From Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden

# PROSPECTIVE AND RETROSPECTIVE MEMORY IN NORMAL AND PATHOLOGICAL AGING

Åsa Livner


Karolinska Institutet

Stockholm 2009

Published by Karolinska Institutet. Printed by E-print


ISBN 978-91-7409-476-3

*Till Isak och Linn*

# ABSTRACT

This thesis aims to explore how prospective and retrospective memory are affected by health in old age. In this regard, we have focused on dementia disorders, depressive symptomatology, and thyroid functions. Prospective memory involves remembering to perform actions, such as paying bills or taking one's medication. Retrospective memory involves remembering previous events or previously learned information, such as the content of a book. The memory process can be divided into three stages: encoding (forming new memories), storage (consolidation of information), and retrieval (remembering what we have previously encoded).

In **Study I**, three groups were included: persons with Alzheimer's disease, persons with vascular dementia, and healthy control persons. The groups were compared on prospective and retrospective memory tasks. The two dementia groups were impaired compared to controls on both prospective and retrospective memory, and the impairment was evident for all stages of the memory process (i.e., encoding, storage and retrieval). However, there were no differences between the two dementia groups regarding the extent or pattern of memory deficits.

**Study II** examined how prospective and retrospective memory were affected during the so called preclinical phase of Alzheimer's disease (i.e., before the disorder had progressed so much that it could be diagnosed). Both prospective and retrospective memory was impaired three years prior to diagnosis. In addition, the results showed that more people at risk of developing Alzheimer's disease could be identified when the combined results from the two memory tasks were taken into account, compared to using only one task at the time. The unique contributions of both memory measures indicate that they are, at least in part, separable entities. When studying retrospective memory in more detail, we found that the impairment in preclinical Alzheimer's disease was present across all three memory stages.

**Study III** examined how depressive symptoms affected prospective and retrospective memory. Depressive symptoms refers to a continuum, ranging from states (such as mild dysphoria) that are common also among healthy persons to severe depressive disorders. The results showed that retrospective memory was negatively affected by depressive symptoms. The effect was evident for storage and retrieval, whereas there was a non-significant trend in the same direction for encoding. Prospective memory, however, was unaffected by depressive symptoms. If these results are valid, this can help us separate persons with depression from persons with early stage dementia, which in many cases is difficult.

**Study IV** examined the effect of thyroid functioning on prospective memory. Thyroid function was measured through serum levels of two hormones: thyroid stimulating hormone (TSH) and thyroxine (T4). All participants were free from thyroid disorders. In spite of this, the results revealed that persons with higher TSH levels performed better on the prospective memory task. T4 levels were not related to memory performance. Previous research has shown a corresponding association between TSH

and retrospective memory. The conclusion is that thyroid functioning has an impact on cognition, even in the absence of overt disease.

To summarize, both prospective and retrospective memory are sensitive cognitive abilities, easily affected by disorders and other factors related to health. There are, however, some differences with regard to when, and how, these two forms of memory are affected. It is important to investigate this issue further, in order to gain a deeper understanding of the cognitive challenges that persons with different disorders or symptoms are facing. This can, in turn, lead to the development of new cognitive aids. In addition, cognitive psychology research can in some cases help us make faster and more accurate diagnoses.

# SAMMANFATTNING

Syftet med denna avhandling är att undersöka hur det prospektiva och retrospektiva minnet påverkas av hälsan i åldrandet. Mer specifikt har vi fokuserat på demenssjukdomar, depressiva symtom och sköldkörtelfunktion. Med prospektivt minne avses förmågan att komma ihåg att utföra handlingar, exempelvis betala räkningar eller ta sin medicin. Med retrospektivt minne avses förmågan att minnas tidigare upplevda händelser eller tidigare inlärd information, t ex innehållet i en bok. Minnesprocessen kan delas in i tre faser: inkodning (då vi ”kodar in” nya minnen), lagring och framplockning (då vi ska minnas det vi tidigare kodat in).

I **Studie I** jämfördes tre grupper: personer med Alzheimer’s sjukdom, personer med vaskulär demens och friska kontroller på prospektiva och retrospektiva minnestest. De två demensgrupperna presterade på en lägre nivå än kontrollgruppen i både det prospektiva och retrospektiva testet, och detta gällde alla faser i minnesprocessen (dvs inkodning, lagring och framplockning). Däremot fanns inga skillnader mellan de två grupperna med Alzheimer’s sjukdom respektive vaskulär demens avseende graden eller arten av minnessvårigheter.

**Studie II** undersökte hur prospektivt och retrospektivt minne var påverkat i den sk prekliniska fasen av Alzheimer’s sjukdom (dvs innan sjukdomen framskridit så långt att en diagnos kan ställas). Resultaten visade att såväl det prospektiva som det retrospektiva minnet var försämrat tre år innan demensdiagnos. Resultaten visade också att fler personer, som var i riskzonen för att utveckla Alzheimer’s sjukdom, kunde identifieras då resultaten från båda minnestesten kombinerades jämfört med när varje test användes separat. Att båda minnestesten lämnade unika bidrag till prediktionen indikerar att prospektivt och retrospektivt minne är delvis olika kognitiva förmågor. När det retrospektiva minnet undersöktes närmare visade det sig att försämringen gällde samtliga faser i minnesprocessen.

**Studie III** undersökte hur depressiva symtom påverkar det prospektiva och retrospektiva minnet. Med depressiva symtom avses såväl tillstånd (exempelvis lätt nedstämdhet) som är vanliga även hos friska personer som svår depressionssjukdom. Resultaten visade att det retrospektiva minnet påverkades negativt av depressiva symtom. Denna påverkan gällde lagring och framplockning, medan det fanns en icke-signifikant trend i samma riktning för inkodning. Det prospektiva minnet, däremot, var opåverkat av depressiva symtom. Om dessa resultat är valida kan fynden bidra till att särskilja personer med depression från personer med begynnande demens, vilket i många fall är svårt.

**Studie IV** undersökte effekten av sköldkörtelfunktion på det prospektiva minnet. Sköldkörtelfunktion mättes genom nivåerna av två hormon: thyroideastimulerande hormon (TSH) och tyroxin (T4) i blodet. Samtliga personer som ingick i studien var fria från sköldkörtelsjukdomar. Trots detta visade resultaten att personer med högre nivåer av TSH lyckades bättre på den prospektiva minnesuppgiften. Nivåerna av T4 var däremot inte relaterade till minnesförmåga. Tidigare forskning har visat ett

motsvarande samband för det retrospektiva minnet. Slutsatsen är att sköldkörtelfunktion, även då sjukdom uteslutits, kan vara intressant att studera eftersom den har betydelse för kognitionen.

Sammanfattningsvis kan sägas att både det prospektiva och det retrospektiva minnet är känsliga förmågor, som lätt påverkas av sjukdomar och andra faktorer relaterade till hälsan. Det finns dock vissa skillnader i hur dessa två former av minne påverkas vid olika tillstånd. Dessa skillnader är viktiga att kartlägga närmare för att få en bättre förståelse för de kognitiva utmaningar som personer med olika sjukdomar eller symtom står inför. Detta kan, i sin tur, leda till utvecklandet av nya kognitiva hjälpmedel. Dessutom kan forskning inom fältet kognitiv psykologi i vissa fall hjälpa oss att ställa snabbare och mer korrekta diagnoser.

# LIST OF PUBLICATIONS

I. Livner, Å., Laukka, E.J., Karlsson, S., & Bäckman, L (in press). Prospective and retrospective memory in Alzheimer's disease and vascular dementia: Similar patterns of impairment. *Journal of the Neurological Sciences*.

II. Jones, S., Livner, Å., & Bäckman, L. (2006). Patterns of prospective and retrospective memory impairment in preclinical Alzheimer's disease. *Neuropsychology, 20*, 144-152.

III. Livner, Å., Berger, A-K., Karlsson, S., & Bäckman, L. (2008). Differential effects of depressive symptoms on prospective and retrospective memory in old age. *Journal of Clinical and Experimental Neuropsychology, 30*, 272-279.

IV. Livner, Å., Wahlin, Å., & Bäckman, L. *Thyroid Stimulating Hormone and prospective memory functioning in old age*. Manuscript submitted for publication.

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADL | Activities of daily living |
| ANCOVA | Analysis of covariance |
| ANOVA | Analysis of variance |
| CDR | Clinical Dementia Rating Scale |
| CPRS | Comprehensive Psychopathological Rating Scale |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| HIS | Hachinski Ischemic Score |
| MANOVA | Multiple analysis of variance |
| MMSE | Mini-Mental State Examination |
| NINCDS-ADRDA | National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association |
| NINDS-AIREN | National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences |
| PRS | Perceptual representation system |
| TSH | Thyroid Stimulating Hormone |
| T4 | Thyroxine |

# 1 INTRODUCTION

As the number of elderly persons in our society is growing rapidly, research that targets health and living conditions in old age becomes even more important. The Kungsholmen project involves a large, population-based database, which gives us opportunities to gain more knowledge about healthy aging as well as various disorders that are common among elderly adults.

Many of the disorders that are common in old age have effects not only on physical health, but also on mental health including cognition. This is true also for many other variables related to health. The aims of this thesis are to explore a few of these disorders and health-related factors. Although it is known that they may have cognitive repercussions, we need to know more about the nature and extent of these influences.

This thesis will focus on memory, and more specifically on episodic memory which can be described as memory for events that we experience personally. Episodic memory can be further divided into prospective and retrospective memory (Meacham & Singer, 1977). Prospective memory involves remembering to perform actions in the future. This is essential in everyday life, and therefore also highly important to elderly persons and their opportunities to function independently. Still, research on this topic has been sparse. Most research has focused on retrospective memory, which involves remembering information or events from the past. Although retrospective memory has been the focus of attention for a long time, many questions remain unanswered. For example, we need to know more about what specific aspects of retrospective memory that are implicated in different disorders.

