Cognitive Functioning in the Preclinical Stages of Alzheimer’s Disease and Vascular Dementia

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ABSTRACT

This doctoral thesis concerns cognitive functioning in the preclinical stages of Alzheimer's disease (AD) and vascular dementia (VaD). It is based on five empirical studies using data from the Kungsholmen Project, a longitudinal population-based study of aging and dementia targeting persons 75 years and older, living in the Kungsholmen District in Stockholm, Sweden.

Although the cognitive deficits in the preclinical phase of AD are well documented, some issues have been neglected. One omission is that investigations of preclinical episodic memory deficits have focused solely on retrospective memory (remembering something from the past) and ignored prospective memory (remembering to perform an action in the future). Therefore, Study I compared retrospective and prospective memory functioning in preclinical AD. Prospective memory was impaired three years before the AD diagnosis. More interestingly, the prospective memory impairment was independent of impairment of retrospective memory. This suggests that prospective and retrospective memory partly involve different cognitive operations. Study I also showed that different processes within a retrospective memory task (i.e., encoding, storage, and retrieval) were impaired prior to diagnosis. Hence, these data indicate that the episodic memory deficit in preclinical AD generalizes across several important dimensions of this form of memory.

In contrast to AD, investigations of the preclinical phase in VaD have been sparse. Studies II and III demonstrated three-year preclinical cognitive deficits on a global measure of cognitive functioning (the Mini-Mental Status Examination), and on three measures of episodic memory functioning (random recall, word recognition, and face recognition) in VaD. Persons in the preclinical stage of AD demonstrated deficits in verbal fluency and visuospatial skills in addition to impairment in global and episodic memory functioning. However, even though the impairments seemed more widespread in preclinical AD, there were no statistically reliable differences between the two preclinical dementia groups.

Although the cognitive deficits appear very similar in the preclinical phases of AD and VaD, Study IV demonstrated that verbal fluency could differentiate between the dementia disorders three years prior to diagnosis. Category and letter fluency have partly different neural underpinnings, although both draw on frontal lobe functioning. Whereas category fluency is more dependent on medial-temporal lobe regions, letter fluency is more dependent on frontal-lobe functioning. Category fluency was more impaired in preclinical AD as compared to VaD. This is consistent with histopathological and imaging data indicating that medial-temporal lobe regions are affected early in AD. Letter fluency was equally impaired in AD and VaD, which is consistent with findings of early pathology in the frontal circuitry in the prodromal phases of both diseases.

Study V investigated whether individual-difference variables could influence the rate of global cognitive decline during the transition from preclinical to clinical AD. The results from this study demonstrate that many variables which are known to affect cognitive functioning in normal aging (e.g., sex, education, depression, vitamin deficiencies, substance use) or are known to increase the risk of AD (e.g., age, apolipoprotein E ε4-allele, poor social network) exerted little influence on the rate of cognitive decline. Thus, even at a preclinical stage, the emerging dementia disease...
appears to make people more cognitively similar. An exception to this rule was that comorbid diseases acquired during the last three years prior to diagnosis exacerbated the rate of cognitive decline.

In conclusion, in preclinical AD most, if not all, aspects of episodic memory functioning seem to be affected. Preclinical cognitive deficits, particularly in episodic memory, can be observed also in VaD. Hence, the similarities in cognitive deficits observed in the clinical stages of these diseases, may be extended to a few years prior to diagnosis. However, despite the similarities, measures such as verbal fluency may be useful in differentiating between the diseases in their preclinical stages. And finally, although most individual-difference variables exert little influence on rate of cognitive decline in the preclinical phase of AD, concomitant diseases may aggravate this decline.
SAMMANFATTNING

Denna avhandling undersöker kognitivt funktioner i den prekliniska fasen av Alzheimer’s sjukdom (AD) och vaskulär demens (VaD). Den är baserad på fem empiriska studier med data från Kungsholmsprojektet, en longitudinell populationsbaserad undersökning kring äldrande och demens hos personer 75 år och äldre från Kungsholmen i Stockholm.

Trots att de kognitiva nedsättningarna i den prekliniska fasen av AD är väldokumenterade, har vissa aspekter försummats. En sådan aspekt är att undersökningarna av episodiskt minne har uteslutande fokuserat på retrospektivt minne (minne för något som redan har inträffat), medan prospektivt minne (minne för något som ska utföras i framtiden) har ignorerats. I Studie I jämfördes därför retrospektivt och prospektivt minne i den prekliniska fasen av AD. Prospecitivt minne var försämrat tre år innan AD diagnosen. Av större intresse var dock att prospektivt minne var försämrat oberoende av retrospektivt minne, vilket antyder att prospektivt och retrospektivt minne involverar delvis olika kognitiva processer. Studie I visade också på nedsättningar i olika processer inom den retrospektiva minnesuppgiften (inkodning, lagring och framlockning). Således tycks den episodiska minnesnedsättningen i den prekliniska fasen av AD vara synnerligen generell.

I motsats till AD så har undersökningar av den prekliniska fasen i VaD varit få. Studie II och III påvisade prekliniska kognitiva försämringar i VaD, på ett globalt kognitivt test och på tre olika episodiska minnestest (fri återgivning, ordigenkänning och ansiktsigenkänning) jämfört med en frisk kontrollgrupp. Utöver försämrade episodiska minnesprestation hade personer med preklinisk AD även nedsättningar i verbalt flöde samt visuospatiala funktioner. Trots att försämringarna verkar något mer spridda i preklinisk AD än i preklinisk VaD, så fanns inga statistiskt säkerställda skillnader mellan de båda demensgrupperna.

Även om de kognitiva nedsättningarna i de prekliniska faserna av AD och VaD är tämligen lika, visade Studie IV att verbalt flöde kunde differentiera mellan de två demenssjukdomarna tre år innan diagnos. Trots att både kategori- och bokstavsfloöde speglar frontal funktioner aktiverar de delvis olika neurala områden. Medan kategori-flöde är mer beroende av områden i mediala temporalloben, så är bokstavsfloöde mer beroende av frontala områden. Resultaten visade att kategoriflöde var mer försämrat i preklinisk AD jämfört med VaD. Dessa resultat är förenliga med histopatologiska fynd och resultat från hjärnavbildningsstudier som visar att områden i mediala temporalloben försärmras tidigt i AD. Bokstavsfloöde var lika försärmat i både AD och VaD, vilket är i linje med resultat som indikerar tidig patologi i frontalloberna i både VaD och AD.

Studie V undersökte huruvida individuella skillnader influerade takten på den kognitiva försämringen i övergången från preklinisk till klinisk AD. Resultaten visade att många variabler som påverkar det kognitiva fungerandet i normalt äldrande (t ex kön, utbildning, depression, vitaminbrist, användning av alkohol och tobak) eller är kända riskfaktorer för AD (t ex ålder, apolipoprotein E ε4-allele, torftigt socialt nätverk) inte påverkade takten av försämringen under de tre sista åren före diagnos. Det verkar således som att sjukdomsporten göra människor mer kognitivt lika. Det enda undantaget från denna regel var att nya sjukdomar som uppkommit några år innan diagnosen påskyndade takten av försämring.
Sammanfattningsvis, i den prekliniska fasen i AD verkar minnesförsämringen omfattar de flesta, om inte alla, aspekter av episodiskt minne. Prekliniska kognitiva försämringar, framför allt i episodiskt minne, finns även i VaD. Således kan likheterna i kognitiva nedsättningar som påvisats i tidig klinisk AD och VaD även påvisas några år innan diagnos. Trots dessa likheter kan test såsom verbalt flöde vara användbara i differentieringen av dessa sjukdomar i deras prekliniska faser. Slutligen, trots att de flesta individuella skillnader har liten effekt på takten av försämring i preklinisk AD, så kan nyligen uppkomna sjukdomar öka takten.
LIST OF ORIGINAL PAPERS

This thesis is based on the studies listed below, which will be referred to in the text by their Roman numerals:


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Introduction

Living many years past retirement is becoming more and more common in Western societies. Life expectancy is continuously increasing, as is the proportion of older people in the population (Kalache, 1996). One negative aspect of this trend is that extending life expectancy also may increase the number of persons with different age-related diseases. One of these disease categories is dementia, which increases dramatically in both prevalence and incidence with advancing age (Fratiglioni, Launer et al., 2000; Lobo et al., 2000).

Dementia of any type is a devastating disorder for the afflicted persons, relatives and carers of these persons, as well as for society as a whole. What might begin with some barely noticeable symptoms such as a slight memory problem will eventually lead to severe global cognitive impairment and complete dependence on other people. A main symptom seen throughout the disease process is a deterioration of cognitive functions. At the present moment there is no cure for dementia. At best, some pharmacological treatment can alleviate symptoms and slow down the rate of cognitive decline, but the disease is irreversible (Cummings, 2004). However, much effort is directed at developing more effective treatments. Conceivably, treatment efficacy is optimized if the intervention is initiated as early as possible in the disease process. Hence, an important goal is to find out more about dementia disorders in their earliest stages. In dementia, early harbingers of the disorder may be present long before any definite clinical symptoms can be established. This so-called preclinical stage of dementia constitutes the focus of the present thesis.

The two most common dementia disorders are Alzheimer’s disease (AD) and vascular dementia (VaD). They differ in etiologies, but show remarkably similar patterns of deficits in the early clinical stages, at least with regard to cognitive functioning (Almkvist, 1994; Almkvist, Bäckman, Basun, & Wahlund, 1993; Erkinjuntti, Laaksonen, Sulkava, Syrjäläinen, & Palo, 1986). An important difference between these dementia types is that VaD is possibly a preventable form of dementia (Hachinski, 1992), whereas no such indications exist for AD so far. Therefore, it is of interest to study cognitive functioning in the preclinical stages of these two dementia disorders. Such studies can provide etiological insights, determine early markers, and identify ways of differentiating between the disorders early on in disease development.

This thesis is organized into four main sections, as follows; The first introductory section provides a general orientation to the main issues addressed, and states the general aims of the thesis. It also includes brief descriptions of AD and VaD, as well as an overview of cognitive functioning in normal aging, clinical dementia, and preclinical dementia. The second section reviews the studies that form the empirical basis of the dissertation. This section includes a short description of the Kungsholmen project (KP), as all data for the empirical studies emanate from this population-based, longitudinal study of aging and dementia. The third section includes a general discussion of issues originating from the empirical findings, and in the final section some avenues for future research are discussed.
Introduction

**Aims**

Focusing on cognitive functioning in the preclinical phases of the two most common dementia disorders, AD and VaD, the overall aim of the thesis is to further our understanding of early cognitive deficits in dementia. Of special interest is to examine whether it is possible to differentiate between AD and VaD on the basis of cognitive performance at a preclinical stage. Two of the studies focus specifically on preclinical cognition in AD (Study I and V), the most common dementia disorder, whereas three studies investigate cognitive similarities and differences in the preclinical stages of AD and VaD (Studies II, III, and IV).

**Dementia disorders**

Dementia is a term covering several disorders affecting the brain. In the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 1994), dementia is defined as "the development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning" (p. 134). Aphasia refers to deterioration of language, apraxia denotes impaired ability to execute motor activities, and agnosia refers to failure in recognizing objects. Executive functioning involves the ability to plan and carry out complex behavior (Lezak, 1995). It is also stated in the diagnostic criteria that the deficits must be severe enough to cause impairment in occupational or social functioning, and must represent a decline from a previously higher level of functioning (American Psychiatric Association, 1994). Hence, a dementia diagnosis is based on symptoms rather than on the underlying cause of the disturbance, and is an umbrella concept encompassing a variety of different brain disorders. Differentiation between different types of dementia is, however, based on the etiologies of the disorders.

