exhibited significant episodic memory impairment, which also contradicts the notion of MCI typically being characterized by memory impairment. In fact 9% of the subjects without memory impairment converted to dementia – 3% to AD – over 2 years, which further demonstrates the importance of impairment other than memory in MCI.

Cognitive profiles of different types of MCI

One aim was to be able to differentiate between "benign" and "malign" forms of MCI, and identify different dementia disorders in their prodromal stages by means of cognitive profiles and aetiologies. Are the cognitive profiles of vascular and degenerative MCI essentially different? The differences between MCI with vascular disease (MCI-vas) and MCI with deviating biomarkers (MCI-dev) were in fact not impressive. When a direct comparison between the groups was made with a t-test (not presented in the results), only 2 tests came out significant: Digit Symbol and Block Design – MCI-dev performed better on both. Nevertheless, patterns of cognitive deficits can be perceived. MCI-vas tended consistently to perform more poorly on speed/attention and executive tests, even though the differences were not significant. More explicit differences were seen when the subjects who converted to dementia within 2 years were compared. Alzheimer's disease (AD) and mixed dementia/vascular dementia (MD/VaD) patients had quite different cognitive profiles at baseline. In study IV the combination of memory, visuospatial and language impairment preceded AD, while speed/attention, visuospatial and executive impairment preceded MD/VaD. The memory performance of AD and MD/VaD also differed according to the PLS-DA. AD performed worse on delayed recall, while MD/VaD performed worse on learning and immediate recall. The same pattern was seen between MCI-vas and MCI-nov, and was in study II explained by poor learning strategies, which are executive deficits rather than episodic memory deficits as such. Taking into account that the vascular group consisted of a majority of mixed dementias –presumably with AD pathology –, the differences appear quite obvious.

“Benign” MCI

As to more “benign” forms of MCI, a reasonable assumption would be that single domain subjects will have a more benign prognosis, since only multiple domain MCI subjects converted to dementia. A large proportion of the single domain MCI subjects, however, had either AD biomarkers or vascular disease, which suggests that they have pathological changes or processes in the brain. One conceivable explanation is that many subjects with impairment in only one domain are in earlier stages of dementia disorders, and will eventually convert to dementia. That may also apply for the subjects who did not show significant cognitive impairment compared to their age norm. Twenty-five percent of them had AD biomarkers and 25% significant vascular disease, indicating pathological changes or processes in the brain. Considering that only 2 MCI subjects without any known aetiology – vascular or degenerative according to biomarkers –converted to dementia, the best suggestion for identifying benign MCI would be single domain (memory or non-memory) MCI without any known aetiology. The MCI-norm (normal biomarkers) group that was compared to MCI-dev (Alzheimer-typical biomarkers) in study III consisted of subjects without any known aetiology and performed within all cognitive domains more like the healthy controls than like MCI-dev. Thus, a large proportion of those subjects, in all likelihood, have benign forms of MCI, caused by stress or other non-degenerative ill-health.

MCI and vascular disease

There are some reports indicating that vascular risk factors and vascular disease increase the risk both of AD and dementia in general, although there still is some discussion in the literature on the subject (Ravaglia et al., 2006; Sepe-Monti et al., 2007). The results presented in study II certainly support the notion that vascular disease affects cognition harmfully. MCI with vascular disease (MCI-vas) performed markedly worse than MCI without vascular disease, and even though the differences were small, MCI-vas rather consistently performed worst of all the groups on the test battery – only on WLM delayed recall did MCI with AD biomarkers (MCI-dev) perform slightly worse. The proportion of MCI-vas that converted to dementia was almost identical to the proportion of MCI-dev converters. Considering that the biomarkers are established dementia markers, the role of vascular disease as a risk factor for dementia seems obvious – even

considering that we have no information about possible biomarkers in the MCI-vas group.

MCI and AD biomarkers

Previous studies have found the AD biomarkers T-tau and Aß42 to be specifically linked to different cognitive functions. Elevated T-tau concentrations have primarily been associated with poor performance on episodic memory tests, whereas decreased Aß42 concentrations have been associated with poor general cognitive performance (Ivanoiu & Sindic, 2005; Schoonenboom et al., 2005). This pattern was not found in the MCI subjects in studies III and IV. In study III the memory test scores of the subjects with high T-tau (MCI-tau) and low Aß42 (MCI-Aß) were almost identical. They also performed almost identically within the other cognitive domains. In study III both biomarkers were associated with generally poorer cognitive performance when compared to MCI subjects with normal biomarker concentrations. The only pattern that could be detected was that when both biomarkers were present, the subjects tended to perform slightly worse. It would seem that not one or the other of the biomarkers, but the biomarkers combined, are associated with markedly poorer memory and general cognitive performance. These results were confirmed by subclassification into MCI subgroups: 12 subjects with only high T-tau belonged to the amnestic groups and 15 to the non-amnestic. Thus, there was no association between biomarkers and specific kind of cognitive impairment or MCI subgroup. The combination of AD biomarkers and memory impairment with additional cognitive impairment, however, seemed to be the best predictor of AD: the combination of maMCI and biomarkers had the highest likelihood ratio for AD.