This thesis focuses on prospective and retrospective memory functioning in dementia, depressive states, and normal aging. The influence of thyroid functions will also be explored. The results from this research can be useful in several ways. First, we hope that the findings will contribute to a better understanding of some of the difficulties that persons with these disorders are facing. Second, many disorders are currently underdiagnosed. In many cases, such as in early-stage dementia and depression, differential diagnosis is difficult. Increasing our knowledge about the patterns of memory impairment that characterizes each disorder will potentially help us to identify individuals in need of interventions, and to make earlier and more accurate diagnoses. From a more theoretical perspective, an additional aim is to add to our understanding of the cognitive processes involved in prospective and retrospective remembering.

## 1.1 HEALTH IN OLD AGE

### 1.1.1 Dementia disorders

Dementia is one of the most common causes of functional impairment as well as death among elderly persons (Qiu, De Ronchi, & Fratiglioni, 2007). Dementia prevalence rates increases exponentially with increasing age, and among persons 90 years and older approximately 40 percent have a dementia disorder (Qiu, De Ronchi, & Fratiglioni, 2007). Memory loss is a hallmark symptom which is evident early in the disease process, and also included in the diagnostic criteria in the Diagnostic and

Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 1994). In addition to memory impairment, disturbances in at least one of the four following domains must be present: aphasia, apraxia, agnosia, or deficits in executive functioning. Aphasia refers to disturbances in language, apraxia refers to difficulties to carry out motor activities (despite normal motor functions) and agnosia refers to impairment in object recognition (despite normal sensory functions). Executive functioning involves complex behavior such as planning, initiating or inhibiting a response. The disturbances must be severe enough to affect social or occupational functioning, and involve significant decline compared to a previous level of functioning. No other disorders or medical states that could possibly have caused the cognitive impairment should be present.

#### *1.1.1.1 Alzheimer's disease*

The most common dementia disorder is Alzheimer's disease, as it is estimated that 50-70 percent of all dementias are due to this disorder (Qiu, De Ronchi, & Fratiglioni, 2007). This is a neurodegenerative disorder which leads to continuous loss of cognitive and ADL functions.

The pathology behind Alzheimer's disease is not fully understood, although two proteins, namely beta-amyloid and tau are suggested to play an important role. Beta-amyloid is accumulating and forms plaques that surround the neurons. Another mechanism involves intracellular, neurofibrillary tangles formed by tau proteins, that disturb neuronal function (Hardy & Selkoe, 2002). Vascular pathology has also been suggested as a possible cause of neurodegeneration, leading to Alzheimer's disease (de la Torre, 2008). The medial temporal lobe, including the hippocampus, is one of the regions of the brain that is most heavily affected by the pathology, and alterations in this area are evident very early in the disease process. Early alterations are also seen in many other regions of the brain, including the frontal cortex (Braak & Braak, 1997; van der Flier et al., 2002).

The NINCDS-ADRDA criteria (McKhann et al., 1984) are often used in research settings to distinguish Alzheimer's disease from other forms of dementia. Requirements for a diagnosis of possible, probable, and definite Alzheimer's disease are defined in these criteria. For probable Alzheimer's disease, dementia has to be established by a clinical examination and neuropsychological tests. In addition, the diagnosis requires deficits in two or more areas of cognition, progressive worsening of cognitive functioning, no disturbances of consciousness and onset between 40 and 90 years of age. For definite Alzheimer's disease, the criteria listed above have to be fulfilled, and histopathological evidence from a biopsy or autopsy must be present.

#### *1.1.1.2 Vascular dementia*

Vascular dementia refers to dementias caused by various forms of cerebrovascular disease. This is the second most common dementia type, accounting for between 15 and 25 percent of all dementias (Qiu, De Ronchi, & Fratiglioni, 2007). There are several types of vascular dementias, including strategic infarct dementia, multi-infarct dementia and small vessel disease. This variation in subtypes may lead to differential patterns with regard to the cognitive domains affected. Also, for dementia following

stroke, the location of the stroke is of course important (Laukka, Karlsson, MacDonald, & Bäckman, 2009).

The NINDS-AIREN workgroup have agreed on criteria for a diagnosis of possible, probable and definite vascular dementia (Roman et al., 1993). For probable vascular dementia, dementia has to be established, and impairment must be present in memory and at least two other cognitive functions. There should also be evidence for cerebrovascular disease, and for a temporal relationship between the cerebrovascular pathology and the dementia development. For definite vascular dementia, the criteria listed above have to be fulfilled, and histopathological support for the diagnosis should also be available.

#### *1.1.1.3 Mixed dementia*

It is important to note that vascular pathology and neurodegenerative factors often occur and contribute to dementia development simultaneously (Barker et al., 2002; Kalaria & Ballard, 1999). Mixed pathology is particularly common among the very old (Aguero-Torres, Winblad, & Fratiglioni, 1999). This fact, along with the fact that vascular disease can cause neurodegeneration, makes it difficult to separate vascular dementia from Alzheimer's disease and vice versa.

The Hachinski Ischemic Score, or HIS (Hachinski et al., 1975) is frequently used to differentiate between Alzheimer's disease, mixed dementia, and vascular dementia. This score takes into account the presence of signs associated with vascular dementia, such as abrupt onset of the dementia disorder, stepwise deterioration, fluctuating course, and a history of stroke.

#### *1.1.1.4 Preclinical dementia*

The development of dementia is a gradual process. With a longitudinal research design, we have the opportunity to examine cognitive performance in healthy persons who receive a dementia diagnoses later on. Thus, the term preclinical dementia refers to persons who are in an early, yet undiagnosed, stage of a dementia disorder.

There are studies that show that the pathological alterations in the brain of Alzheimer patients starts many years before they receive the diagnoses (Braak & Braak, 1997; van der Flier et al., 2002). It is also well documented that cognitive deficits are present during this early stage (Bäckman, Jones, Berger, Laukka, & Small, 2005; Elias et al., 2000; Jacobs et al., 1995; Small, Fratiglioni, Viitanen, Winblad, & Bäckman, 2000).

Quite recently, researchers have started to direct their attention toward the preclinical phase of vascular dementia, which share many similarities with preclinical Alzheimer's disease in terms of the nature of the cognitive losses (Bäckman & Small, 2007; Laukka, Jones, Small, Fratiglioni, & Bäckman, 2004). It is reasonable to suspect that the vascular risk factors associated with an increased risk of developing vascular dementia, also cause alterations in the brain that lead to cognitive impairment already during the preclinical phase (Laukka, Karlsson, MacDonald, & Bäckman, 2009).

### 1.1.2 Depression

The concept of depression includes a continuum of symptoms ranging from mild dysphoria, which most people experience from time to time, to severe depressive disorders that require psychiatric treatment (Paykel & Priest, 1992; see Figure 1). Two examples of depressive disorders are major depression and dysthymia. A diagnosis of major depression involves a two-week period or longer with pronounced symptoms of either dysphoria or loss of interest for pleasant things, along with other symptoms such as appetite or sleep disturbances, change in psychomotor activity, loss of energy, feelings of guilt, concentration difficulties and suicidal thoughts (American Psychiatric Association, 1994). Dysthymia is a milder form of depression, although more chronic in nature with a duration of at least two years (American Psychiatric Association, 1994).

Depressive disorders are among the most common psychiatric syndromes in old age (Blazer, 2003; Gottfries, 2001). Also among persons who do not fulfil the criteria for any depressive disorder, depressive symptoms frequently occur (Bäckman, Hill, & Forsell, 1996; Paykel & Priest, 1992).

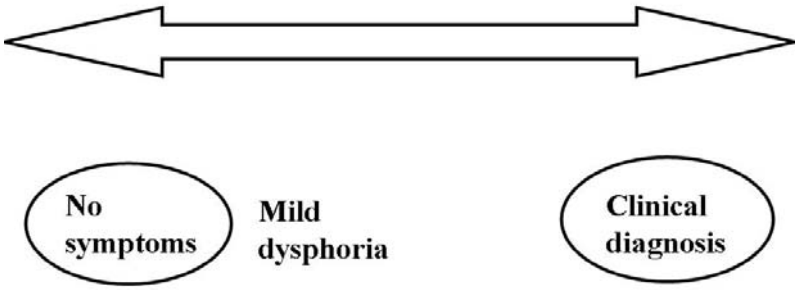


**Figure 1.** A continuity view of depression

Depression is associated with a large number of structural as well as functional changes in the brain, and some of these abnormalities are evident even after symptom remission. The alterations include decreases in hippocampal volume (Campbell, Mariott, Nahmias, & MacQueen, 2004; Steffens et al., 2000; Videbech & Ravnkilde, 2004), and it is known that the hippocampus and the amygdala are very sensitive to the increases in cortisol levels that appear as a result of depression and stress (J. J. Kim & Diamond, 2002). Among the other regions affected by depression are frontal areas. There is evidence for functional changes, as well as volumetric reductions, in the prefrontal cortex among persons with depressive disorders (Drevets, 2000).

### 1.1.3 Thyroid functions

In addition to age-related disorders, numerous other health-related factors are of interest in cognitive aging research. One example is thyroid functions, which will be explored in more detail in this thesis.

Thyroid stimulating hormone (TSH) and thyroxine (T4) levels are two indicators of thyroid functioning. TSH is secreted by the pituitary gland to regulate the levels of thyroid hormones, including T4. Hypothyroidism (i.e., underfunctioning of the thyroid gland) involves lowered levels of T4, which leads to higher levels of TSH through a compensatory mechanism. Correspondingly, hyperthyroidism (i.e., overfunctioning of the thyroid gland) involves raised T4 levels and lower levels of TSH.

Although alterations of the thyroid gland may appear in normal aging, pathological thyroid alterations are also frequent in old age. Yet, many symptoms associated with thyroid disease (such as cardiovascular pathology or muscle dysfunction) are frequently attributed to other disorders or to the general effects of aging. As a result, thyroid disorders are underdiagnosed (Biondi & Cooper, 2008; Griffin & Solomon, 1986). Also, as it is often unclear what constitutes normal and pathological thyroid-hormone levels, there has been much debate about which cut-off to use (Biondi & Cooper, 2008). Therefore, so-called subclinical variations in thyroid functioning are also of interest for researchers, as they may have implications for health.