**Alzheimer’s disease (AD)**

AD is the most common type of dementia, accounting for about 50-70 percent of all prevalent cases (Fratiglioni, De Ronchi, & Agüero-Torres, 1999; Fratiglioni, Launer et al., 2000). It is an irreversible neurodegenerative disease characterized by the accumulation of plaques containing amyloid β-peptide (Aβ) and neurofibrillary tangles containing tau protein in brain tissue. Although the cause of AD is unresolved, there is increasing consensus that the production and accumulation of Aβ is the primary influence in the pathogenesis, and that the formation of neurofibrillary tangles is secondary and caused by an imbalance between production and clearance of Aβ (Hardy & Selkoe, 2002).

Although the amyloid hypothesis is the leading hypothesis for the pathogenesis in AD, a recent proposition is that AD is not a neurodegenerative but rather a vascular disorder (de la Torre, 2002, 2004). This notion is based on the assumption that neurodegeneration is caused by brain hypoperfusion, which in turn is caused by vascular risk factors. Findings that vascular risk factors precede dementia in most cases of AD, overlap in the pathologies of AD and VaD, and that vascular factors appear to aggrevate the pathogenesis support this hypothesis (de la Torre, 2002, 2004).
The onset of AD is insidious and progressive, and the first alterations are typically found in medial-temporal lobe structures (Braak et al., 1999; Braak & Braak, 1991; Fox, Warrington, Freeborough et al., 1996). However, changes in other brain structures and functions have been observed early in the pathogenesis, including volume reductions in the frontal cortex (van der Flier et al., 2002), white-matter hyperintensities (Wolf, Ecke, Bettin, Dietrich, & Gertz, 2000), decreased blood flow in the cingulate and parietal regions (Kogure et al., 2000), and reduced whole-brain glucose metabolism (Silverman et al., 2001). Indeed, eventually most parts of the brain are affected (Braak et al., 1999; Braak & Braak, 1991).

According to DSM-IV, three criteria need to be met for a clinical diagnosis of AD. These are dementia, insidious onset, and exclusion of all other possible causes of dementia. Neuroimaging with computed tomography (CT) or magnetic resonance imaging (MRI) is recommended in the diagnosis of AD, specifically to exclude alternative origins of dementia (Knopman et al., 2001). A definite diagnosis of AD cannot be made in vivo, but can only be rendered with access to autopsy data. However, for research practices other criteria, for example those devised by the National Institute of Neurological and Communicative Disorders and Stroke- the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984), are most often used. These criteria differentiate between probable and possible AD and are thus more specific than the DSM-IV criteria.

The etiology of AD is complex with both genetic and environmental factors influencing the pathogenesis. Old age, familial aggregation, apolipoprotein (APOE) ε-4 genotype, and Down’s syndrome are factors that are commonly agreed upon as risk factors for AD (Fratiglioni & Rocca, 2001). In addition, many possible risk factors for AD have been discussed in the literature. These include, but are not limited to, female gender (Fratiglioni et al., 1997; Gambassi et al., 1999), head trauma (Lye & Shores, 2000; Plassman et al., 2000), the use of alcohol and tobacco (Wang, Fratiglioni, Frisoni, Viitanen, & Winblad, 1999), a poor social network (Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000), personality (Balsis, Carpenter, & Storandt, 2005), proneness to stress (Wilson et al., 2003), and vascular factors, such as blood pressure (Qiu, 2003); stroke (Snowdon et al., 1997), and atrial fibrillation (Ott et al., 1997).

**Vascular dementia (VaD)**

VaD is the second most common type of dementia and accounts for about 20-30 percent of all prevalent cases (Fratiglioni et al., 1999). The concept of VaD has moved from being synonymous with multi-infarct dementia (MID) to encompassing a variety of disorders resulting from an interaction of cerebrovascular disease (CVD) and vascular risk factors that produce pathological changes in the brain. The changes include infarcts, white matter lesions and atrophy. The interest in VaD has increased in recent years much due to the fact that VaD might be a preventable form of dementia (Hachinski, 1992).

Although in the following VaD will be considered as one entity, it is important to note that VaD can be divided into several separate subtypes (Brun, 2000; Erkinjuntti, 1999; Rockwood, Bowler, Erkinjuntti, Hachinski, & Wallin, 1999). In contrast to AD, the pathological process can vary greatly across individuals. VaD can have an abrupt onset and stepwise progression or the onset can be insidious.
Pathologically, VaD can be divided into large-vessel dementia, small-vessel dementia, hypoxic-ischemic/hypoperfusive dementia, and haemorrhagic dementia (e.g., Brun, 2000). The concept of VaD is further complicated because it can coexist with AD. The term mixed dementia is used to denote this condition, which is characterized by a combination of clinical features of AD and VaD (Langa, Foster, & Larson, 2004; Rockwood et al., 1999).

According to DSM-IV, the clinical diagnosis of VaD is based on the following criteria: dementia, focal neurological signs and symptoms, and evidence of CVD, which are judged to be etiologically related to the disease. Focal neurological signs include extensor plantar response, pseudobulbar palsy, gait abnormalities, exaggeration of deep-tendon reflexes, and weakness of an extremity. Brain imaging techniques, such as CT or MRI, can be used to demonstrate multiple vascular lesions in the cerebral cortex and/or in subcortical structures, but this is not necessary for the diagnosis. The Hachinski Ischemic Score (HIS; Hachinski et al., 1975) can be used to aid the diagnosis. This score includes symptoms of: abrupt onset, stepwise deterioration, fluctuating course, nocturnal confusion, preservation of personality, depression, somatic complaints, emotional incontinence, history of hypertension, history of stroke, associated atherosclerosis, focal neurological symptoms, and focal neurological signs. The symptoms are given a score, weighted on the basis of their importance. A total HIS score of 7 or more is indicative of VaD. The HIS score is based on the concept of MID and meta-analytic evidence indicates that the HIS score does a good job in differentiating between MID and AD (Moroney et al., 1997).

Various sets of clinical criteria can be used for the differential diagnosis of dementia. Although the differences between criteria do not vary much in the diagnosis of AD, they do so in the diagnosis of VaD. Specifically, Gold et al. (2002) validated four different sets of clinical criteria for VaD (DSM-IV, International Coding of Diseases [ICD] -10, the State of California Alzheimer’s Disease Diagnostic and Treatment Centers [ADDTC], and the National Institute for Neurological Disorders and Stroke – Association Internationale pour la Recherche et l’Enseignement en Neurosciences [NINDS-AIREN]) and found that the criteria were not interchangeable. For example, the ADDTC criteria were more sensitive in detecting VaD compared to the other sets of criteria, whereas the DSM-IV criteria were more effective in differentiating between VaD and mixed dementia. Importantly, the different sets of criteria did not select the same persons as having VaD.

As with AD, both genetic and environmental risk factors presumably contribute to the pathogenesis. However, because there is no consensus as to the clinical criteria of VaD, studies on risk factors have revealed mixed findings. Age is the only consistent risk factor found so far, but probable risk factors include sex and race. Men are believed to be at a higher risk, as are Oriental and Black populations, compared to Caucasian populations (Fratiglioni & Rocca, 2001). Other possible risk factors for VaD include hypertension (Paglieri et al., 2004), diabetes (Xu, Qiu, Wahlin, Winblad, & Fratiglioni, 2004), and carrying an APOE â-4 allele (Hsiung, Sadovnick, & Feldman, 2004).
Cognition

Cognition is sometimes referred to as the science of the mind. Cognitive functioning involves skills as diverse as perception, attention, mental speed, memory, logical thinking, verbal ability, visuospatial skill, and intelligence. In other words, it refers to all the processes needed for acquiring, manipulating, storing, and retrieving information. The next section will briefly discuss those cognitive domains that are assessed in the empirical studies of this thesis.

Global functioning

In studies of aging and dementia, global measures of cognitive functioning are often of interest, to index general level of cognitive functioning, or as screening tools. In the KP, the Mini Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975) was used for both these purposes. The MMSE includes 11 items and has a maximum score of 30. A key advantage is that the test is short; it typically requires only about 5-10 minutes for administration. It covers several cognitive domains, for example immediate and delayed memory, orientation, and visuospatial skill. Obvious drawbacks are that no cognitive domain is thoroughly measured, and the variability in test scores may be poor. Specifically, most cognitive domains are assessed with only one question resulting in a score that can be either 1 or 0. As a result ceiling effects among cognitively intact persons are legion.

![Figure 1. Schematic overview of memory systems (Adapted from Baddeley, 1986; Squire, 1992; Tulving, 1983).](image)

Memory

Memory is perhaps the cognitive function most commonly associated with dementia. Memory can be described in different ways and at various levels of abstraction. I chose to describe this cognitive function using the memory-systems view (Squire, 1992; Tulving, 1983; see Figure 1). According to this view, memory can be divided into different systems. These systems do, at least in part, depend on different areas of the brain (see Cabeza & Nyberg, 2000, for an overview). Although the memory systems are described as separate entities, it is worth noting that the differentiation is not always clearcut, and that the different systems are not completely independent of each other (Tulving, 1972, 1983). They also share
common features and can be associated with similar brain activation patterns (Nyberg, Cabeza, & Tulving, 1996; Nyberg, Forkstam, Petersson, Cabeza, & Ingvar, 2002; Nyberg & Tulving, 1996). Nonetheless, separating memory into different types or systems may be useful, given that these are differentially affected by different disorders and by normal aging (Bäckman, Small, & Wahlin, 2001; Nyberg & Tulving, 1997).

First, memory can be separated into short-term and long-term memory. Short-term memory maintains information in a relatively untransformed fashion (primary memory), or allows manipulation of immediately available information (working memory); hence, it deals with temporary storage of information (Baddeley, 1986, 1992). In contrast, long-term memory retains information over longer periods, from minutes up to decades. Whereas short-term memory is thought to be limited in terms of the number of items that can be held in memory at the same time, the capacity of long-term memory is thought to be more or less unlimited. Long-term memory, in turn, can be subdivided into procedural memory, perceptual representation system, semantic memory, and episodic memory.

Procedural memory involves memory for skills and actions, for example, memory for how to ride a bike, or playing the piano. Although procedural information may be relatively difficult to acquire, once representations are formed, retrieval tends to be rather automatic, and procedural memories are typically resistant to forgetting (Bäckman, Small, & Wahlin, 2001; Squire, 1992). Another form of memory where retrieval is rather unconscious is priming. Priming refers to the facilitation in terms of processing a certain item (e.g., a word or an object) following previous exposure to the same or a related item (Schacter, 1990). In the memory-systems taxonomy, priming is subserved by the perceptual representation system.

Semantic memory involves facts that we know about the world. Information stored in semantic memory does not necessarily have a connection to when and where the representation was formed (Tulving, 1983). Knowing that Madrid is the capital of Spain, that a pike is a species of fish, or that the association between chair and table is stronger than that between chair and wallet all constitute examples of semantic memory information. Semantic memory may be assessed with tests of general knowledge or verbal fluency; hence, semantic memory tests do not typically tap memory for something that was learnt during a particular study session, but rather assess information that has been acquired over a longer period of time.

Episodic refers to the type of memory by which personal events and episodes from the past are recollected. Thus, episodic memory has a temporal-spatial referent and involves mentally traveling backwards in time at retrieval (Tulving, 1983; Wheeler, Stuss, & Tulving, 1997). An example is remembering going up the Eiffel Tower when visiting Paris, or remembering the plot in a film. In the laboratory, episodic memory is typically assessed by asking persons to remember a list of words, or pictures that was presented earlier.

Important features of long-term memory are the various processes operating within the memory systems, specifically encoding, consolidation, and retrieval. Disruption at any of these processes is detrimental to memory performance. Interestingly, different brain areas are involved in the different processes. For example, in younger adults encoding of episodic information has been shown to
predominantly activate left frontal areas of the brain, whereas right frontal regions are more involved during episodic retrieval (Nyberg & Tulving, 1996).