Young dementia patients

A recurring theme in all 4 studies has been that the subjects in the studies have been younger than in most comparable studies (Alexopoulos et al., 2006; Amieva et al., 2004; Arnaiz et al., 2004; Grundman et al., 2004; Lautenschlager, Riemenschneider, Drzezga, & Kurz, 2001; Loewenstein et al., 2006; Luis et al., 2004; Sepe-Monti et al., 2007; Storandt, Grant, Miller, & Morris, 2002). That also is true for the subjects converting to dementia; the mean age of the dementia patients was lower than in most studies (Amieva et al., 2004; Geslani, Tierney, Herrmann, & Szalai, 2005; Herukka et al., 2007). Nevertheless, the distribution of dementia diagnoses in study

IV was quite similar to the majority of prevalence figures (Aggarwal & Decarli, 2007; Ferri et al., 2005). Almost 50% were AD, 27% MD and 18% VaD. These proportions support the suggestion that MD is one of the most common forms of dementia (Langa et al., 2004; Nagga et al., 2004). The mean age of the AD patients was at the time of diagnosis below 65, which means that a large proportion of them were early onset AD. That is reflected in the cognitive profiles of the AD patients, which were the typical "early onset profiles" described in the literature, with predominantly "temporoparietal symptoms", that is visuospatial and language deficits (Blennow & Wallin, 1992; Reid et al., 1996). The cognitive profile of MD/VaD was also rather typical for subcortical VaD: poor performance in the speed/attention and executive domains (Roman et al., 2002; Roman & Royall, 1999). The fact that MD patients according to the literature cognitively resemble AD more than VaD (Schmidtke & Hull, 2002) raises the question about how great the impact of vascular disease early in the course of the disease is. The finding that MD and VaD seemingly had a reasonably uniform cognitive profile supports the notion of including MD in the VaD diagnosis (Nagata et al., 2007). Considering that the patients in study IV were quite clearly younger than in most other studies, the question is whether the dementia diagnosis today is given earlier than before. Since the decisive criterion for dementia is that the cognitive impairment should be of such a magnitude that the patient no longer is able to manage his or her everyday life without support, the hypothesis can not be ruled out. There is much evidence that we today live in a society more cognitively demanding than ever before, as stated above. Consequently, the demands on a patient with cognitive decline would increase, the cognitive deficits would be apparent earlier than before and the patient would lose independence at an earlier stage, resulting in a dementia diagnosis.

Importance of the findings/conclusions

Considering the fast increasing number of patients suffering from dementia, the rising costs, and new emerging therapies, the need for early and exact diagnostic methods is obvious. One of the problems many memory clinics face is the increasing number of patients with cognitive impairment caused by conditions other than prodromal dementia – stress, depression and other ill-health. These patients often fear that they have early signs of a dementia disorder and sometimes live with that fear for years. Much suffering could be avoided with more exact diagnostic methods. Both in the interest of the society in large and the individual patient, this task is urgent. I believe that a

comprehensive neuropsychological examination is an indispensable part of more exact diagnostic methods. The MCI subtypes are to some degree useful but need to be refined, with information about the specific cognitive domains that are impaired. Multiple domains amnestic MCI obtained the highest Likelihood ratio for dementia in general – unspecific cognitive impairment predicting unspecific dementia. I believe that cognitive profiles – information about which cognitive domains are impaired – is an important step toward a more exact early diagnosis of dementia. I find the high Likelihood Ratios and reasonable sensitivities and specificities for AD and MD/VaD that were obtained by combining MCI subtype and aetiology encouraging. I believe that the prognostic accuracy of that combination can be much increased when a larger number of patients are followed over a longer period of time. Thus, in my view, a comprehensive neuropsychological assessment providing more exact and refined cognitive profiles will make a crucial contribution when diagnosing dementia disorders in their earliest manifestations.

Limitations

As stated in the introduction, the ambition of a cognitive psychologist is to generate models of cognitive processes in order to compare them to data from humans. There, in all likelihood, are many important cognitive functions and processes that we thus far do not have the adequate tests to measure. One obvious such function is prospective episodic memory – to remember to remember, or to remember what one has planned to do. My impression is that a substantial proportion of the patients at our memory clinic experience prospective memory problems, but we do not have a test to measure those problems with. That may be one reason why only hardly half the patients had significantly reduced results on the memory tests. I do consider the neuropsychological battery both comprehensive and well balanced, but certainly it also has its limitations. With a different combination of tests, the results may have had been different.

MCI and dementia diagnostics is not an exact science. Even though we have applied specific research criteria, there always is some degree of arbitrariness, both in the inclusion process and the specific dementia diagnoses. Considering the slightly inexact inclusion criteria, some subjects may have been included in the study with not much more than subjective cognitive complaints. Furthermore, the subgroupings – both in terms of aetiology and MCI subclassification – may be somewhat inexact. When

subgroupings and –classifications are made by means of cut-off scores, there always will be some degree of arbitrariness. Nevertheless, considering the results, all in all both inclusion, subgroupings and diagnoses seem to be as stringent as can be required.

Future directions

As suggested above, the next step will be to evolve the MCI concept by applying different cognitive profiles to it. How many different profiles will make clinical sense? One with mainly language and visuospatial deficits, and one with speed/attention and executive deficits? Can we identify additional patterns, for example a pattern typical for stress or depression; a benign, reversible MCI profile? I believe that there still is much to do in terms of exploring cognitive profiles for different conditions characterized by cognitive ill-health.

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