Studies performed on animals as well as humans have shown that thyroid hormones are important for the metabolic activity in the brain, and that thyroid-hormone deficiency is associated with global reductions in functional brain activity (Bauer et al., 2003). Several studies in this area have investigated limbic-subcortical circuits and the prefrontal cortex, as these regions seem to be very sensitive to the effects of thyroid alterations (Bauer et al., 2003). There is evidence suggesting that variations in thyroid functioning can alter the electrical activity (Munte, Radamm, Johannes, & Brabant, 2001), perfusion (Fukui, Hasegawa, & Takenaka, 2001), and metabolism (Bhatara, Tripathi, Sankar, Gupta, & Khushu, 1998; Fukui, Hasegawa, & Takenaka, 2001) in prefrontal regions.

## 1.2 MEMORY

### 1.2.1 Memory systems

As portrayed in Figure 2, human memory is commonly divided into different subsystems, with partly different functions and properties (Tulving, 2002). First, memory can be separated into short-term and long-term memory, with short-term memory referring to memories that are kept active in mind for a shorter period, but never encoded into long-term memory (and thus forgotten once we direct our attention elsewhere). Within short-term memory, primary memory deals with untransformed information (such as remembering a series of digits) and working memory deals with information that requires other mental operations (such as performing arithmetic tasks or remembering a series of digits in reverse order).

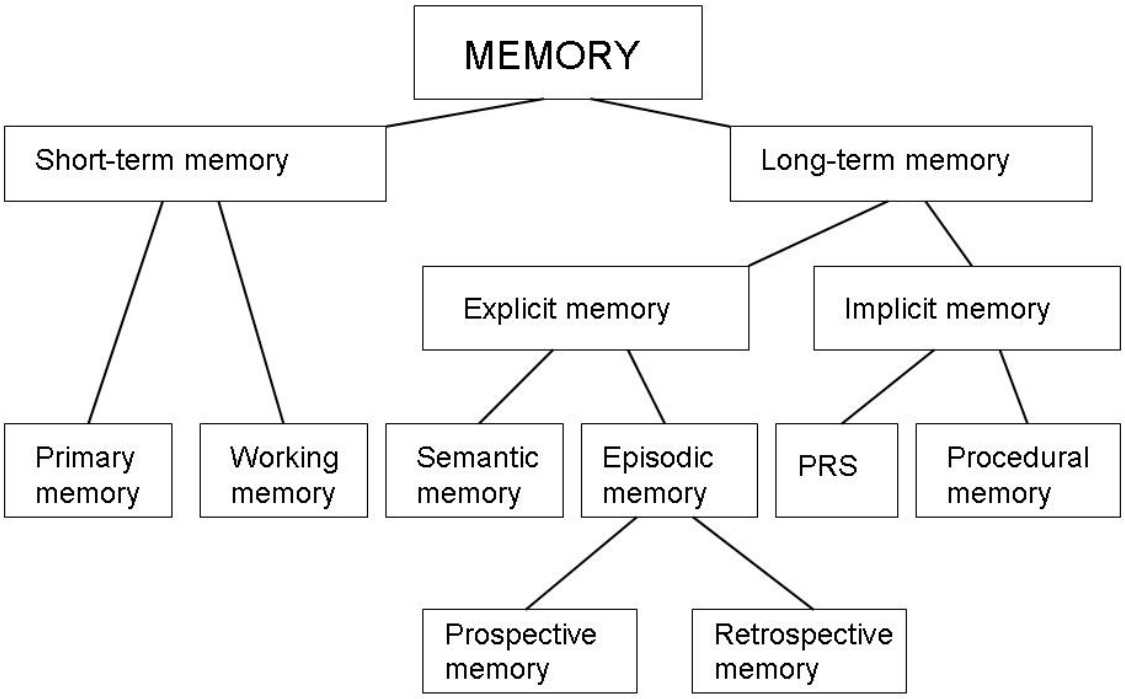


**Figure 2.** Overview of memory systems. Adapted from Baddeley (1986), Squire (1992), and Tulving (1983)

The capacity of short-term memory is very limited, as opposed to long-term memory which involves all those memories that we can retrieve again after focusing on something else for a shorter or longer time period. Long-term memory can further be divided into implicit and explicit memory. Implicit memory includes procedural memory, which helps us to perform routine actions such as walking and the perceptual representation system (PRS) which makes it possible for us to rapidly identify common objects, words, and other things that we are frequently exposed to.

Common to PRS and procedural memory is that memories can be retrieved relatively automatically. Explicit memory, on the other hand, requires conscious effort at retrieval. Explicit memory can be divided into semantic and episodic memory. Semantic memory includes general knowledge, such as facts and the meaning of words. It is unconnected to any temporal or spatial context, meaning that we generally are unable to remember when or where the learning took place. Episodic memory refers to memory for personal experiences, and thus has a temporal as well as a spatial referent. In contrast to semantic memory, episodic memory requires autonoetic consciousness, or self-awareness. Episodic memory is one of the cognitive abilities that are most sensitive to aging as well as many age-related disorders (Tulving, 2002).

When using the term episodic memory, most researchers have retrospective memory in mind. However, it is possible to separate episodic memory into prospective and retrospective remembering (Meacham & Singer, 1977). In this thesis, episodic memory

is used as a general term and prospective and retrospective memory are used to describe these different forms of episodic memory.

#### *1.2.1.1 Retrospective memory*

Retrospective memory involves remembering events experienced in the near or distant past. This includes so called autobiographical memories of personally important events, as well as memories for more neutral information such as the content of books or TV-programs. Everyday retrospective memory errors are frequently reported by healthy young and old adults (G. Smith, Della Sala, Logie, & Maylor, 2000). Among persons with age-related disorders, such as Alzheimer disease patients, retrospective memory errors are even more frequent. It is also known that these memory failures are regarded as frustrating by the patients themselves and their carers (G. Smith, Della Sala, Logie, & Maylor, 2000).

In experimental settings, retrospective memory is often measured by presenting a list of words or similar stimuli to the participants, and then asking them to recall as many words as possible (as in free recall tasks) or to distinguish previously presented items from new items (as in recognition tasks).

Retrospective remembering involves brain activity in a large distributed network, including the hippocampus, thalamus, cerebellum, parietal regions, and the fronto-striatal circuitry (Cabeza & Nyberg, 2000). Regions in the medial temporal lobe, including the hippocampus, are especially important to retrospective memory functioning (Nyberg & Tulving, 1996; Squire, 1986; Vargha-Khadem et al., 1997).

#### *1.2.1.2 Prospective memory*

Prospective memory involves remembering to perform an action at some point in the future. This is still a rather new area of research, which has attracted an increasing amount of attention during the last years. A common distinction is made between actions carried out at a certain time point (i.e., time-based prospective memory tasks), and actions performed in a specific setting (i.e., event-based prospective memory tasks; Einstein & McDaniel, 1990). Examples of everyday prospective memory tasks are to remember to take one’s medication at a certain hour or to post a letter when passing a mailbox. Prospective memory functioning is of great importance to all adults, including elderly persons who want to remain independent in daily life (Einstein & McDaniel, 1990; Kliegel & Martin, 2003). Prospective memory problems are also frequently reported among healthy older adults as well as patients in memory clinics (Kliegel & Martin, 2003) and may be frustrating for the persons affected as well as for their families (G. Smith, Della Sala, Logie, & Maylor, 2000). Interestingly, evidence suggests that persons who report memory problems in everyday life show objective deficits in prospective memory tasks, but not necessarily in retrospective memory tasks (Mäntylä, 2003).

In a research setting, prospective memory is often difficult to measure in a way that combines high external validity and good measurement properties (Maylor, 2008). In many studies, the participants are asked to monitor the environment for certain prospective memory cues such as target words appearing on repeated occasions among

other words presented. Thus, these prospective memory tasks involve constant monitoring of ongoing activity during a shorter time frame. Other tasks assess the ability to retrieve an intention after a longer retention interval. These types of tasks may have advantages regarding external validity, but are often suboptimal in terms of measurement properties.

All prospective memory tasks involve two components: one component which is a more "true" measure of prospective memory and one component which essentially resembles retrospective memory (Graf & Uttl, 2001). Whereas the prospective component involves remembering that an action should be carried out, the retrospective component involves remembering what type of action is supposed to be performed.

Frontal, medial temporal, and parietal regions of the brain as well as the extrastriate cortex are all implicated in prospective remembering (West, 2008). Prefrontal regions have been identified as especially important, and it is suggested that the rostral prefrontal cortex plays a significant role in the control or attentional processes involved in the prospective component of the task (Burgess et al., 2008). A study using behavioral data provides additional support for strong frontal involvement in prospective memory (McDaniel, Glisky, Rubin, Guynn, & Routhieaux, 1999). This study showed that prospective memory performance was significantly better among persons who performed well on composite measures of frontal lobe functioning, whereas there was no association between composite measures of medial temporal functioning and prospective memory. Further, there is evidence that memory for the retrospective component of prospective memory tasks is depending mainly on medial-temporal regions (Kliegel, Jäger, Altgassen, & Shum, 2008).

#### *1.2.1.3 Similarities and differences between prospective and retrospective memory*

It has been debated whether it is relevant to make a distinction between prospective and retrospective memory. From a theoretical perspective, an essential difference is that prospective memory includes not only memory for content, but also to "remember to remember", and therefore relies heavily on self-initiated retrieval (Einstein & McDaniel, 1996; Graf & Uttl, 2001). Many different types of studies also support that prospective memory involves additional cognitive processes than those typically involved in retrospective memory. A study using regression analysis found that prospective memory performance could not predict retrospective memory performance and vice versa (Einstein & McDaniel, 1990). In a correlational study, the association between scores on prospective and retrospective memory tasks was modest, although significant (Graf, Uttl, & Dixon, 2002). Furthermore, the correlation was attenuated when controlling for the retrospective component of the prospective memory task. Other studies have used factor analysis and found that scores on prospective and retrospective memory tasks load on separate factors (Maylor, Smith, Della Sala, & Logie, 2002; Uttl, Graf, Miller, & Tuokko, 2001). In studies on self-reported memory failures, similar results were found (Crawford, Smith, Maylor, Della Sala, & Logie, 2003; Rönnlund, Mäntylä, & Nilsson, 2008). A tripartite model with a general memory factor and separate orthogonal factors for prospective and retrospective memory had the best fit.