**Prospective memory**

In the above description of memory systems, episodic memory was described in terms of something being remembered from the past, or retrospective memory (RetM). Another form of episodic recollection involves remembering an action to be performed in the future. This form of memory is labeled prospective memory (ProM), and includes tasks such as remembering to buy groceries on the way home from work, or to take medication at certain timepoints (Einstein & McDaniel, 1996; Maylor, Darby, Logie, Della Sala, & Smith, 2002). ProM differs from retrospective memory in several respects; (1) ProM is thought to consist of two components: remembering the intention to perform an action (prospective component), and remembering the content of the action (retrospective component); (2) ProM requires monitoring of the environment for a cue to appear, whereas in RetM the cue is normally provided by someone else; and (3) ProM is always embedded in an ongoing task, whereas RetM is typically performed in isolation.

In this thesis ProM was assessed using an event-based task, with a rather long retention interval. Specifically, at the beginning of an approximately one-hour long test session participants were asked to remind the test leader to make an important phone call when the testing was finished.

**Verbal fluency**

Verbal fluency is typically assessed by asking a person to generate as many words as possible from a certain taxonomic category (category fluency), or words beginning with a given letter (letter fluency). The task is often used as a measure of semantic memory, as it is dependent on the person’s general knowledge of words. It is also seen as a measure of the integrity of the semantic system (Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Chan, Butters, & Salmon, 1997). Further, verbal fluency tasks entail an executive component, and performance on such tasks tends to be impaired in patients with circumscribed frontal lesions (West, 1996), as well as activate frontal regions in normal persons (Cabeza & Nyberg, 2000). Thus, these tasks are also used as measures of frontal lobe functioning in the neuropsychological literature (Lezak, 1995).

**Visuospatial skill**

Visuospatial skill involves analyzing spatial information as well as constructional skills. It draws primarily on right-hemisphere brain regions, but because visuospatial tasks typically have constructional demands, left-hemisphere areas may also be involved (Benton, 1985). In this thesis visuospatial skill was assessed with the Block design subtest from the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981), and the clock test (Christensen, 1984). In Block design the task is to reproduce a drawn pattern with three-dimensional blocks. The clock test included clock setting, drawing the hands of the clock to indicate a certain time, and clock reading, which involved “telling the time” from seeing the hands of a drawn clock. Clock setting mainly involves visuoconstructional skills, and clock
Cognitive functioning in normal aging

Cognitive functioning is not stable during the adult life course, but exhibits both gains and losses, although the latter clearly dominate. With advancing adult age certain cognitive skills deteriorate, for example processing speed (Salthouse, 1996), working memory (Park et al., 1996; Salthouse & Babcock, 1991), and episodic memory (Nyberg et al., 2003; Park et al., 1996). Other forms of memory, such as priming and semantic memory remain rather unaffected by the aging process at least until late senescence (Nyberg et al., 2003; Park et al., 1996), and the latter of these may even improve from young to middle and old age (Bäckman, Small, & Larsson, 1999; Nyberg et al., 2003).

Despite the general pattern described above, it should be noted that there is great variation among individuals. Some older adults may well maintain their cognitive functioning at a high level into very old age, whereas others start deteriorating early on. The old-age heterogeneity in cognitive functioning is typically larger in late senescence than among younger elderly individuals. An important reason thereof may be that health conditions that negatively affect cognitive functioning such as depression, diabetes, high blood pressure, and vitamin deficiencies become more common in late life (Bäckman, Small, & Wahlin, 2001).

Considerable effort has been directed at investigating if there is a single mechanism that can account for age-related deficits in higher-order cognitive skills, for example episodic memory. Speed of processing (Salthouse, 1996), sensory functioning (thought to serve as an indicator of the integrity of brain functioning; Lindenberger & Baltes, 1994), and working memory (Craik & Byrd, 1982) are factors that have been proposed as such mechanisms, and they have all been fairly successful in explaining the age-related variation in tasks assessing episodic memory and intelligence.

Recently, imaging techniques such as positron emission tomography (PET), magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) have made it possible to study the relationship of structural and functional brain changes to the cognitive changes observed in older age. Findings from these studies have shown that age-related cognitive deficits may be due to loss of brain volume (Raz, 1999), particularly in the hippocampus, prefrontal cortex, and portions of the cerebellum. Functionally, different patterns of brain activation have been observed in older as compared to younger persons in the same cognitive tasks (Cabeza, 2002). On the one hand, older persons show under recruitment of some brain areas (e.g., right prefrontal cortex) during performance in certain episodic or working memory tasks. On the other hand, older persons also tend to recruit brain areas not normally utilized by younger people in the same tasks. Whether this additional recruitment is adaptive and serves compensatory purposes (Cabeza, Anderson, Locantore, & McIntosh, 2002) or rather reflects lack of specificity of neural processing (Bäckman & Farde, 2004; Li, Lindenberger, & Sikström, 2001) remains to be determined. In addition, there is loss of cognitively relevant neurotransmitters with advancing age. In particular, strong relationships have been
observed between age-related loss of PET-derived dopaminergic markers and age-related cognitive deficits (Bäckman et al., 2000; Volkow et al., 1998).

**Cognitive functioning in AD and VaD**

The fact that cognitive functioning is impaired in both AD and VaD should come as no surprise. Of greater interest is whether the pattern of cognitive deficits differ in these two dementia diseases. A number of studies have suggested that it is possible to differentiate between AD and VaD on the basis of patterns of neuropsychological deficits. Some of these studies have shown that AD patients have greater deficits in verbal episodic memory (Hassing & Bäckman, 1997; Kertesz & Clydesdale, 1994; Lafosse et al., 1997; Villardita, 1993) and language (Kertesz & Clydesdale, 1994; Villardita, 1993), whereas VaD patients are more impaired on measures of motor performance (Almkvist et al., 1993; Kertesz & Clydesdale, 1994), clock reading (Fahlander, Wahlin, Almkvist, & Bäckman, 2002) and verbal fluency (Lafosse et al., 1997). Thus, some evidence suggests that language and memory are more impaired in AD, whereas executive functioning is more impaired in VaD (see Looi & Sachdev, 1999, for a review). Note however, that these studies do not suggest that language and memory are unimpaired in VaD or that executive functioning is unimpaired in AD, as compared to persons who are not demented.

However, several other studies have failed to differentiate between these two dementia disorders on the basis of cognitive test scores (Almkvist et al., 1993; Almkvist, Fratiglioni, Agüero-Torres, Viitanen, & Bäckman, 1999; Erker, Searight, & Petersen, 1995; Erkinjuntti et al., 1986); for a review see (Almkvist, 1994). Note that in all studies referenced above the dementia groups were matched on severity of cognitive impairment, hence this should not be a reason for the discrepancies in the findings. The mixed findings may in part reflect differences in the criteria used for diagnosing AD and VaD. Further, as noted VaD is a heterogeneous collection of disorders, which may also contribute to the contradictory findings. At any rate, similarities in patterns of cognitive deficits appear more prominent than differences. For example, the most affected cognitive ability in both diseases is episodic memory (Almkvist, 1994).

**Cognitive functioning during the transition to dementia**

In the past 15 years a vast number of studies have demonstrated cognitive deficits several years before diagnosis in persons who are destined to receive a dementia diagnosis. Most of these studies have involved persons in the preclinical phase of AD, although some studies have included all types of dementia. Preclinical cognitive deficits have been observed for global measures of cognitive functioning (Fabrigoule et al., 1998; Small, Fratiglioni, Viitanen, Winblad, & Bäckman, 2000), as well as in specific cognitive domains such as episodic memory (Bäckman, Small, & Fratiglioni, 2001; Grober & Kawas, 1997), visuospatial functioning (Howieson et al., 1997; Small, Herlitz, Fratiglioni, Almkvist, & Bäckman, 1997), processing speed (Fabrigoule et al., 1998), executive functioning (Albert, Moss, Tanzi, & Jones, 2001; Chen et al., 2001), and verbal functioning (Jacobs et al., 1995; Linn et al., 1995).

A recent quantitative analysis of the available studies on preclinical cognitive deficits in AD (Bäckman, Jones, Berger, Laukka, & Small, in press) showed that of the specific cognitive domains targeted, episodic memory, perceptual speed, and
executive functioning were most impaired in prodromal AD. However, as portrayed in Figure 2, substantial preclinical impairment, was seen for several other cognitive domains including verbal and visuospatial ability as well as attentional functioning. The only exception to this pattern was primary memory (PM), for which no preclinical impairment was obtained. Hence, the cognitive deficits in preclinical AD appear to be rather global in nature, which was also indicated by the fact that global measures of cognitive functioning (including the MMSE) revealed sizeable impairment.

The fact that cognitive deficits are evident in AD several years before diagnosis makes biological sense, given that the pathological changes start long before a diagnosis of dementia can be rendered (Braak & Braak, 1991; Fox, Warrington, Stevens, & Rosser, 1996). Although the first pathological changes in AD may occur in medial-temporal regions, recent observations suggest that multiple brain areas can be affected years before diagnosis, including frontal (Yamaguchi, Sugihara, Ogawa, Oshima, & Ihara, 2001), and temporoparietal (Fox et al., 2001) regions. In view of such findings, a global cognitive impairment should indeed be expected prior to the AD diagnosis.

Preclinical cognitive deficits in AD across multiple cognitive domains.

Preclinical cognitive deficits are not exclusive to AD, but have been demonstrated also in other dementia disorders. For example, deficits in attentional set shifting and category fluency were observed before diagnosis in Huntington’s disease (Lawrence et al., 1998) and deficits in tests assessing frontal-lobe function were observed several years before fronto-temporal dementia (Geschwind et al., 2001). Preclinical deficits in VaD have not been thoroughly investigated, although some indications of cognitive impairment before diagnosis in VaD have emerged recently (Ingles, Wentzel, Fisk, & Rockwood, 2002; Meyer, Xu, Thornby,
Chowdhury, & Quach, 2002; Meyer, Xu, Thornby, Chowdhury, & Quach, 2002; Xu, Meyer, Thornby, Chowdhury, & Quach, 2002).

Although few would dispute whether cognitive deficits exist many years before the AD diagnosis, evidence pertaining to the trajectory of preclinical decline is mixed. In two studies from the KP (Bäckman, Small, & Fratiglioni, 2001; Small et al., 2000), evidence indicated relative stability of the preclinical deficit from 6 to 3 years before diagnosis for measures of episodic recall and recognition as well as global cognitive ability. The Bäckman et al. (2001) data are portrayed in Figure 3. By contrast, other studies have estimated that accelerated decline may start up to five years before the dementia diagnosis (Hall, Lipton, Sliwinski, & Stewart, 2000). There is consensus, however, that precipitous decline characterizes the final portion of the preclinical period (Chen et al., 2001; Fox, Warrington, Freeborough et al., 1996; Rubin et al., 1998).

![Course of Preclinical Memory Impairment](image)

**Figure 3.** The course of episodic memory decline in Alzheimer’s disease and nondemented aging.

In the empirical studies in this thesis, cognitive functioning in the preclinical stages of dementia has been the focal point. Study I investigated aspects of episodic memory in prodromal AD that have largely been ignored in earlier research. Specifically, in this study ProM impairment and impairment in encoding, storage, and retrieval processes within a retrospective episodic memory task were examined. Study II – IV focused on the preclinical phase in VaD, with special emphasis on potential differences in patterns of cognitive impairment during the preclinical stages of VaD and AD. As noted, although the preclinical phase of AD has been abundantly investigated, investigations of the preclinical phase in VaD are sparse. And finally, Study V investigated individual differences in rate of global cognitive decline during the final years before the AD diagnosis.
Empirical studies

The Kungsholmen Project

The Kungsholmen Project (KP) is a population-based longitudinal study carried out in Stockholm, Sweden. A detailed description of the study can be found elsewhere (Fratiglioni, Viitanen, Bäckman, Sandman, & Winblad, 1992) and only a brief description will be given here. The aim of the KP is to study aging and dementia from medical, psychological, and social perspectives. The study started in 1987 and five follow-ups, at approximately 3-year intervals, were completed before the data collection was terminated in the year 2000. In this thesis, data from the baseline and first two follow-ups of the KP were used in all empirical studies.