As noted, there may be differences with regard to the neural underpinnings of prospective and retrospective memory. Prospective memory is depending heavily on regions in the frontal lobe (Burgess et al., 2008; McDaniel, Glisky, Rubin, Guynn, & Routhieaux, 1999), whereas retrospective memory relies on medial-temporal regions to a larger extent (Nyberg & Tulving, 1996; Squire, 1986; Vargha-Khadem et al., 1997).

However, there are also some similarities with regard to the cognitive processes involved. Both strategic cognitive processes and more automatic (e.g., associative, or cue-dependent) processes are involved in remembering, and this is true for prospective (McDaniel & Einstein, 2000; McDaniel, Guynn, Einstein, & Breneiser, 2004) as well as retrospective (Moscovitch & Melo, 1997) memory. Evidence suggests that strategic and more automatic processes are supported by different neural systems. Automatic processes are thought to depend mainly on medial-temporal regions, whereas strategic processes are more frontally mediated (Cohen & O'Reilly, 1996; Kramer et al., 2005; Moscovitch, 1992; Moscovitch & Melo, 1997). To be sure, task characteristics as well as situational and individual factors, can influence the extent to which automatic and strategic cognitive processes are involved in a memory task (McDaniel & Einstein, 2000).

### 1.2.2 Memory processes

The systems approach is frequently used to describe memory. A complimentary way of understanding and categorizing long-term memory is the process view. This approach focuses less on differences between various forms of memory systems, and more on the different types of processes involved when performing memory tasks. Long-term memory processes are commonly divided into encoding, storage, and retrieval. Encoding refers to the situation where we acquire memories by directing our attention towards some new information. Storage refers to the retention interval, during which time we keep the information in our memory before using it at the retrieval stage (Brown & Craik, 2000). For prospective memory, additional stages of execution and output monitoring (i.e., evaluating whether the intention was successfully carried out), have been described (Ellis & Freeman, 2008).

## 1.3 EPISODIC MEMORY IN AGING

### 1.3.1 Normal aging and episodic memory

As a result of the aging process, multiple structural and functional changes appear in the brain. This includes reductions in volume, metabolism and blood flow, mainly in frontal and temporal regions (Anderson & Craik, 2000). Episodic memory is one of the most age-sensitive cognitive abilities (Nilsson, 2003; Tulving, 2002). Even in normal aging, the ability to remember episodic information is decreased compared to middle and young adulthood (Nilsson, 2003).

For retrospective memory, the age-related impairment is well established (Balota, Dolan, & Duchek, 2000). Previous research also demonstrates that the impairment is more pronounced for the encoding and retrieval stages, whereas storage seems to be relatively spared (Balota, Dolan, & Duchek, 2000). Although performance starts to decline rather early on during the life course, the ability to benefit from cognitive

support is spared in high age, as has been demonstrated by many studies. For example, elderly persons can benefit from more study time at encoding (Wahlin, Bäckman, & Winblad, 1995), item organizability (Bäckman & Wahlin, 1995) and cues at the time of retrieval (Bäckman & Wahlin, 1995; Wahlin, Bäckman, & Winblad, 1995).

For prospective memory, it was unknown for a rather long period of time whether the ability was spared, or even improved, in old compared to young age. However, most researchers now seem to agree that prospective memory is also negatively affected as a result of aging, at least in tasks performed under experimental control (Henry, MacLeod, Phillips, & Crawford, 2004). Importantly, these age-related deficits in prospective memory seem to be present even when a large number of biological, psychometric, and demographic factors are controlled for (Mäntylä & Nilsson, 1997). In naturalistic tasks, on the other hand, a common finding is that elderly participants are more successful than their younger counterparts. This phenomenon is known as the "age-prospective memory paradox" (Maylor, 2008). Possible explanations for this paradox include age differences in life structure, use of memory aids, and other factors that have an impact on performance in naturalistic settings (Henry, MacLeod, Phillips, & Crawford, 2004; Phillips, Henry, & Martin, 2008).

It has also been suggested that the presence, or magnitude, of age differences in prospective memory performance depends on the type of task and the cognitive demands involved in it (Maylor, 2008). For example, older persons are presumed to perform worse on tasks that rely more heavily on attention-demanding strategic processes, such as time monitoring. In contrast, they are presumed to perform relatively well on tasks that involve more automatic memory processes, that is when the environmental conditions provide strong prospective memory cues (Henry, MacLeod, Phillips, & Crawford, 2004; McDaniel & Einstein, 2000).

### 1.3.2 Dementia and episodic memory

As previously described, memory impairment is part of the diagnostic criteria for dementia (*Diagnostic and statistical manual of mental disorders*, 1994). Several studies have shown that retrospective memory starts to decline very early in the disease process (Almqvist & Bäckman, 1993; Bäckman, Jones, Berger, Laukka, & Small, 2005); this impairment is often evident several years before the clinical diagnosis of Alzheimer's disease (Bäckman, Jones, Berger, Laukka, & Small, 2005; Bäckman, Small, & Fratiglioni, 2001). This could be explained by the fact that temporal-lobe pathology appears very early in the disease course (Braak & Braak, 1997).

In vascular dementia, the extent and patterns of cognitive deficits are often very similar compared to Alzheimer's disease (for review, see Laukka, Karlsson, MacDonald, & Bäckman, 2009). Retrospective memory impairment is frequently a very early sign, although other cognitive symptoms can sometimes be more dominant. For example, it has been suggested that vascular dementia patients often perform better on tests of verbal retrospective memory, and worse on frontal-executive tasks, compared to Alzheimer patients (Looi & Sachdev, 1999). Also in the preclinical phases, there are studies suggesting that the patterns of cognitive impairment are quite similar in vascular dementia and Alzheimer's disease (Jones, Laukka, Small, Fratiglioni, & Bäckman,

2004; Laukka, Jones, Small, Fratiglioni, & Bäckman, 2004), although one study found that the retrospective memory losses are somewhat more pronounced in preclinical Alzheimer's disease (Ingles, Boulton, Fisk, & Rockwood, 2007). However, it is important to recognize that different subtypes of vascular dementia can have differential effects on cognition (Laukka, Karlsson, MacDonald, & Bäckman, 2009).

With regard to the encoding, storage and retrieval stages, it remains unknown whether persons with Alzheimer's disease and vascular dementia show similar or differential patterns of impairment. Several studies have found evidence for an increased rate of forgetting in the early clinical stages of Alzheimer's disease (Herlitz & Viitanen, 1991; Larrabee, Youngjohn, Sudilovsky, & Crook, 1993). Forgetting over time is an indicator of problems with memory storage. It is also found that measures of delayed recall (as they are sensitive to forgetting) are particularly effective in identifying persons with preclinical Alzheimer's disease (Tierney et al., 1996). Consistent with these results, some studies comparing the two dementia etiologies suggest that persons with Alzheimer's disease are more impaired in memory storage, whereas persons with vascular dementia have more retrieval difficulties (Laukka, Karlsson, MacDonald, & Bäckman, 2009). This is concluded as persons with vascular dementia benefit more from the retrieval support provided in cued recall or recognition tasks (Cummings, 1993; Yuspeh, Vanderploeg, & Kershaw, 1998). Other studies, however, have failed to find differences between Alzheimer's disease and vascular dementia regarding the relative impairment across encoding, storage and retrieval (Almqvist, Fratiglioni, Aguero-Torres, Viitanen, & Bäckman, 1999).

For prospective memory, impairment is evident in the early clinical phase of Alzheimer's disease (Duchek, Balota, & Cortese, 2006; Huppert & Beardsall, 1993; Huppert, Johnson, & Nickson, 2000; Maylor, Smith, Della Sala, & Logie, 2002). Whether the impairment is present already before the diagnosis can be received was uncertain when this dissertation project started, as no study had investigated this before. Prospective memory impairment could be expected, however, as alterations in the frontal cortex are evident already in the preclinical stage (van der Flier et al., 2002; Yamaguchi, Sugihara, Ogawa, Oshima, & Ihara, 2001). Little was also known about the influence of vascular dementia on prospective memory functioning. As frontal-subcortical regions are among the regions most often affected by vascular pathology (Cummings, 1993), prospective memory deficits could be expected also in vascular dementia. Some support for this notion comes from a study investigating prospective memory functioning following stroke (Brooks, Rose, Potter, Jayawardena, & Morling, 2004).

### 1.3.3 Depression and episodic memory

Depression is associated with deficits in many different cognitive domains (Christensen, Griffiths, Mackinnon, & Jacomb, 1997). This is not surprising, as brain-imaging studies have indicated a number of depression-related alterations, including decreases in hippocampal volume (Campbell, Mariott, Nahmias, & MacQueen, 2004; D. H. Kim, Payne, Levy, MacFall, & Steffens, 2002; Steffens et al., 2000; Videbech & Ravnkilde, 2004) and altered activity in frontal regions (Drevets, 2000; Manji, Drevets, & Charney, 2001).

Among the studies that have examined episodic memory functioning in depression, most have focused on retrospective memory functioning. Depression-related impairment has been observed in samples with clinical depression as well as in samples with depressive symptoms below the clinical threshold (Burt, Zembar, & Niederehe, 1995; Bäckman, Hill, & Forsell, 1996; Christensen, Griffiths, Mackinnon, & Jacomb, 1997; Kindermann & Brown, 1997). Although problems at encoding, storage, and retrieval have been implicated in depression (Bäckman & Forsell, 1994; Johnson & Magaro, 1987), little research has compared the three stages in order to see whether the memory impairment affects them to a similar or differential extent.