Figure 4. Overview of the study design of the Kungsholmen Project

Figure 4 provides a schematic outline of the data collections in the KP. At Time 1 (baseline), completed between 1987-1989, all persons 75 years of age and older (born before 1912) in the Kungsholmen parish of Stockholm were invited to participate in the study. The initial study population consisted of 2,368 persons, living either at home or in institutions. Out of these, 181 had died and 86 had moved before the first assessment, and 291 refused to participate; hence, the baseline population included 1,810 persons. The baseline consisted of two phases. At Phase I of the baseline, all persons were given the MMSE and a social interview. In addition, data on vital parameters (functional status, blood pressure, height and weight), multiple blood parameters, and drug use were collected. In Phase II, all persons with an MMSE score below 24 (n = 314) and a random sample of those with an MMSE score above 23 (n = 354) were assessed with a complete medical examination, social
and family interviews, laboratory blood analyses, and a comprehensive cognitive test battery.

At the first follow-up, between 1991-1993, the original sample was invited back. Of these, 1099 persons were assessed. In the second follow-up, between 1994-1996, the sample size had been reduced to 680 persons. In all follow-ups, the participants were assessed with the same comprehensive test battery as was used in the second phase of the baseline.

**Diagnostic procedures**

At baseline (Time 1), participants with dementia were detected in two phases. In Phase I, a screening procedure was used to detect suspected cases of dementia (MMSE < 24), and in Phase II a clinical examination was used to detect participants with dementia. The same clinical assessment, diagnostic procedure, and criteria were used at the Phase II examination and the two follow-up examinations. Dementia diagnosis was obtained using a three-step diagnostic procedure. In Step 1, a preliminary diagnosis was made by geriatricians, who had examined the participants and reviewed their social and family history. Step 2 involved a second preliminary diagnosis of all participants by a physician expert in dementia, based on computerized data only. In Step 3, the two preliminary diagnoses were reviewed again to ascertain causes of agreement and disagreement. This eliminated most of the discordant diagnosis. However, in those cases where disagreement persisted, the final diagnosis was made by a supervising physician. This process yielded a diagnosis of the presence or absence of dementia according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition Revised* (DSM-III-R; American Psychiatric Association, 1987). To obtain a dementia diagnosis for participants who had died before the follow-up examination, individual hospital records and death certificates were examined by physicians, following the procedure described above.

The differential diagnosis of AD and VaD was based on clinical data only because of the lack of possibility of morphological examinations of the brain. Symptoms and signs of cerebrovascular disorders as well as progression of the disease and the temporal sequence of relevant events were taken into account. Specifically, gradual onset and progressive deterioration was required for a diagnosis of AD. Also, all other specific causes of dementia were ruled out. For a diagnosis of VaD, abrupt onset, stepwise deterioration, history of stroke, and/or focal deficits were required. The HIS (Hachinski et al., 1975) was used to support the clinical judgment regarding the differential diagnosis between AD and VaD. A HIS score greater than 6 was defined as an indication of VaD, a score between 5 and 6 mixed dementia, and a score below 5 was defined as an indication of AD.

Diagnosis of depression and other psychiatric disorders were made according to DSM-III-R at baseline (Time 1), and according to DSM-IV in the follow-ups.

**Sampling procedures for the empirical studies**

In all five empirical studies, the samples included those who were non-demented at baseline (Phase 1, \( n = 1473 \)). Some of these persons received a dementia diagnosis at either the first or the second follow-up. Persons who were diagnosed with a type of dementia other than AD or VaD were excluded. To increase the sample sizes in the dementia groups, the data for the incident dementia cases from
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both the first and the second follow-up were aggregated. Baseline (preclinical) data were always taken from the measurement point preceding the time at which the persons were diagnosed with dementia (approximately three years earlier). Hence, for persons who received a dementia diagnosis at the first follow-up, baseline data were taken from Time 1 and for persons who were diagnosed at the second follow-up, baseline data were taken from the first follow-up. For the non-demented controls, baseline data were randomly taken from either Time 1 or the first follow-up. The proportion of controls that had baseline data from Time 1 versus the first follow-up were approximately the same as for the incident demented. The randomized procedure to obtain baseline data for control persons was done separately for each study. The sample sizes for the incident dementia groups vary across studies, depending on the specific cognitive measures used as well as with screening criteria employed.

Patterns of retrospective and prospective memory in preclinical dementia (Study I)

Most studies investigating cognitive markers in preclinical AD have included tests of episodic memory (Bäckman et al., in press). This is makes sense given that episodic memory impairment is considered the cardinal symptom of AD (American Psychiatric Association, 1994; McKhann et al., 1984). However, all of these studies have focused on RetM, remembering something from the past. By contrast, ProM, remembering to do something in the future, has been ignored in the cognitive literature on preclinical AD. A main aim of Study I was therefore to investigate potential ProM deficits in preclinical AD. The results showed clear ProM deficits three years before the AD diagnosis. This was so although the ProM task used had suboptimal measurement properties. The participants were simply asked to remind the test leader to make an important phone call after the whole cognitive test battery was completed. Participants either managed to remember the task without prompting (free recall) or after being prompted by the test leader (cued recall). Despite the apparent simplicity of the task, marked differences between persons in the preclinical phase of AD and those who were not going to get a dementia diagnosis at the three year follow-up were evident.

Further, we examined the relative predictive power of ProM and RetM tasks in identifying future AD cases. There has been some debate as to whether ProM and RetM represent distinct entities of episodic memory. Some researchers have claimed that ProM and RetM share so many features that there is no need of distinguishing between the two (Crowder, 1996; Roediger, 1996). However, others have claimed that ProM is a distinct form of episodic memory, because it involves remembering intentions for the future (Goschke & Kuhl, 1993; McDaniel & Einstein, 1992; Mäntylä & Sgaramella, 1997). In Study I we investigated whether ProM and RetM would give independent contributions in predicting dementia incidence over the three-year follow-up interval. In order to obtain a measure of RetM comparable to the ProM measure, we used an organized recall task, including assessment of both free and cued recall. The results showed that although both ProM and RetM are impaired in preclinical AD, both types of episodic memory are independently associated with dementia incidence over a three-year period. In both free and cued recall, RetM was somewhat more predictive of forthcoming AD, although ProM
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added systematic variance to group classification over and above RetM. This pattern of results is consistent with the notion that ProM is largely frontally mediated (Burgess, Quayle, & Frith, 2001; Okuda et al., 1998), whereas medial-temporal areas are strongly implicated in RetM (Nyberg & Tulving, 1996; Vargha-Khadem et al., 1997). Alterations in both these areas have been demonstrated before the AD diagnosis (Fox, Warrington, Freeborough et al., 1996; van der Flier et al., 2002).

An additional aim was to explore potential deficits in the processes within both ProM and RetM. Previous studies have shown that the prospective component of ProM is more age-sensitive than the retrospective component (Cohen, Dixon, Lindsay, & Masson, 2003; West & Craik, 2001). In Study 1, being successful in ProM free recall was defined as being successful in the prospective component, and failing to recall the task even with prompting, was defined as failure in the retrospective component. The magnitude of the difference between preclinical AD cases and controls was virtually identical in these tasks (approximately 20 %), suggesting a similar impairment for both components in the ProM task.

For RetM, deficits in encoding, retrieval and forgetting were explored. This was done using the same organizable word list as in the comparison of ProM and RetM described above, where the words could be organized into four taxonomic categories at encoding and retrieval. At retrieval, participants were first assessed with free recall, and then with cued recall with the category names serving as cues. From these tests, it is possible to determine how many words that were remembered in each category, the number of categories remembered, and the number of words forgotten from free to cued recall. The number of words remembered per category is thought to reflect organizational processing at encoding, whereas the number of categories recalled was used as a proxy for the participant’s retrieval plan (Craik & Mansini, 1969; Hultsch, 1975; Smith, 1980). The proportional loss of information from free to cued recall was used to indicate forgetting (Bäckman & Wahlin, 1995). The results showed deficits in all three indices approximately three years before the AD diagnosis. Interestingly, forgetting was the most sensitive predictor, despite the fact that it occurred over a very brief period of time. However, the indicators of encoding and retrieval ability added unique variance to group classification.

Hence the overall conclusion from Study I was that the preclinical deficit in AD generalizes across different types of episodic memory (i.e., ProM and RetM) as well as across different memory operations within ProM and RetM tasks. Having further explored the episodic memory deficits in preclinical AD in Study I, the next two studies focused on preclinical cognitive deficits in VaD.

Cognitive deficits in preclinical VaD (Study II and Study III)

Although preclinical cognitive deficits in AD have been abundantly investigated in the last 15 years, potential preclinical deficits in VaD have not been considered in a systematic fashion until quite recently. Yet, several observations make preclinical cognitive deficits biologically plausible also in VaD. First, circulatory disturbances may cause gradual changes in the brain before an actual stroke. VaD patients often have a history of cerebrovascular disease (Nyenhuis & Gorelick, 1998; Skoog, 1994), and many cerebrovascular conditions (e.g., high blood pressure, atrial fibrillation, and white matter abnormalities) have been associated with cognitive deficits in non-demented individuals (Breteler, Claus, Grobbee, &
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Hofman, 1994; Elias, Wolf, D'Agostino, Cobb, & White, 1993; Fahlander et al., 2000). Second, there is an overlap in pathology between AD and VaD patients (Kalaria & Ballard, 1999; Skoog, Kalaria, & Breteler, 1999). Specifically, the amyloid plaques and neurofibrillary tangles in AD may be caused by cerebrovascular disease, and conversely, amyloid depositions in cerebral blood vessels as a result of AD increases the risk for stroke and thereby VaD (Langa et al., 2004). Given this overlap and given the robust evidence for preclinical cognitive deficits in AD, such deficits may be expected in VaD as well. Third, as described in a previous section, there are strikingly similar patterns of cognitive deficits in the early clinical stages of AD and VaD (Almkvist et al., 1993; Erker et al., 1995; Erkinjuntti et al., 1986). Hence, in Study II and III, we investigated preclinical cognitive deficits in VaD three years before diagnosis. Persons in the preclinical phase of AD were also included to enable comparisons between the two dementia types.

In Study II, the total score and individual items of the MMSE were used as outcome measures. Persons in the preclinical phase of VaD showed deficits in the total score and three of the individual items: orientation to time, orientation to place, and delayed recall. Note that all of these items have an episodic memory referent. The pattern was the same for the preclinical AD cases. In a logistic regression analysis, the same items were associated with dementia incidence over a three-year period. Delayed memory was the best predictor in both preclinical AD and preclinical VaD. Hence, the pattern of preclinical MMSE deficits was very similar in AD and VaD.

In Study III, these similarities were extended to include more refined measures of cognitive functioning. In this study the samples of preclinical VaD and AD cases were much smaller due to the two-phase baseline assessment in the KP. Measures of episodic memory (free recall of random words, free and cued recall of organizable words, word and face recognition), short-term memory (digit span forward and backward), visuospatial ability (block design, clock reading, clock drawing), and verbal fluency (category and letter fluency) were examined. Compared to a control group, the VaD group performed worse on three of the episodic memory tasks, random recall, word recognition, and face recognition. The preclinical AD group showed deficits in all episodic memory tasks, and also on the fluency and visuospatial measures. However, there were no statistically reliable differences between the two dementia groups on any of the measures. In logistic regression analyses, face recognition was the only variable that was related to VaD incidence, whereas in AD face recognition, block design, and word recognition were significantly associated with future dementia status.