For prospective memory, there is limited knowledge about the potential influence of depressive symptoms. In some studies, depressive symptoms have been associated with impaired prospective memory performance (Kliegel & Jäger, 2006; Rude, Hertel, Jarrold, Covich, & Hedlund, 1999). However, other studies have failed to find an effect of depressive symptoms on prospective memory (Harris & Menzies, 1999; Kliegel & Jäger, 2006). In a review article, it was suggested that negative effects of depressive states are present in time-based laboratory tasks, but smaller or non-existent for event-based laboratory tasks or naturalistic tasks (Kliegel & Jäger, 2006). However, this possibility has to be confirmed. It should also be pointed out that the laboratory tasks used in the studies mentioned above all required constant monitoring during a shorter time frame, while performing an ongoing task.

### 1.3.4 Thyroid function and episodic memory

Both hypo- and hyperthyroidism are suspected to impair cognitive performance. The same is true for different types of subclinical thyroid alterations. It should be mentioned, however, that the associations between thyroid functioning and cognition are not always clear, due to many possible confounders (Biondi & Cooper, 2008). Two previous studies on data from the Kungsholmen Project have addressed the effect of thyroid status on cognitive functioning among persons free from clinical thyroid disorders. Persons with lower serum levels of TSH (although still within the normal range) performed worse on tests of retrospective memory compared to persons with higher TSH levels (Wahlin, Robins Wahlin, Small, & Bäckman, 1998). Interestingly, a longitudinal follow-up study showed that declining TSH levels preceded the memory impairment, which supports the idea of a causal association (Wahlin, Bunce, & Robins Wahlin, 2005).

For prospective memory, little is known about the potential impact of TSH variations. In one study on age-related differences in prospective memory, TSH was included as a background variable (Mäntylä & Nilsson, 1997). In the first set of analyses, TSH levels were negatively associated with prospective memory performance, although this association disappeared when a cross-validation sample was analyzed. Thus, the authors concluded that the effects of TSH on prospective memory functioning is limited in the age range examined (i.e., 35-80 years of age).

To the best of our knowledge, no other research on TSH and prospective memory has been performed. Thus, very little is known on this topic. From a theoretical perspective,

an effect of TSH on prospective memory could be expected, given that previous research has indicated that hyperthyroidism and related states can cause alterations in many regions of the brain, including the frontal lobes. These prefrontal alterations include electrical activity (Munte, Radamm, Johannes, & Brabant, 2001), perfusion (Fukui, Hasegawa, & Takenaka, 2001), and metabolism (Bhatara, Tripathi, Sankar, Gupta, & Khushu, 1998; Fukui, Hasegawa, & Takenaka, 2001).

# 2 RESEARCH OBJECTIVES

The general objective of this thesis was to gain more knowledge of how prospective and retrospective memory are affected by disorders that are common in old age as well as by other health-related factors. A second aim was to find out in more detail how the two components in a prospective memory task (prospective and retrospective), and how the memory stages in retrospective memory (encoding, storage and retrieval) are affected by the conditions investigated. The specific aims for the four studies included in this thesis were:

Study I: To investigate how the components of prospective memory and stages of retrospective memory are affected in mild to moderate Alzheimer's disease and vascular dementia, compared to normal aging.

Study II: To investigate how the components of prospective memory and stages of retrospective memory are affected in preclinical Alzheimer's disease (three years prior to diagnosis) compared to normal aging.

Study III: To investigate how depressive symptomatology affects the components of prospective memory and the stages of retrospective memory.

Study IV: To investigate how serum levels of TSH and T4, among persons free from thyroid disorder, affect the components of prospective memory.

# 3 EMPIRICAL STUDIES

## 3.1 THE KUNGSHOLMEN PROJECT

The studies included in this thesis are all based on data from the Kungsholmen Project, which is a longitudinal, population-based study. The Kungsholmen project focuses on medical, psychological and social aspects of aging. The Kungsholmen project has been approved by the ethics committee of Karolinska Institutet, Sweden (Dnrs. 87:234, 90:251, 94:122, 97:413, 99:308, 99:025 and 01:020), and informed consent was obtained from all participants or next-of-kin. The project has been described in more detail elsewhere (e.g., Fratiglioni, Viitanen, Bäckman, Sandman, & Winblad, 1992), and only a brief description will be given here.

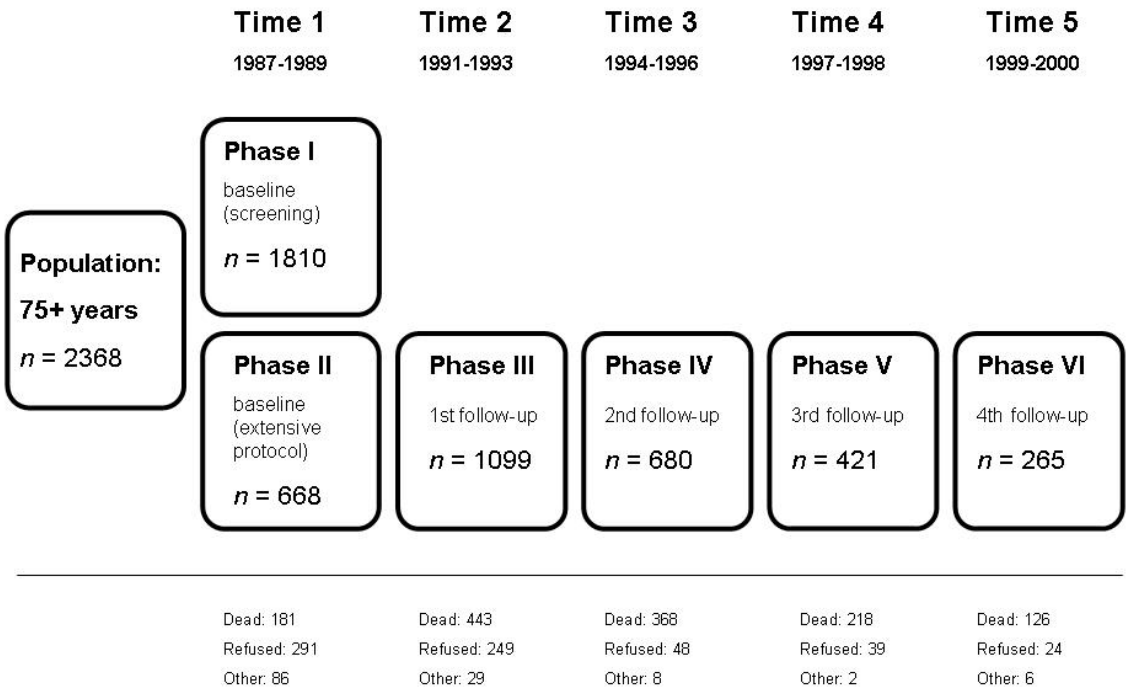


**Figure 3.** Overview of study design and participants in the Kungsholmen project

The original sample included all inhabitants, 75 years and older, living in the Kungsholmen parish of Stockholm, Sweden on October 1, 1987 (*n*=2,368). People living at home as well as in institutions were included. The baseline examination consisted of two phases. First, 1,810 persons participated in a screening phase, which consisted of a health examination and an interview including the Mini-Mental State Examination, or MMSE (Folstein, Folstein, & McHugh, 1975). Second, participants who scored 23 or lower on the MMSE (*n*=314) and a random sample matched on age and sex (*n*=354), were re-examined using a more extensive protocol including a medical, psychiatric and neurological examination, laboratory blood analyses, social interviews, and a comprehensive cognitive test battery. At the follow-up examinations, with approximately three-year intervals, the same protocol was used as in the extensive

baseline examination. All participants from the screening phase were then invited. The project was finished in the year 2000, when five waves of data collection had been completed.

### 3.1.1 Dementia diagnoses

The dementia diagnoses were based on clinical data only, as no brain imaging data were available, and were made according to DSM-III-R criteria (American Psychiatric Association, 1987). The diagnoses were made through a three step procedure, which was part of the extensive version of the protocol (Time 1, Phase II and Time 2-5). First, a preliminary diagnosis was made by the geriatrician who had examined the participant and reviewed the medical and family history. Second, a physician expert in dementia and external to the data collection made a new preliminary diagnosis based on computerized data. Third, the two preliminary diagnoses were compared and in case of agreement, this was considered as the final diagnosis. In cases of disagreement, the final diagnosis was made by a supervising physician.

To make the differential diagnosis of Alzheimer's disease and vascular dementia, the Hachinski Ischemic Score (HIS) was used to support the clinical judgment (Hachinski et al., 1975). A HIS score above 6 is an indicator of vascular dementia, a HIS score of 5 or 6 is an indicator of mixed dementia, and a HIS score lower than 5 is an indicator of Alzheimer's disease. The sensitivity as well as specificity of the HIS is high in differentiating between Alzheimer's disease and vascular dementia (Moroney et al., 1997). The Alzheimer diagnosis corresponds to probable Alzheimer's disease according to the NINCDS-ADRDA criteria (McKhann et al., 1984), and the diagnosis of vascular dementia corresponds to possible vascular dementia according to the NINDS-AIREN criteria (Roman et al., 1993). In the Kungsholmen project, a majority of the participants diagnosed with vascular dementia had a history of stroke. Thus, the diagnosis of vascular dementia is largely a diagnosis of strategic or multiinfarct dementia.

For those participants who died during the follow-up period, the dementia diagnoses were based on the information available through clinical records, discharge diagnoses, and death certificates.

### 3.1.2 Assessment of depression

A structured interview using The Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg, Montgomery, Perris, Schalling, & Sedvall, 1978) was also included in the extensive protocol. The CPRS consists of items assessing a variety of psychiatric symptoms, such as depression and anxiety, and includes questions to the participant as well as observations made by the physician. The nine items measuring depressive symptoms map on to the DSM criteria for depression and include dysphoria (created from two original items, one observed by the clinician and one reported by the participant), feelings of guilt (also created from two original items measuring feelings of inferiority and self-reproach), suicidal ideation, loss of interest, lack of energy, altered psychomotor activity observed by the clinician, appetite disturbance, sleep disturbance, and concentration difficulties. These data were the basis for the diagnoses of major depression and dysthymia. The diagnoses were made according to DSM-III-R

criteria (American Psychiatric association, 1987) at baseline and DSM-IV criteria (American Psychiatric Association, 1994) at the follow-ups. In addition to the clinical diagnoses of depression, a continuous measure of depression was also used in study III, which was based on the number and severity of depressive symptoms reported and observed during the CPRS interview.