The main conclusion from Study II and III is that the similar patterns of cognitive deficits in clinical AD and VaD appear to extend to the preclinical stages of the diseases. However, given the different etiologies of AD and VaD, there still may be some measures that differentiate between these diseases in the preclinical stages. This issue was examined in Study IV.

**Differential verbal fluency deficits in preclinical AD and VaD (Study IV)**

Given that the pathological changes in AD begin in medial-temporal regions (Braak & Braak, 1991), whereas the first structural changes in VaD are normally
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seen in the frontostriatal circuitry (Chui, 2000; Román & Royall, 1999), it is conceivable that some tasks can yield differential patterns of cognitive deficits in the preclinical phases of the diseases. Category and letter fluency are similar in that they both tap the ability to access semantic memory, and both are thought to draw on frontal lobe functioning (Lezak, 1995). However, behavioral studies (Martin, Wiggs, Lalonde, & Mack, 1994), as well as structural (Mungas et al., 2001) and functional (Pihlajamäki et al., 2000) imaging research have shown that category fluency is more dependent on medial-temporal lobe functioning, whereas letter fluency is more dependent on frontal-lobe functioning. Therefore, we hypothesized that category fluency would be more impaired in the preclinical stage of AD, whereas letter fluency would be more impaired in preclinical VaD, or possibly equally impaired in both diseases. The latter outcome would be consistent with recent evidence of frontal pathology also in preclinical AD (van der Flier et al., 2002; Yamaguchi et al., 2001). The results from Study IV supported the hypothesis that category fluency is more impaired in preclinical AD, although letter fluency was equally impaired in the preclinical stages of both AD and VaD.

We also investigated whether there are differential patterns of impairment over the retrieval interval in the fluency tasks, in terms of whether the patterns of early and late word generation differ in AD and VaD. Several studies have shown that the generation of words decreases over time in verbal fluency tasks, such that fewer words are generated in the last 30s as compared to the first 30s of the task both in younger and older persons (Crowe, 1998; Fernaeus & Almkvist, 1998). Evidence suggests that early generation is related to fluid measures of intelligence, whereas late generation is related to crystallized measures of intelligence (Fernaeus & Almkvist, 1998). These findings have lead to the hypothesis that retrieval during the first 30s is guided by semiautomatic processes, whereas retrieval during the last 30s requires more effortful search processes.

The results showed that these patterns generalized to the preclinical stages of AD and VaD. Although fewer words were produced in both category fluency and letter fluency in the preclinical stage of AD and in letter fluency in the preclinical stage of VaD, more words were produced in the first 30s as compared to the last 30s for all three groups. This finding may appear counterintuitive given that more automatic cognitive processes are normally better preserved than effortful operations in the early phases of dementia (Albert et al., 2001; Small et al., 1997). Hence, early generation may be expected to be less impaired than late generation. However, the similar degree of impairment observed across the retrieval interval may reflect the fact that in preclinical dementia early generation is hampered by a slowing down of lexical retrieval (Albert et al., 2001; Bäckman et al., in press; Fabrigoule et al., 1998). Thus, the speed demands during the early phase may balance the greater demands on effortful search strategies in late retrieval, the net effect being similar fluency deficits across the 60s period in preclinical dementia.

Having explored patterns of cognitive deficits in the preclinical phases of AD and VaD, we wanted to investigate factors that may influence rate of preclinical cognitive decline. This was done in Study V. However, because of the small number of persons in the preclinical phase of VaD, this study was restricted to preclinical AD persons.
Rate of cognitive decline in preclinical AD (Study V)

It is well established that persons who will be diagnosed with AD show precipitous cognitive decline during the last 2-3 years preceding diagnosis (Bäckman, Small, & Fratiglioni, 2001; Chen et al., 2001; Small et al., 2000). In Study V, the aim was to investigate whether different individual-difference variables would affect the rate at which cognitive functioning declines in AD from three years before diagnosis until the time of diagnosis. Although the effects of most individual-difference variables (e.g., age, sex, education, depression) on cognitive performance are reduced or non-existent in clinical AD (Buckwalter, Sobel, Dunn, Diaz, & Henderson, 1993; Bäckman, Hassing, Forsell, & Viitanen, 1996; Fahlander, Berger, Wahlin, & Bäckman, 1999; Teri, Hughes, & Larson, 1990), it remains unknown whether such differences can influence rate of cognitive decline during the transition from preclinical to clinical AD. The independent variables included were those that have been shown to influence cognition in normal aging, such as demographic factors, health factors (e.g., number of diseases leading to hospitalization, depression, vitamin B deficiency), and substance use (Bäckman et al., 1999; Hultsch, Hertzog, Dixon, & Small, 1998), as well as variables that are associated with an increased risk of developing AD, such as having an APOE-ε4 allele (Bondi, Salmon, Galasko, Thomas, & Thal, 1999) and a poor social network (Fratiglioni, Wang et al., 2000).

The study sample was different from those used in the previous studies. Specifically, in Study V we only included persons who were non-demented at baseline and who received a dementia diagnosis at follow-up. Degree of cognitive decline from preclinical to clinical AD was measured using the MMSE. The average annual decline was 1.81 MMSE points between baseline and follow-up. This change estimate can be compared to the corresponding figure in clinical AD, which typically averages around 3 points (Clark et al., 1999; Wilson, Gilley, Bennet, Beckett, & Evans, 2000).

Of the potential predictors, only age and number of diseases resulting in hospitalization between baseline and follow-up were related to rate of MMSE change. Increasing age and an increasing number of diseases were associated with greater decline on the MMSE.

However, the effect of age on rate of MMSE decline was mediated by recent diseases. When age was entered before recent diseases in a hierarchical regression analysis, both variables significantly contributed to rate of decline. However, when the order of entry was reversed, only recent diseases was related to rate of decline. The effect of number of recent diseases on rate of MMSE decline is shown in Figure 5.

The results from Study V indicated a rather limited influence of the individual-difference variables selected on rate of MMSE decline during the final portion of the preclinical period in AD. Hence, the influence of many individual-difference variables which are associated with cognitive performance in normal aging, or implicated as risk factors for AD appears to be overshadowed by the dementing process already before the clinical diagnosis of AD.
Figure 5. Performance on the MMSE at baseline and at 3 year-follow-up for persons with 0, 1-2, or 3+ recent diseases.

However, an increasing number of recent diseases seems to be an exception to this pattern. The fact that number of recent diseases was the only variable that made an independent contribution to rate of decline may reflect the fact that serious health conditions have a stronger impact on cognition in normal aging, compared to the other predictor variables examined (e.g., sex, education, social network; Bäckman et al., 1999; Hultsch et al., 1998). As a result, although the influence of individual-difference variables on cognition is reduced in preclinical AD compared to normal aging, residual effects may be more easily observed for a variable where the effects are rather strong among non-demented elderly people.
Discussion

The findings from this thesis can be summarized in the following main points: (1) The episodic memory deficit in preclinical AD generalizes across both different types of episodic memory (retrospective and prospective), as well as across different processes within prospective (prospective and retrospective components) and retrospective (encoding, forgetting, and retrieval) episodic memory tasks; (2) Preclinical cognitive deficits can be detected also in VaD, and these deficits appear to be quite similar to those seen in AD; (3) Verbal fluency may be a useful measure in differentiating between AD and VaD in the preclinical stages; and (4) In the preclinical phase of AD, the impact on rate of cognitive decline of many cognitively relevant factors as well as risk factors is limited, a possible exception being other recently acquired diseases.

Why is episodic memory so sensitive?

Although the preclinical phase of AD is characterized by a rather global cognitive impairment (Bäckman et al., in press), episodic memory has consistently emerged as the single most sensitive cognitive measure when differentiating preclinical AD cases from controls (e.g., Grober & Kawas, 1997; Masur, Fuld, Blau, Crystal, & Aronson, 1990; Tierney, Szalai, Dunn, Geslani, & McDowell, 2000; Tierney et al., 1996). It has been demonstrated that the deficit generalizes across different aspects of episodic memory, such as verbal and non-verbal materials (Small et al., 1997), immediate and delayed testing (Albert et al., 2001; Tierney et al., 2000), as well as recall and recognition (Bäckman & Small, 1998; Jacobs et al., 1995). Further, Study I demonstrated that the preclinical deficits in AD also generalize across different types of episodic memory (retrospective and prospective), as well as across different processes within both retrospective (encoding, consolidation and retrieval) and prospective (retrospective and prospective components) memory tasks. Hence, the episodic memory deficit in preclinical AD appears to affect most, if not all, aspects of this type of memory, although perhaps not to the same degree.

However, episodic memory problems are not exclusive to AD. Decline in episodic memory is characteristic of normal aging (Bäckman et al., 1999; Nyberg et al., 2003), and marked episodic memory deficits are observed in a variety of disorders and conditions, including stroke, schizophrenia, depression, vitamin deficiencies, and sleep deprivation, to mention a few among several possible examples (Bäckman, Small, & Wahlin, 2001). In addition, Study II and III showed that episodic memory was impaired at least 3 years before diagnosis also in VaD. Hence, episodic memory deficits appear to be a hallmark of many conditions that affect the brain. There may be several reasons for the sensitivity of episodic memory to alterations in brain functioning.

With regard to the current data, there is a trivial reason for the primacy of episodic memory as an early harbinger of dementia. Given that the KP has a focus on aging and dementia, and that cognitive battery was devised by experimental memory researchers in the mid 1980s, the tasks selected focused mainly on episodic memory. Other domains which may be just as sensitive to incipient dementia, such as executive functioning or working memory, were not well represented in the protocol. Hence, although it is evident that there are episodic memory problems in both
Cognitive Functioning in the Preclinical Stages of AD and VaD

preclinical AD and preclinical VaD, we cannot rule out the possibility that other cognitive domains would be similarly impaired in both prodromal dementia states. The dominance of episodic memory in investigations on preclinical dementia appears not to be a limitation in the KP only. Judging from the studies included in a recent meta-analysis (Bäckman et al., in press), most studies on preclinical AD have included tests of episodic memory, whereas other specific cognitive domains are represented in considerably fewer studies.

Tulving (1999) speculated that one reason for the vulnerability of episodic memory to different kinds of brain dysfunctions is that this form of memory was the last to evolve phylogenetically (i.e., in the evolution of the human beings) and is also the latest to develop ontogenetically. Perhaps as a function of its evolved nature, a number of brain regions support episodic remembering. Brain imaging evidence suggests that both encoding and retrieval of information activates medial-temporal regions, the frontostriatal circuitry, anterior cingulate, distinct parietal and temporal regions, as well as the cerebellum (Cabeza & Nyberg, 2000). Thus, alterations at any one component in this widespread network may be capable of disrupting performance. This may be a key reason for the apparent sensitivity of episodic memory to diverse conditions that affect brain functioning.

Analogously, at the cognitive level, successful episodic memory functioning rests not only on encoding, storage, and retrieval capabilities, but also on executive and attentional skills, as well as visuospatial and verbal abilities, depending on the nature of the stimulus materials. Thus, again, episodic memory deficits may occur as a function of alterations in a variety of task-relevant cognitive skills.

Although it makes biological sense that episodic memory is a sensitive indicator of preclinical dementia and many other conditions, it is important to note that findings from the meta-analysis referred to above suggest that several other cognitive domains (i.e., perceptual speed, executive functioning) are impaired to an equal degree in preclinical AD, and that global measures of cognition (such as the MMSE), demonstrated the greatest preclinical impairment. Hence, measures that include several cognitive domains, and thus tap the integrity of several brain areas appear to be most sensitive to early signs of AD. This view is consistent with recent evidence that prodromal AD is associated with alterations in multiple brain structures and functions, including volume reductions in cingulate and temporal sulcus (Killiany et al., 2000), posterior cingulate and neocortical temporoparietal regions (Fox et al., 2001), and frontal regions (van der Flier et al., 2002); decreased blood flow in posterior cingulate and precuneus (Kogure et al., 2000); reduced glucose metabolism in temporoparietal regions (Arnáiz et al., 2001); and deposits of amyloid plaques in temporal (Morris & Price, 2001) and frontal (Yamaguchi et al., 2001) cortex.

Similar patterns of cognitive deficits in preclinical AD and VaD

Studies I-IV compared different aspects of cognitive functioning three years before the clinical diagnosis of AD and VaD. The results are summarized in Table 1. The patterns of impairment were similar on both a global measure of cognition (MMSE) and on specific measures of episodic memory. An examination of the individual items of the MMSE showed that all items where impairment was found had an episodic memory referent; hence, episodic memory indeed appears to be
vulnerable in the preclinical phase of both dementia diseases. This is so although the first changes in AD are typically observed in medial-temporal lobe regions (Braak & Braak, 1991; Fox, Warrington, Stevens et al., 1996), whereas VaD is traditionally thought to first affect the frontostriatal circuitry (Chui, 2000; Román & Royall, 1999).

Table 1. Summary of similarities and differences among preclinical AD cases, preclinical VaD cases, and controls in Studies I – IV.

<table>
<thead>
<tr>
<th>Measure</th>
<th>AD vs controls</th>
<th>VaD vs controls</th>
<th>AD vs VaD</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Study I (AD, n = 46; VaD, n = 15</em>; controls, n = 188)</em>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ProM free recall</td>
<td>AD &lt; controls</td>
<td>VaD &lt; controls*</td>
<td>AD = VaD*</td>
</tr>
<tr>
<td>ProM prospective component</td>
<td>AD &lt; controls</td>
<td>VaD &lt; controls*</td>
<td>AD = VaD*</td>
</tr>
<tr>
<td>ProM retrospective component</td>
<td>AD &lt; controls</td>
<td>VaD &lt; controls*</td>
<td>AD = VaD*</td>
</tr>
<tr>
<td>RetM free recall</td>
<td>AD &lt; controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encoding</td>
<td>AD &lt; controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrieval</td>
<td>AD &lt; controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forgetting</td>
<td>AD &lt; controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study II (AD, n = 170; VaD, n = 35; controls, n = 494)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE total</td>
<td>AD &lt; controls</td>
<td>VaD &lt; controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>MMSE orientation to time</td>
<td>AD &lt; controls</td>
<td>VaD &lt; controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>MMSE orientation to place</td>
<td>AD &lt; controls</td>
<td>VaD &lt; controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>MMSE delayed recall</td>
<td>AD &lt; controls</td>
<td>VaD &lt; controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td><strong>Study III (AD, n = 43; VaD, n = 15; controls, n = 149)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random recall</td>
<td>AD &lt; controls</td>
<td>VaD &lt; controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>Organized recall</td>
<td>AD &lt; controls</td>
<td>VaD = controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>Word recognition</td>
<td>AD &lt; controls</td>
<td>VaD &lt; controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>Face recognition</td>
<td>AD &lt; controls</td>
<td>VaD &lt; controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>Block design</td>
<td>AD &lt; controls</td>
<td>VaD = controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>Clock setting</td>
<td>AD &lt; controls</td>
<td>VaD = controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>Clock reading</td>
<td>AD = controls</td>
<td>VaD = controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>Category fluency</td>
<td>AD &lt; controls</td>
<td>VaD = controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>AD &lt; controls</td>
<td>VaD = controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>Digit span – forward</td>
<td>AD = controls</td>
<td>VaD = controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td>Digit span – backward</td>
<td>AD = controls</td>
<td>VaD = controls</td>
<td>AD = VaD</td>
</tr>
<tr>
<td><strong>Study IV (AD, n = 66; VaD, n = 20; controls, n = 267)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category fluency</td>
<td>AD &lt; controls</td>
<td>VaD = controls</td>
<td>AD &lt; VaD*</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>AD &lt; controls</td>
<td>VaD &lt; controls</td>
<td>AD = VaD</td>
</tr>
</tbody>
</table>

* Data not included in Study I

The hippocampus and related areas are strongly implicated in episodic remembering based on evidence from both lesion (Squire & Zola, 1998; Vargha-Khadem et al., 1997) and imaging (Fox, Warrington, Freeborough et al., 1996; Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996) studies. However, the frontostriatal network is also critically involved in episodic encoding and retrieval, as demonstrated in lesion (Kopelman & Stanshope, 2002; Schacter, 1987) as well as imaging (Buckner, Kelley, & Petersen, 1999; Cabeza & Nyberg, 2000) work. Thus, a functionally similar
impairment of episodic memory in preclinical AD and VaD is not biologically unreasonable, although there may be etiological differences regarding the extent of impairment in different brain areas.

Further support for the view that episodic memory may be similarly impaired in preclinical AD and VaD comes from unpublished data from the KP (see Table 1). Specifically, these data show that the similarities in patterns of episodic memory deficits may extend to ProM as well. In VaD, approximately 13\% (AD = 11\%, controls = 33\%) were successful in the free recall task and about 60\% (AD = 56\%, controls = 80\%) successfully remembered the task when provided with a cue. Additionally, about 40\% of the prodromal VaD cases (AD = 43\%, controls = 20\%) failed on the retrospective component of the ProM task, and about 22\% (AD = 19\%, controls = 41\%) succeeded on the prospective component. Hence, the impairment appears to generalize across different types of episodic memory also in VaD. These data were derived from 15 preclinical VaD cases who were diagnosed with dementia either at first or second follow-up in the KP, and who had ProM data three years before incidence.

The fact that the VaD cases showed similar ProM (and RetM) impairment as the AD cases is interesting in view of the fact that ProM is thought to be more frontally mediated (Burgess et al., 2001; Okuda et al., 1998), whereas RetM is more contingent on medial-temporal lobe regions (Convit et al., 2000; Nyberg, McIntosh et al., 1996; Small, Perera, DeLaPaz, Mayeux, & Stern, 1999). Thus, these unpublished data provide additional evidence against a bold version of the hypothesis that AD and VaD are distinguishable entities across tasks that span the frontal-medial-temporal dimension.

Figure 6. Category and letter fluency performance across group at baseline and follow-up.
By contrast Study IV showed that verbal fluency could differentiate between the preclinical dementia disorders. Hence, in this case it seems that preclinical AD and VaD can be separated on the basis of cognitive tasks that differentially tap the medial-temporal lobes and the frontal cortex. Specifically, category fluency was more impaired in preclinical AD, whereas letter fluency was equally impaired in the preclinical stages of these dementia disorders. This pattern may have a dual origin: (a) Category fluency is more dependent on medial-temporal regions, whereas letter fluency is more dependent on frontal regions; and (b) Although frontal alterations may be present before diagnosis in both AD and VaD, the degree of medial-temporal involvement may be greater in AD. However, at follow-up, when a clinical diagnosis could be made the difference disappeared (see unpublished data in Figure 6). These results suggest that at the time of diagnosis, the pathologies of both diseases have become more widespread and the differential pattern can no longer be observed. This suggests an interesting possibility with regard to the timing in the differentiation between these dementia disorders. Specifically, specific cognitive tests may be differentially sensitive in distinguishing between the dementia disorders at certain time points in the early pathogenesis of AD and VaD.

The cognitive similarities observed in the preclinical stages of AD and VaD, despite differing etiologies may have several reasons. First, in the KP (much like in other related studies), the diagnosis of dementia (both AD and VaD) is based on DSM-III-R criteria. In these criteria, episodic memory needs to be impaired in order to receive a dementia diagnosis. This might bias the results such that some cases of VaD, who may display other cognitive deficits, may have been missed in the diagnostic procedures. However, as mentioned in the previous section, the episodic memory deficits in both diseases may be due to the fact that this type of memory is particularly vulnerable to all kinds of insult to the brain, with disruption at multiple regions being able to cause impairment. Thus, a more likely reason for the similar cognitive deficits may be that there is much overlap with regard to underlying brain pathology in AD and VaD (de la Torre, 2002; Shi, Perry, Smith, & Friedland, 2000). Cerebrovascular pathology is present in most AD cases (Kalaria & Ballard, 1999) and some researchers argue that AD in fact is a vascular disorder (de la Torre, 2002, 2004).

Another factor to take into account here is the possibility that the cognitive impairment in AD starts earlier than that in VaD. A recent study showed no reliable differences between those who would be diagnosed with VaD within the next 6 years and non-demented controls, on the total score or individual items of the MMSE (Laukka, Jones, Fratiglioni, & Bäckman, 2004). Three years before diagnosis group differences could be observed, much like the findings in Study II. Note that deficits on MMSE total score and the delayed recall item were observed among prodromal AD cases six years before diagnosis (Small et al., 2000). Thus, these results may possibly reflect that a preclinical phase with cognitive deficits exists for a longer period of time in AD as compared to VaD. In that case, time to diagnosis becomes an important variable to consider when trying to detect differences between the dementias in their preclinical stages. Shorter retest intervals than those used in the KP may be necessary to address this issue.
How early can cognitive deficits be detected?

An interesting issue in this context is the length of the preclinical phase in dementia. Obviously, it is important to identify persons who are at risk of dementia as early as possible to maximize intervention efficacy, but such an endeavor may also contribute to our understanding of the pathogenetic process. The question is then how early cognitive deficits can be detected in those who will be diagnosed with dementia at some later point? In the KP, cognitive deficits have been demonstrated approximately seven years before diagnosis in AD (Small et al., 2000), and three years before diagnosis in VaD (Study II-IV). These studies are very restricted in the sense that the sample was very old at the start of the study (75 + years). In other longitudinal population-based studies, where the initial inclusion age has been lower, cognitive deficits have been observed more than 10 years before dementia diagnosis (Elias et al., 2000). However, also these samples are limited to older age ranges, restricting the possibility to estimate when cognitive deficits first can be observed. A few studies have shown that lower cognitive performance measured early in life, such as poorer linguistic ability in the 20s (Snowdon et al., 1996) and lower childhood intelligence (Whalley et al., 2000), were associated with dementia incidence in old age. Hence, there may be reasons to believe that persons at increased risk of dementia can be detected rather early on in life, at least on a group level. However, these data may be interpreted in terms of vulnerability or less cognitive reserve, rather than as early markers of dementia. Educational attainment, which has been used as a proxy for cognitive reserve capacity, may delay the clinical onset of dementia (Alexander et al., 1997; Stern et al., 1994), and may also be beneficial in terms of rate of cognitive change after diagnosis (Le Carret et al., 2005), although there are mixed findings regarding the latter issue (Katzman et al., 1983; Qui, Bäckman, Winblad, Agüero-Torres, & Fratiglioni, 2001; Stern, Tang, Denaro, & Mayeux, 1995).