### 3.1.3 Blood analyses

The laboratory blood analyses covered a variety of health indices, including TSH and T4. All analyses were performed by the same laboratory. The immunoradiometric assay method was used for analyzing TSH levels (Seth et al., 1984). This method is very sensitive for detecting low values of TSH. For the analyses of T4, the radioimmunoassay method was used (Giles, 1982).

### 3.1.4 Prospective memory task

A prospective memory task was included in the cognitive test battery. The same prospective memory task was used in all studies. The participants were instructed at the beginning of the test session to remind the test leader to make an important phone call after completion of all tests. Performance was first measured with free recall. For those participants who were not successful in this task, a cued recall test followed where they were given a prompt by the test leader (see Figure 4).

The responses in the prospective memory task were recorded into 5 categories:

1- remembers correctly without a prompt
2- remembers incorrectly without a prompt
3- remembers correctly with a prompt
4- remembers incorrectly with a prompt
5- does not remember

*Free recall condition:* If a participant spontaneously reminded the test leader to make a phone call after being told that the session was finished, this was recorded as 1. If the participant spontaneously reminded the test leader to do something, but failed to remember or was incorrect about what the test leader was supposed to do, this was recorded as 2.

*Cued recall condition:* For those participants who completely failed to remind the test leader in the free recall condition, the cued recall condition followed. The test leader gave the prompt by asking: "What was I supposed to do when we were finished with the testing?" If the participant then remembered the instruction correctly, this was recorded as 3. If the participant remembered that they had been asked to remind the test leader, but failed to recall what the testleader was supposed to do, this was recorded as 4. If the participant did not remember the instruction at all, this was recorded as 5.

With regard to the two components involved in prospective memory, a score of 1 requires memory for both components, a score of 2 requires memory for the prospective component only, and a score of 3 requires memory for the retrospective component only. A score of 4 or 5 indicates failure to remember for both components.

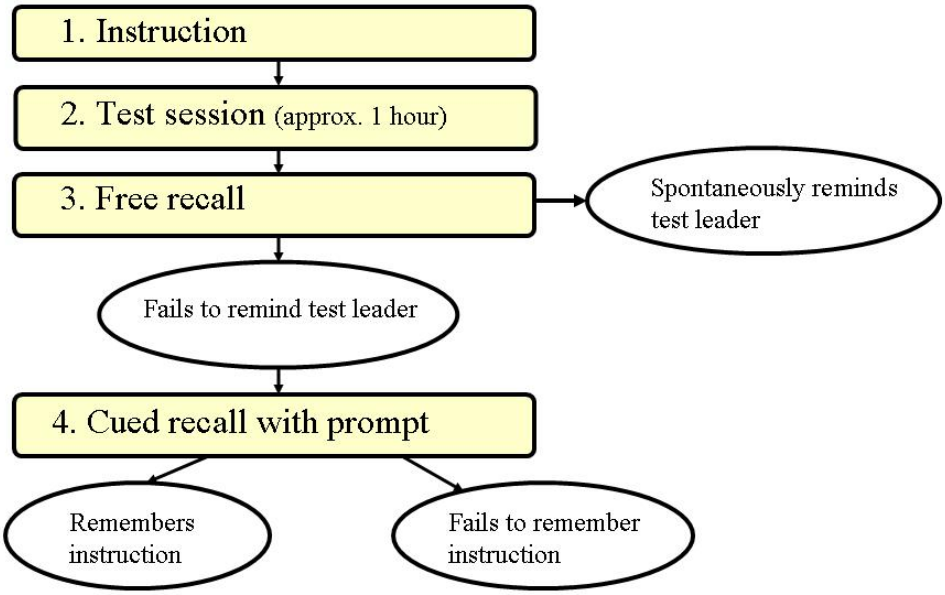


**Figure 4.** Prospective memory task

### 3.1.5 Retrospective memory task

The retrospective memory task consisted of a word list including 12 nouns from four different taxonomic categories (professions, clothes, furniture, and musical instruments). The words were presented in random order both visually and orally at a rate of 5 sec per word. The participants were not informed in advance that the words were possible to organize into categories. All words were typical of their respective categories, according to previously established norms (Nilsson, 1973).

*Free recall condition:* Immediately after presentation of the last item in the list, the participants were asked to freely recall as many words as possible.

*Cued recall condition:* Immediately following free recall, a cued recall task was given, in which the participants were provided with the category names as retrieval cues. They were again instructed to recall as many words as possible, including those already remembered in the free recall task (see Figure 5).

Performance was measured with free, cued and total recall (total number of words remembered in either free or cued recall). Also, three qualitative indicators of retrospective memory were computed, reflecting different stages of remembering. Number of categories represented in the response protocol for free recall reflects the participants´ plan at retrieval, whereas number of items remembered per category reflects the degree of semantic organization at encoding (Craik & Mansini, 1969; Dixon et al., 2004; Hultsch, 1975; A. D. Smith, 1980; Tulving & Pearlstone, 1966). Also, a measure of forgetting (indicating difficulties to consolidate memories) was included. In order to control for initial free recall performance, forgetting ratio was calculated as the number of words remembered in free recall but forgotten in cued recall, divided by the free recall score.

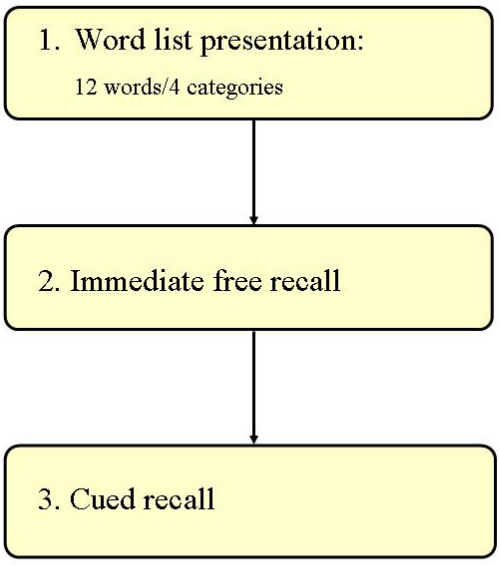


**Figure 5**. Retrospective memory task

## 3.2 STUDY I

This study examined prospective and retrospective memory performance in persons with Alzheimer's disease (*n*=79), vascular dementia (*n*=21), and controls (*n*=352).

Participants who received a diagnosis of either Alzheimer's disease or vascular dementia at baseline or any of the two first follow-ups were included in this study. The cognitive data were taken from the phase when the participant was diagnosed. Thus, the majority of the demented participants had fulfilled the diagnostic criteria for dementia rather recently. The Clinical Dementia Rating Scale (CDR) was used to determine dementia severity (Hughes, Berg, Danzinger, Cohen, & Martin, 1982). The majority of the demented participants had mild or moderate dementia, although two persons had a severe form of Alzheimer's disease. Importantly, there were no significant differences in dementia severity between the Alzheimer and vascular dementia groups. In addition to the two dementia groups, a healthy control group was included. This group consisted of persons screened for dementia, dementia in a preclinical phase, and other disorders that may affect cognitive performance.

The prospective memory data were divided into two components that were analyzed separately. The prospective component of the task involved remembering to remind the test leader without being given the additional prompt. This corresponds to an original score of either 1 or 2, as can be seen in the previous task description. The majority of participants who remembered to do so also recalled the content of the instruction correctly (i.e., that the test leader was supposed to make a phone call), whereas a minority (*n*=10) failed to remember correctly what was supposed to be done. The retrospective component of the task involved remembering the content of the instruction either with or without a prompt. This corresponds to an original score of either 1 or 3. Retrospective memory was measured with free, cued and total recall. In

addition, the three qualitative measures of retrieval (number of categories), encoding (items per category), and storage/consolidation (forgetting ratio) were included.

To analyze the prospective memory data, $\chi^2$-analyses were performed. These analyses revealed that the controls outperformed both dementia groups. This was true for both the prospective and the retrospective component. However, there were no differences between the dementia groups for either component.

To analyze the retrospective memory data, separate analyses of covariance (ANCOVAs), controlling for age, sex, and education, were performed. Both dementia groups were outperformed by the controls on free, cued, and total recall as well as on the three qualitative indicators. Again, no performance differences were observed between the Alzheimer and vascular dementia groups.

To examine the effects of retrieval support provided in cued recall, a 3 (group) x 2 (task: free recall, cued recall) mixed analysis of variance (ANOVA), with repeated measures on the last factor, was carried out. The results revealed no main effect of task. However, a significant interaction between group and task was found. Whereas the controls improved their performance in cued recall compared to free recall, the demented groups did not. Another mixed ANOVA was computed where cued recall was substituted with total recall. As previously described, the total recall score denotes all words that once have been encoded into memory, including additional items retrieved following the provision of category cues. The results revealed a significant main effect of task. Importantly, there was no longer an interaction between group and task, indicating that all three groups improved their performance to a similar extent in total compared to free recall. Thus, all three groups were able to benefit from retrieval support. When contrasting these two analyses, it is clear that the group x task interaction found in the free-cued recall analysis is due to forgetting from the time of free to cued recall in the dementia groups. This reflects dementia-related forgetting over a rather short retention interval, indicating pronounced difficulties with storage and consolidation of retrospective memories.

The main finding in this study was that, although the groups with Alzheimer's disease and vascular dementia showed deficits compared to controls, on all aspects of episodic memory, there were no differences whatsoever between the two dementia groups. Thus, both dementia groups were equally impaired on the two components of the prospective memory task, and on all measures of retrospective memory including the indicators of encoding, storage, and retrieval. These results are in agreement with previous research showing similar patterns of cognitive impairment in Alzheimer's disease and vascular dementia, including retrospective memory functioning, and extend previous findings to prospective memory.

### 3.3 STUDY II

In this study, 46 persons in the preclinical phase of Alzheimer's disease and 188 non-demented control persons were compared on prospective and retrospective memory tasks.