The fact that dementia becomes more prevalent with increasing age is an interesting fact to consider in relation to the length of the preclinical phase. The prevalence of dementia increases greatly across late adulthood. For example, at the age of 60 years approximately 1% of the population is demented, whereas at the age of 80 the prevalence is around 20% (Fratiglioni, Launer et al., 2000). The incidence of dementia continues to increase also in the oldest old (95+), where the prevalence has been estimated to about 48% (von Strauss, Viitanen, De Ronchi, Winblad, & Fratiglioni, 1999). These data pose an intriguing question: If all individuals were to live long enough, would they then all become demented? Prevalence figures indeed suggest that this possibility is not completely unlikely. However, in very old age, dementia becomes increasingly difficult to diagnose, as it is difficult to differentiate from normal aging. One main reason thereof is that sensory impairments become more common, and very old persons find it difficult to complete cognitive tests. Further, sample sizes decrease with increasing age and the power to observe differences between those who are demented and those who are not, is reduced. However, this intriguing issue may be resolved in the future, given the marked increase in life expectancy in the years to come. An interesting implication of this possibility is that if most, or even all, persons are destined to get dementia if they live long enough, then most, or even all, persons are in a preclinical stage of dementia from very early on in life. Consequently, what
we observe as predictors of dementia are in fact predictors of the proximity to dementia (or death). In this type of research, then, the best we can do is to compare people at different preclinical stages of the disease. Observations of dementia pathology (i.e., plaques and tangles) in older persons who have not received a dementia diagnosis before dying (Jellinger & Attems, 2005; Schmitt et al., 2000), provide further support for this line of reasoning. This may also be a reason for the overlap in cognitive functioning between those who we have defined as being in the preclinical stage of dementia and those defined as non-demented, a topic that will be discussed in the next section.

**Are cognitive tests sufficient to detect future dementia cases?**

A key purpose of research on preclinical AD and VaD is to identify early markers of impending dementia. And clearly, differences between those who will render either an AD or a VaD diagnosis are observed several years before diagnosis. However, there is a great overlap in cognitive performance between those who will and those who will not develop dementia across a certain time interval. An overlap between 41 and 62% was shown on all measures revealing impairment in the meta-analysis of preclinical AD (Bäckman et al., in press), including those that showed the greatest group differences (i.e., global cognitive function and episodic memory). This is an important limitation, because it makes it extremely difficult to implement this information on an individual level to predict who will become demented.

In related research, different classificatory systems (e.g., Mild Cognitive Impairment or MCI, Cognitive Impairment, No Dementia or CIND) have been used to identify cognitively impaired persons at risk of developing dementia. These persons are then followed prospectively over a period of time, with dementia being diagnosed at follow-up assessment. However, those classified as cognitively impaired is a rather heterogeneous group of people, some of whom become demented, others die, and some remain stable or even improve over the retest interval (Larrieu et al., 2002; Palmer, Wang, Bäckman, Winblad, & Fratiglioni, 2002). This clearly indicates that cognitive tests are not sufficient in detecting future dementia cases.

Having said that, both prospective studies of the above kind (Palmer, Bäckman, Winblad, & Fratiglioni, 2003) and retrospective studies (Small et al., 1997) have shown that including several cognitive difference variables into the same prediction model greatly improves predictivity. However, whereas these models typically are excellent at determining who will remain non-demented over the retest period, they only identify a fraction of those who eventually will receive a dementia diagnosis.

One way of enhancing sensitivity in the prediction models may be to include other categories of variables that have been associated with dementia incidence. This possibility will be discussed in the final section of this thesis, in which avenues for future research are outlined.

**Progression of cognitive decline**

Cognitive functioning declines at different rates in AD (e.g., Clark et al., 1999; Wilson et al., 2000), although most individual-difference variables appear to have little effect on disease progression in clinically manifest AD. Hence, the disease appears to make persons with AD cognitively more similar. Study V extended these
findings to the preclinical phase of the disease. Although persons destined to get AD within a few years showed variability in rate of cognitive decline, increasing number of recent diseases was the only variable related to rate of decline. Hence, the influence of many individual-difference variables that are associated with cognitive performance in normal aging (e.g., demographic factors, depression, vitamin status, and substance use) or are implicated as risk factors for AD (e.g., ApoE genotype, poor social network), appear to be overshadowed by the dementing process already before the clinical diagnosis of AD. A similar lack of reliable associations between predictor variables and rate of cognitive decline has been observed in other recent studies (Storandt, Grant, Miller, & Morris, 2002; Wilson et al., 2000).

The fact that so few other variables were related to rate of cognitive decline in Study V could possibly reflect at least two factors. The first concerns the analytical methods used in the studies. Traditional regression analysis may not be sensitive enough to identify factors that are related to variability of cognitive decline. Other analytical methods, such as hierarchical linear modeling (Raudenbush & Bryk, 2002) may be more sensitive in this regard.

Second, in Study V, the selection of predictor variables was, of course, made on the basis of the data available in the KP. It is possible that other variables than those chosen for this study would be related to rate of progression in preclinical AD. For example, a candidate variable that was not examined, although it is a risk factor for AD, is previous head trauma (Lye & Shores, 2000; Plassman et al., 2000). Other variables that would be of interest to examine in this context are lifestyle variables such as those related to social, physical, and cognitive activity patterns. Many recent studies (see Fratiglioni, Paillard-Borg, & Winblad, 2004 for an overview) have linked such variables to dementia incidence, but it remains unknown whether they also influence rate of preclinical cognitive change. In addition to providing knowledge on the nature of early disease development, data on variables that modify rate of preclinical decline can contribute to the management of early AD individuals. With regard to the findings from Study V, perhaps preventing comorbid disease can be one way of postponing the time of clinical diagnosis.

**Limitations**

The external validity of all studies in the present thesis can be considered to be high. The studies were based on data from a population-based study including all persons in a certain geographical area. Age and gender distributions were similar to those in other parts of Sweden. Further, the dropout rates in the KP have been found to be very low (von Strauss et al., 1999). However, several limitations concerning the empirical studies deserve mentioning.

**The sample**

Even in a rather large epidemiological study, the number of incident VaD cases is very small, which limits the power in the analyses. Therefore, it is possible that the preclinical cognitive deficits in VaD are underestimated in the current studies. In order to increase the number of VaD cases, we aggregated data from two phases. Even so, the number of VaD cases remained rather low, especially when variables from the complete cognitive test battery were examined in Study III.
In Study I-III the sample sizes were further reduced because persons with depression and other psychiatric disorders were excluded (in Study IV and V, persons with depression were included). However, it is debatable whether it is correct to exclude persons with, for instance, depression, as this can be a marker of early dementia rather than a comorbid disorder (Berger, Fratiglioni, Forsell, Winblad, & Bäckman, 1999). Furthermore, these are the kinds of problems that people present with when seeing a health professional. Hence, it can be argued that persons with depression should have been included. However, in Study I-III, the purpose was to investigate AD and VaD in their purest preclinical form, and also to compare VaD cases to AD cases and healthy controls. Furthermore, the screening procedure was the same for all three groups. Thus, although the external validity may be somewhat jeopardized by the exclusion criteria adopted, these criteria likely increased the internal validity of the studies.

In addition, the findings from all studies in this thesis can only be generalized to the very old population, as the persons included in the KP were 75 years of age or older when recruited. Although the bulk of cognitive dementia research indicates that age (and onset age) influence performance relatively little, the findings obtained in all studies need to be replicated in samples with younger age groups. Indeed, judging from a recent meta-analysis on cognitive deficits in preclinical AD (Bäckman et al., in press), the degree of cognitive impairment can be expected to be greater in younger elderly individuals. Specifically, in this analysis, the size of the preclinical impairment in tasks assessing episodic memory and global cognitive functioning was larger in persons below 75 years of age than in those 75 years and older.

The measures

The cognitive test battery in the KP specifically targeted episodic memory. Other domains such as executive functioning and working memory, which would have been of interest for example in the early identification of VaD, or in differentiating AD and VaD, were largely ignored. Thus, although these studies yield a reasonable picture of episodic memory deficits in preclinical AD and VaD, other areas of theoretical interest were missed and should be thoroughly investigated in future research on preclinical dementia.

Some of the cognitive measures, particularly the ProM task (Study I) and the MMSE (Studies II and V) have very restricted variability. The ProM task and some items in the MMSE only vary between pass and fail. In these cases, floor and ceiling effects are difficult to avoid. Obviously, ceiling effects are particularly relevant for persons who are cognitively intact, and floor effects are pertinent for those whose cognitive functions are severely compromised. In these studies, the sample sizes may partly have counteracted these concerns, and significant effects were found despite the poor metric properties of these measures. Preferably though, the findings need to be replicated with more refined measures. This was done in the case of preclinical VaD in Study III.

A limitation in Study V has to do with missing data on some of the variables for almost half of the persons included in the study. This results in at least two potential problems. The first problem concerns low power in the analyses. After all, the time frame in the study was relatively short, only about three years. Further, the study included a homogeneous group of people; all were destined to get AD during this
short period of time. For variables, such as vitamin B₁₂ (n = 126 rather than 230), it is possible that the sample became too small to detect an effect of the variable. However, the p-values for the effect of B₁₂, as well as for the other variables found to be unrelated to rate of preclinical change, were not even close to conventional significance. A second, albeit related problem, is that the persons who had no data on a certain variable could differ from the persons included. However, the risk of this possibility should be rather small, because of the random sampling procedure employed in the initial phase of the KP. Furthermore, persons with missing data did not differ from those who had complete data on the demographic variables.

The dementia diagnosis

A major caveat in these studies is that the diagnosis of dementia and the differential diagnosis of dementia types were based on clinical information only. The diagnoses were not supported by neuroimaging data or verified by post-mortem neuropathological evidence. This problem is not unique to the KP, but rather shared by many large epidemiological studies, in which neuroimaging and neuropathological examinations are difficult to implement. However, a three-step diagnostic procedure was used, with a high inter-rater reliability (Fratiglioni et al., 1997), which increases the reliability of the diagnosis. Further, differential diagnosis was supported by HIS scores. These have been found to accurately differentiate between AD and multi-infarct dementia, as confirmed by histopathological evidence (Moroney et al., 1997). Hence, the findings may apply at least to this category of VaD.
Avenues for Future Research

Although our knowledge about the preclinical phase of dementia – the grey zone between normality and pathology – has increased substantially over the past decade, there are issues that remain unclear. In this final section, I will outline some avenues for future research that seek to address these issues. As noted, a large number of factors have been implicated in the AD process. These include, but are not limited to, chronological age (Burns, Jacoby, & Levy, 1991; Wilson et al., 2000), sex (Fratiglioni et al., 1997; Gambassi et al., 1999), APOE genotype (Bondi et al., 1999), social factors (Fratiglioni, Wang et al., 2000), personality (Balsis et al., 2005; Wilson et al., 2003), blood pressure (Qiu, 2003), and cognitive performance (Bäckman, Jones, Berger, Laukka, & Small, 2004). However, it is not always clear at which stage and in which way these factors are implicated. Specifically, the issue is whether a certain factor linked to the occurrence of AD should be characterized as a risk factor, a precipitating factor (i.e., a factor that accelerates the transition from the preclinical to the clinical stage), or as an early marker.

As mentioned previously, cognitive impairment has been demonstrated in preclinical AD several years (Elias et al., 2000; Small et al., 2000), or even decades (Snowdon et al., 1996; Whalley et al., 2000) before actual diagnosis. During most of this time there seems to be stability in the impairment, where the preclinical AD cases perform at a consistently lower level than persons who are not destined to become demented. A few years before diagnosis those who will go on to develop AD show precipitous decline in cognitive functioning (Bäckman, Small, & Fratiglioni, 2001; Hall et al., 2000; Hall et al., 2001; Small et al., 2000), eventually leading to a dementia diagnosis. This pattern could be interpreted to mean that accelerated cognitive decline in AD may not be expected until various biological events (e.g., the accumulation of amyloid and neurofibrillary tangles, inflammation, oxidative stress, loss of synapses, death of neurons) have reached a certain critical threshold (Hardy & Allsop, 1991). This notion rests on the assumption that the brain is capable of counteracting AD-related neural changes to a point at which compensatory responses are no longer possible. Indeed, there is evidence from cognitive psychology (Verhaegen, Marcoen, & Goossens, 1992), neuroimaging (Cabeza, 2002), histopathology (Schmitt et al., 2000), and neurochemistry (DeKosky et al., 2002) that the aging brain possesses compensatory capabilities. However, it is unclear which factors are implicated in the acceleration of cognitive deterioration in the transition from preclinical to clinical AD (i.e., which factors are precipitating factors).