In the preclinical Alzheimer's disease group, all participants who received an Alzheimer diagnosis either at the first or the second follow-up were included. Their cognitive data were taken from the phase before they received the diagnosis, that is from baseline (for those who were found demented at the first follow-up) or from the first follow-up (for those who were found demented at the second follow-up). The control group consisted of persons, with cognitive data from baseline or the first follow-up, who remained non-demented at the next follow-up. All persons who were demented already at baseline, or who were diagnosed with another form of dementia during the follow-up period, were excluded. In addition, we excluded persons with other disorders known to have a negative impact on cognition.

As we wanted to compare prospective and retrospective memory with regard to the predictive value in identifying persons at risk of developing dementia, we tried to make the memory measures as similar as possible. Thus, prospective memory performance was measured with free and total recall in this study. Being successful in the free recall condition involved remembering correctly without a prompt, and corresponds to an original score of 1. Data from the cued recall condition were not used in the analyses, as this test was only given to those who were unsuccessful in the free recall condition. Instead, we used a measure of total recall (remembering correctly either with or without a prompt, corresponds to an original score of either 1 or 3). In addition, we included a measure of strict recall. This was done in order to obtain a purer measure of memory for the prospective component. Strict recall was calculated from the subsample that was successful in total recall (i.e., remembered the retrospective component). For successful strict recall performance, success in the free recall condition was required as well. Retrospective memory performance was again measured with free, cued, and total recall as well as with the qualitative indicators (number of categories, items per category, and forgetting ratio).

Preclinical Alzheimer's disease was associated with impairment on both types of tasks, as analyzed with $\chi^2$ (for prospective memory) and multiple analysis of variance (MANOVA; for retrospective memory). The impairment was evident for all performance variables included. In the prospective memory task, the measures of free, total and strict recall all revealed impaired performance in prodromal dementia. Within retrospective memory, persons in the preclinical phase showed deficits in free, cued, and total recall, as well as for the indices of encoding, storage (forgetting), and retrieval of information.

In a second step, we analyzed the predictive value of the two memory tasks in group classification. Two logistic regression analyses were performed; one model based on free recall scores for prospective and retrospective memory and one model based on total recall scores. In both models, age, gender, years of education and length of test session (which is the retention interval for the prospective memory task) were included as covariates. In addition, MMSE scores (Folstein, Folstein, & McHugh, 1975) were entered before the memory variables, in order to control for global deterioration of cognitive performance. Most interestingly, prospective memory made an independent contribution to the prediction of future dementia diagnosis over and above the predictive value of retrospective memory.

These findings suggests that the two types of memory tap partly different cognitive operations. Also, the findings indicate a rather global episodic memory impairment in preclinical Alzheimer's disease that cuts across type of memory assessed as well as across different components or stages of both prospective and retrospective memory.

### 3.4 STUDY III

This study examined the effects of depressive symptomatology on prospective and retrospective memory.

Participants from baseline and the two first follow-ups were included in this study (*n*=404). Depression was measured with the CPRS and treated as a continuous variable, taking number and severity of symptoms into account. Of all participants, 3.5% were diagnosed with major depression and 1.5% with dysthymia. Among those who were not clinically depressed, 71.6% still had specific depressive symptoms, whereas 28.4% had no symptoms. Thus, the variation in depressive symptomatology ranged from no symptoms to presence of a clinical depression. The cognitive data were taken from the same phase as the CPRS data. Participants who were on antidepressive or antipsychotic medication were excluded, as were persons with dementia, preclinical dementia and other disorders known to affect cognition.

The prospective and retrospective memory measures were the same as in study II. Prospective memory was measured with free, total and strict recall. Retrospective memory was measured with free and total recall. As indicators of the different memory stages, we used the same qualitative measures as in studies I and II (i.e., number of categories, items per category, and forgetting ratio).

To examine the effects of depressive symptoms on memory, logistic regression analyses (for prospective memory) and linear regression analyses (for retrospective memory) were performed. The memory measures served as outcome variables. Age, sex, and education were included as covariates in all analyses. For the analyses of prospective memory, length of test session was also included.

For prospective memory, the only effect of depressive symptoms was seen in total recall where performance decreased as a function of increasing number of symptoms. This variable reflects the retrospective component of the task. Free recall, which involves successful remembering of both the prospective and the retrospective component, was unaffected by depressive symptoms. Consistent with this pattern, no association was found between depressive symptoms and strict recall (which is a purer measure of the prospective component).

For retrospective memory, the results revealed a rather global impairment as a result of depressive symptoms. Both free and total recall were negatively affected by depression. Analyses of the qualitative indicators showed that increasing depressive symptomatology had a negative impact on retrieval, as measured with number of categories recalled, and consolidation, as measured with forgetting ratio. For encoding, measured as the number of items remembered per category, there was a trend in the same direction that did not attain conventional significance.

To summarize, depressive symptomatology had a negative effect on retrospective memory including consolidation and retrieval. However, only the retrospective component of prospective memory was negatively affected by depressive symptoms, whereas the prospective component was unaffected. Thus, the results suggest a dissociation of prospective and retrospective memory in old age depression.

## 3.5 STUDY IV

The aim of this study was to investigate the effect of thyroid functioning on prospective memory. Specifically, the study focused on thyroid functioning in the absence of thyroid disease.

This study targeted prospective memory only, because previous studies within the Kungsholmen project have already examined thyroid function and retrospective memory. Comparable to one of these previous studies, the sample was taken from persons who participated in the baseline cognitive testing ($n$=103). Only persons who were not diagnosed with any thyroid disorder were included. Also, for the two thyroid hormones that were measured (TSH and T4), we used cut-off values that excluded participants with hormone levels outside normal range. All persons with dementia, or other disorders with potential cognitive consequences, were also excluded from participation.

Serum levels of TSH and T4 were used as indicators of thyroid functioning. The prospective memory measures were the same as in study I. Thus, the prospective component of the task involved remembering to remind the test leader to perform an action, without being given the additional prompt. The retrospective component of the task involved remembering the content of the action that the test leader was supposed to perform, either spontaneously or after the prompt.

The data were analyzed with logistic regression analysis. As covariates, we included age, sex, education, mood symptoms, and length of test session. Mood symptoms were measured with those specific items from the CPRS that target mood alterations. This was included as a covariate as mood status in some previous studies on thyroid functions and cognition has been identified as a mediating factor. The results revealed that TSH levels were positively associated with prospective memory performance, so that persons within the upper-range interval performed better on this task. However, this association was found only for the prospective component; the retrospective component showed no association with TSH levels. To be sure, this reflects a ceiling effect for this variable, as 93 percent of the participants successfully remembered the retrospective component of the task. T4 levels were unrelated to both components of prospective memory. A possible explanation for the differential effects of the two thyroid variables is that TSH is a more sensitive indicator of thyroid function.

In a second step, we wanted to examine whether the association between TSH and the prospective component was similar across the whole continuum of the TSH variable. When the sample was divided into quartiles, it was found that the proportion of persons with successful memory increased dramatically in the group with the highest TSH

levels (see Figure 6). Further analyses revealed that the variation at the upper end of the TSH interval alone accounted for the significant effect observed in the previous analyses.

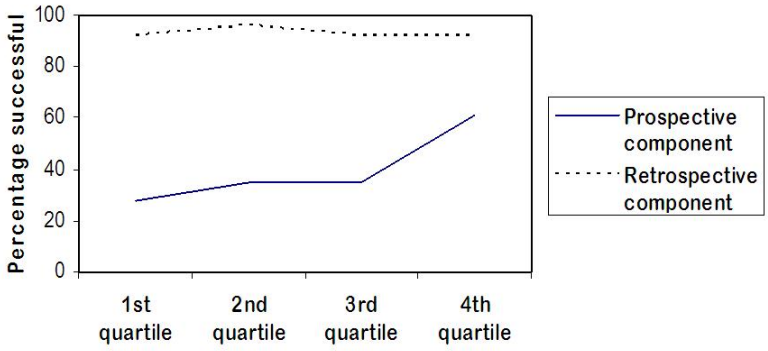


**Figure 6.** Percentage successful participants on the prospective memory task in different TSH quartiles

# 4 DISCUSSION

## 4.1 ARE DIFFERENT COGNITIVE PROCESSES INVOLVED IN PROSPECTIVE AND RETROSPECTIVE REMEMBERING?

To date, most researchers seems to agree that it is relevant to make a distinction between prospective and retrospective memory. Support for this view comes from factor-analytic work (Crawford, Smith, Maylor, Della Sala, & Logie, 2003; Maylor, Smith, Della Sala, & Logie, 2002; Rönnlund, Mäntylä, & Nilsson, 2008; Uttl, Graf, Miller, & Tuokko, 2001) as well as correlational studies (Einstein & McDaniel, 1990; Graf, Uttl, & Dixon, 2002). These studies have identified the two memory constructs as at least partially different. Still, when this dissertation project started, it was uncertain to what extent and in what way these two forms of memory were distinct.

Although this thesis did not primarily aim at examining differences and similarities between the cognitive processes involved in prospective versus retrospective memory, some of the studies included can contribute information on this issue. In Study II, we found that prospective memory performance in elderly persons, who were non-demented at baseline, significantly contributed to predicting Alzheimer's disease at follow-up three years later. Specifically, predictivity improved when prospective memory variables were entered in the regression model, even after retrospective memory performance was taken into account. In addition, although the correlation between prospective and retrospective memory performance was significant, it was still fairly low ($r$=.15 and $r$=.24, for free and total recall, respectively). Altogether, these findings support the view that prospective memory partly relies on cognitive processes not involved in retrospective memory tasks. Specifically, prospective memory tasks generally require the ability to form and maintain an intention over a long retention interval, recognizing the prospective cue at the same time as performing an ongoing task, performing the right action, and evaluating whether the task has been correctly performed.