Previous studies, including Study V in this thesis, suggest that it is difficult to relate individual-difference variables to rate of preclinical cognitive decline (Bäckman, Jones, Small, Agüero-Torres, & Fratiglioni, 2003; Storandt et al., 2002; Wilson et al., 2000). The negative findings may reflect that individual-difference variables are overshadowed by emerging pathogenetic processes. However, they could also, in part, be a function of the analytical methods employed (e.g., ANOVA or regression procedures with listwise deletion). These methods may not be sensitive enough in identifying factors that share systematic relationships with rate of cognitive change in preclinical AD. Other analytical tools such as multilevel modeling may be better adapted for these purposes (Johansson et al., 2004; Reynolds, Finkel, Gatz, & Pedersen, 2002). These kinds of models may be more sensitive in identifying precipitating factors.
during the preclinical phase of dementia. In addition, such models may also be useful in
determining the extent to which certain variables remain stable, increase, or decrease in
importance as a function of time to diagnosis, regarding their relationship to final
dementia status. Information pertaining to this issue could help in delineating whether a
certain factor (e.g., depressive symptoms, social involvement) should be conceived of
as a risk factor, a precipitating factor, or an early marker of dementia.

A related unresolved issue pertains to the specific cognitive abilities for which
precipitous decline can be detected. Although there is consensus that persons who will
develop AD show precipitous cognitive decline during the last 2-3 years before
diagnosis (Chen et al., 2001; Rubin et al., 1998), evidence is mixed regarding whether
accelerated decline can be observed earlier. KP data demonstrate stability of the degree
of preclinical impairment in AD for global cognitive functioning (Small et al., 2000)
and episodic memory (Bäckman et al., 2001) from six to three years before diagnosis.
However, in two studies (Hall et al., 2000, 2001) accelerated decline in episodic
memory was demonstrated more than 5 years before diagnosis, although speeded
measures of performance IQ exhibited accelerated decline around 2 years before
diagnosis. These equivocal findings may be contributed to sample selection methods.
Specifically, stricter selection criteria (e.g., removal of persons with other conditions
that affect cognitive functioning) may make it possible to observe accelerated cognitive
decline earlier. However, it could also be the case that different cognitive abilities are
differentially sensitive at certain time points during the preclinical stage. For example,
episodic memory may show accelerated decline earlier in the preclinical stage, whereas,
for example, speed and executive functioning may show accelerated decline later (Chen
et al., 2001; Hall et al., 2000). Further, different processes within an episodic memory
task (e.g., encoding, consolidation, and retrieval) may be affected at different time
points. Additional information on these important issues require longitudinal
assessment using relatively short retest interval as well as careful selection of cognitive
indicators across multiple domains of interest.

Another interesting issue to consider is whether the course of cognitive decline,
with relative stability for several years followed by precipitous decline and diagnosis,
is unique to AD. A recent study from the KP demonstrated that preclinical deficits in
VaD can be detected three, but not six, years before diagnosis (Laukka et al., 2004).
This may suggest that the preclinical phase of VaD is characterized by accelerated
decline only, and not by a long, (and rather stable) preclinical phase as observed in
AD. More studies on persons who will receive a VaD diagnosis, with longer follow-
up intervals are needed in order to resolve this issue.

Finally, a key issue in future studies on preclinical dementia is the great overlap
in cognitive performance scores between incident dementia cases and controls, as
discussed in a previous section. Obviously, in order for such research to be clinically
useful, the overlap needs to be reduced considerably. Toward this end, including
indicators of other domains of functioning implicated in the dementia process may
help in identifying at-risk individuals. These include multiple measures of brain
structure and function such as volumetric measures (van der Flier et al., 2002),
glucose metabolism (Silverman et al., 2001), blood flow (Kogure et al., 2000), CSF
markers of amyloid deposition and neurofibrillary tangles (Klunk, 1998), and white-
matter hyperintensities (Wolf et al., 2000). It also includes markers for genetic
predisposition such as presence of the APOE-ε4 allele (Farrer et al., 1997) as well as
subjective memory complaints (Geerlings, Jonker, Bouter, Adèr, & Schmand, 1999; Pearman & Storandt, 2004), family reports of cognitive impairment (Daly et al., 2000), and depressive symptoms (Berger et al., 1999). The identification of precipitating factors may provide further help in differentiating between preclinical AD and cognitive impairment of other origins. Possible precipitating factors include medical events such as unrecognized hypertension (Launer et al., 2000), head trauma (Plassman et al., 2000), diabetes (Hassing et al., 2002), and stroke (Snowdon et al., 1997) as well as social factors such as isolation (Fratiglioni, Wang et al., 2000) and previous life style and leisure activities (Crowe, Andel, Pedersen, Johansson, & Gatz, 2003).

From a clinical perspective, the point is that although a variety of classes of factors may show relatively good predictive accuracy in identifying persons in a preclinical phase of AD and VaD, these factors are rarely used in the same prediction model. By combining predictors from different behavioral, clinical, and biological domains in the detection of preclinical AD and VaD cases, identification accuracy may be enhanced. Such a multivariate approach should not only increase overall prediction accuracy; it also enables examining possible interactive effects among various preclinical markers. In addition, this approach provides a means for comparing the relative efficiency of different categories of preclinical markers in identifying AD and VaD cases at the earliest possible time. Thus, the prediction models that emerge could be tested for their ability to identify clusters of individuals with various probabilities to develop dementia, clusters that may also respond differentially to pharmacological interventions.
References


References


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References


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Appendix

Dissertations from the Division of Geriatric Epidemiology and Medicine, Department of Neurotec, Karolinska Institutet, 1998–2004

1998


Bogdanovic Nenad. Towards a multifaceted approach in neuropathological diagnosis.

Fagerberg Ingegerd. Nursing students’ narrated, lived experiences of caring, education and the transition into nursing, focusing on care of the elderly.


Hassing Linda Björk. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden).

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis).


Pei Jin-Jing. Protein phosphatases and kinases implicated in Alzheimer’s disease abnormal tau phosphorylation.

Tham Kerstin. Unilateral neglect: Aspects of rehabilitation from an occupational therapy perspective.


1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and postdeath experiences.


Elffors Lars. Hip fractures – A European perspective.

Jelic Vesna. Focus on quantitative EEG in relation to genetic, biochemical and neuroimaging markers.

Jensen Malene. Amyloid â-peptide and tau the diagnosis and pathogenesis of Alzheimer’s disease.

Sonde Lars. Low-TENS treatment on post-stroke paretic arm. (Licentiate thesis).

von Euler Mia. Experimental spinal cord injuries – a histopathological, neurological, and pharmacological study in the rat.

Zhu Li. Cerebrovascular disease and dementia. A population-based study.

Zou Li-Ping. Immunoregulation and immunotherapy in experimental autoimmune neuritis.

2000

Andreasen Niels. Search for reliable diagnostic markers for Alzheimer’s Disease.

Ebbeskog Britt. Elderly people’s daily living with chronic leg ulcer: Evidence and suffering experience. (Licentiate thesis, in collaboration with the Department of Science and Health, University of Karlskrona/Ronneby, Sweden).

Emami Azita. “We are deaf, though we hear; we are dumb, though we talk; we are blind, though we see”. Understanding Iranian late-in-life immigrants. Perceptions and experiences of health, illness and culturally appropriate care.

Eriksson Charlotta. Region-specific expression of the interleukin-1 system in rat brain following endotoxin challenge and excitotoxic neurodegeneration.

Hansebo Görel. Assessment of patients’ needs and resources as a basis in supervision for individualised nursing care in nursing home wards.

Herzberg Annika. Relatives’ and nursing home staff’s experiences of and views on each others. (Licentiate thesis).

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden).

Jonsson Hans. Anticipating, experiencing and valuing the process from worker to retiree. A longitudinal study of retirement as an occupational transition.


Lilja Margareta. Elderly disabled persons in the home setting. Aspects of activities in daily life.


Palo-Bengtsson Liisa. Social dancing as a caregiver intervention in the care of persons with dementia.

Pham Therese. Effects of neonatal handling and enriched environment of neurotrophins and cognitive function.

Robinson Petra. Younger persons with suspected and early stage dementia: Their experiences, concerns and need for support. (Licentiate thesis).

Skog Margareta. Teaching for learning and learning for teaching in care of elderly with dementia at Silviahemmet.
Cognitive Functioning in the Preclinical Stages of AD and VaD

Sunvisson Helena. Att beskriva och utvärdera betydelsen av interventions-program riktade till personer med Parkinson sjukdom för skapande av nya möjligheter att hantera vardagen. (Licentiate thesis).


2001


Froelich Fabre Susanne. Genetic studies of frontotemporal dementia.


Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.


Sonde Lars. Rehabilitation after stroke. Effects of length of stay and treatments to facilitate motor recovery after stroke.

Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.


2002


Giron Stella-Maria T. The rational use of drugs in a population of very old persons.

Hemmingsson Helena. Student-environment fit for students with physical disabilities.

Herzberg Annika. We, not them and us – a utopia? Relatives’ and nursing home staffs’ views on and experiences with each other.

Lindau Maria. Clinical differentiation between frontotemporal dementia and Alzheimer’s disease.
Appendix

Nilsberth Camilla. Distribution and pathophysiological role of amyloid precursor protein and presenilin 1.

Randers Ingrid. Upholding older adults’ innate and inherent dignity within a caring context.


2003

Abbas Ahmed N. Immunomodulation of cytokine and chemokine production in animal models of neuroinflammatory and neurodegenerative disorders.

Bao Lei. Immunomodulation and immunopathogenesis in the autoimmune disease with emphasis on autoimmune neuritis and arthritis.

Ebbeskog Britt. Elderly patients with slow-healing-leg ulcers.

Götell Eva. Singing, background music and music-events in the communications between persons with dementia and their caregivers.


Mulugeta E. Muscarinic M1 and M4 receptor subtypes in normal and pathological conditions in the central nervous system: Studies on human and animal tissues using subtype selective ligands.

Saletti Anja. Nutritional status in elderly receiving municipal services and care. (Licentiate thesis)

Sunvisson Helena. The embodied experience of living with Parkinson’s disease.

Zhu Yu. Immunoregulation of experimental autoimmune neuritis focuses on cell immunity.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer’s disease

Chen Zhiguo. Excitotoxic neurodegeneration in mouse brain. Roles of immune cells and cytokines

Cornelius, Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project

Kostyszyn Beata. Studies of presenilin function in neurodegeneration and in human embryonic CNS during development

Popescu Bogdan O. Cell death and signal transduction pathways in Alzheimer's disease: The role of presenilin 1

Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study
Cognitive Functioning in the Preclinical Stages of AD and VaD

Palmer Katie. Early detection of Alzheimer’s disease and dementia in the general population.


Flood Fiona. Alzheimer’s disease-related amyloid precursor protein and presenilin genes: Normal function and pathophysiology.


El-Bakri Nahid Karrar. Estrogen effects on different neurotransmitters in rat hippocampus: Implications for cognitive function.

2005

Adikari Sanjaya. Cytokine-modulated dendritic cell immunotherapy in autoimmune diseases.

Larsson Mauleon Annika. Care for the elderly – a challenge in the anaesthesia context.

Häggström Elisabeth. Municipal care for older people – experiences narrated by caregivers and relatives.

Kihlgren Annica. Older patients in transition – from home care towards emergency care.

The above can be ordered from:

Sektionen för Geriatrik, Huddinge Sjukhus, B84, S-14186