In Study III, we found that prospective and retrospective memory were differentially affected by depressive symptoms. Retrospective memory performance decreased as a function of increasing depressive symptomatology. Prospective memory, on the other hand, was largely unaffected. The only aspect of prospective memory that was sensitive to depressive symptoms was the retrospective component, where persons with more depressive symptoms had a larger tendency to fail. This is essentially a form of retrospective memory. Thus, the results were interpreted as further support for the idea that prospective and retrospective memory operations are separable, as they were differentially affected by depressive symptoms.

## 4.2 IS PROSPECTIVE MEMORY SENSITIVE TO HEALTH STATUS?

Retrospective episodic memory is known to be especially sensitive to many clinical conditions (Tulving, 2002). For several reasons, it could be expected that this would also be the case for prospective memory. First, prospective memory is a complex function that involves many different types of cognitive processes (Kliegel, Jäger, Altgassen, & Shum, 2008). These include encoding, storage and retrieval of the

retrospective content, but also other processes more related to executive functioning such as planning, monitoring, shifting and inhibition. Accordingly, many brain regions including prefrontal, medial temporal, parietal and extrastriatal areas are important to prospective remembering (West, 2008). This complexity also makes it more likely that prospective memory is sensitive to cognitive decline.

Second, prospective memory problems are reported by patients with many different forms of disorders, and also by carers and clinicians. In addition, objective findings of prospective memory impairment comes from a large variety of clinical populations, including patients with head injuries, Parkinson's disease, multiple sclerosis, HIV, herpes simplex encephalitis, substance abuse, schizophrenia and developmental disorders such as ADHD and autism (Kliegel, Jäger, Altgassen, & Shum, 2008).

In the studies included in this thesis, we found that prospective memory was negatively affected by Alzheimer's disease and vascular dementia. The impairment was evident already during the preclinical phase of Alzheimer's disease, whereas it remains unknown whether the same is true for preclinical vascular dementia. Thyroid functioning, even in the absence of clinical disease, can also have implications for prospective memory functioning. In general, then, the results show that prospective memory is a cognitive sensitive indicator for many health conditions in late life.

However, one exception was found in Study III, where depressive symptoms affected the retrospective component only. Similar depression-related deficits are frequently observed for various retrospective memory tasks (Burt, Zembar, & Niederehe, 1995; Bäckman, Hill, & Forsell, 1996; Christensen, Griffiths, Mackinnon, & Jacomb, 1997; Kindermann & Brown, 1997). Given the importance of the medial-temporal lobe for retrospective memory (Nyberg & Tulving, 1996; Vargha-Khadem et al., 1997), these findings may reflect the fact that the hippocampus and the neighboring regions show shrinkage as a function of depression (Campbell, Mariott, Nahmias, & MacQueen, 2004; Steffens et al., 2000; Videbech & Ravnkilde, 2004). When the prospective component of the task was considered, we did not find any effect of depressive symptoms. The effect was non-existent also when the subsample with clinical diagnoses (i.e., major depression, $n = 14$, or dysthymia, $n = 6$) was compared to the rest of the sample. It is interesting to note that previous studies on depression and prospective memory have yielded somewhat conflicting results, as described in the introduction section of this thesis. Some studies have found a negative association between depressive symptoms and prospective memory (Rude, Hertel, Jarrold, Covich, & Hedlund, 1999), whereas other studies did not find an association (Harris & Menzies, 1999). A review article suggested that a depression-related prospective memory impairment is present in time-based laboratory tasks, but smaller or non-existent for event-based laboratory tasks or naturalistic tasks (Kliegel & Jäger, 2006). It should also be pointed out that many tasks used in previous studies required regular monitoring during a shorter time frame, at the same time as performing an ongoing task. Thus, these tasks were rather different from the task used in this thesis, where participants were asked to perform a prospective memory task at a single occasion after a long retention interval. Future research can hopefully help to increase the understanding of which task-related or other factors that underlie the discrepant results.

## 4.3 ENCODING, STORAGE AND RETRIEVAL IN RETROSPECTIVE MEMORY

In the Kungsholmen project, data which indicated performance during the three memory stages were available for the retrospective memory task. Number of categories represented among the words recalled is an indicator of the participants´ plan at retrieval, and number of items remembered per category indicates the degree of semantic organization at encoding (Craik & Mansini, 1969; Dixon et al., 2004; Hultsch, 1975; A. D. Smith, 1980; Tulving & Pearlstone, 1966). These distinctions are based on findings showing negligible effects of providing category names as retrieval cues once an item from that category has been freely recalled. Thus, the number of items per category variable is insensitive to retrieval manipulations. By contrast, providing the name of a category from which a subject has not recalled any items typically leads to performance benefits. Thus, the number of categories variable is sensitive to retrieval factors. Finally, as an indicator of storage operations, a measure of forgetting (difficulties to consolidate memories) was included.

The data on encoding, storage and retrieval were used in the first three studies, as they focused on episodic memory in general. Taken together, the results showed that all three stages of the retrospective memory process are sensitive to the effects of vascular dementia and Alzheimer's disease, as well as for Alzheimer's disease in the preclinical stage.

The only exception to this generalized impairment was found in Study III, which focused on depressive symptoms. In this study, we found a significant negative effect on storage and retrieval, but failed to find an effect for encoding. The fact that storage operations were impaired is in agreement with previous research, showing that a) hippocampal pathology is common in depression (Campbell, Mariott, Nahmias, & MacQueen, 2004; Steffens et al., 2000; Videbech & Ravnkilde, 2004) and b) hippocampus plays a significant role when memories are consolidated (Squire, 1986; Vargha-Khadem et al., 1997). In addition, the conclusion that depressive symptoms had an effect on retrieval but not on encoding is consistent with the finding from our study that depression-related deficits were greater in free recall than in cued recall (where extra retrieval support was provided).

In Study II, which focused on identification of persons at risk of Alzheimer's disease, the predictive ability of the three indicators was compared. Here, we found that our measure of forgetting (which indicates problems with consolidation) was the most powerful predictor of incident Alzheimer's disease at follow-up. This is consistent with evidence from previous research of hippocampal pathology early in the disease process (Braak & Braak, 1997; van der Flier et al., 2002). In addition to our findings, several other studies have indicated pronounced forgetting in the early clinical or preclinical stages of Alzheimer's disease (Herlitz & Viitanen, 1991; Larrabee, Youngjohn, Sudilovsky, & Crook, 1993; Tierney et al., 1996).

## 4.4 PATTERNS OF COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA

In Study I, we examined episodic memory functioning in Alzheimer's disease, vascular dementia and controls. A small group with a diagnosis of mixed dementia ($n$=6) were included among the persons with vascular dementia. Importantly, however, subsequent analyses where they were excluded yielded similar results.

Overall, no performance differences emerged between the groups with Alzheimer's disease and vascular dementia. Instead, the magnitude as well as the pattern of deficits were similar. For both disorders, we found that the episodic memory impairment was global in nature. Deficits were evident in both prospective and retrospective memory. Also, the deficits were apparent on both components of the prospective memory task, as well as for all stages of retrospective memory. The fact that retrieval support during the retrospective memory task did not alter the pattern (the two dementia groups were still equally impaired), is in line with the notion of a similar global impairment in both disorders.

The majority of persons in the vascular dementia group had previously had a stroke, and in some cases multiple infarcts. A study using other diagnostic tools may have captured more persons with other types of vascular disease, such as subcortical pathology. It is possible that this might have rendered performance differences between the groups with Alzheimer's disease and vascular dementia. In subcortical forms of vascular dementia, executive deficits are often pronounced due to damage to frontal-subcortical brain circuits (Almqvist, Fratiglioni, Aguero-Torres, Viitanen, & Bäckman, 1999; Cummings, 1993; Laukka, Karlsson, MacDonald, & Bäckman, 2009). Therefore, more research is needed to verify whether the results from this study generalize to other subtypes of vascular dementia. This is especially true for the results concerning prospective memory. As very little research has been carried out in this area, the current findings are preliminary.

In Study II, we showed that global episodic memory deficits are present up to three years before a diagnosis of Alzheimer's disease. We did not, however, examine whether the same type or magnitude of impairment occur in preclinical vascular dementia. Previous research has shown that the two dementia etiologies are often similar with regard to cognitive symptoms during the preclinical phase (Jones, Laukka, Small, Fratiglioni, & Bäckman, 2004; Laukka, Jones, Small, Fratiglioni, & Bäckman, 2004; Small, Fratiglioni, Viitanen, Winblad, & Bäckman, 2000). However, to my knowledge, no studies on preclinical vascular dementia have included measures of prospective memory functioning. Thus, we do not know whether prospective memory is impaired in preclinical vascular dementia, or, if that is the case, whether the prospective memory impairment is of equal magnitude as in preclinical Alzheimer's disease. In my view, prospective memory impairment could be expected in preclinical vascular dementia, given that (a) previous research has revealed striking cognitive similarities between the two dementia subtypes during the preclinical phase and (b) vascular dementia is typically characterized by fronto-striatal disturbances and marked deficits in executive functioning (Cummings, 1993; Jones, Laukka, & Bäckman, 2006).

## 4.5 LIMITATIONS

### 4.5.1 The samples

The participants in the Kungsholmen project were 75 years or older already at baseline, and obviously still older at the follow-ups. This is not necessarily a limitation, although we should be careful in generalizing the findings to younger populations. A potential effect of having such an old sample can be an increase in between-person variability, which in turn can decrease the effect of a single factor on cognitive performance. Age-related cognitive decline is a multidetermined phenomenon, and most individual difference variables contribute relatively little to the performance variation when they are examined in isolation (Bäckman et al., 2004).

What is perhaps a more serious limitation is the fact that the samples, at least for some of the diagnostic groups in the studies, were fairly small. Although the Kungsholmen project is a large study, with an unusually high rate of participation, is can still be difficult to gather large enough groups to study the effects of medical conditions that are less common in the general population. Still, a population-based design has many advantages to other types of studies, especially in terms of generalizability.

A small sample increases the risk of type II-errors, denoting failure to show a significant association in cases where a true association exists. This applies particularly to Study I, where we had a small sample of vascular dementia patients ($n$=21). Nevertheless, we showed that both Alzheimer's disease and vascular dementia are associated with episodic memory deficits. Thus, these results are not likely to be altered with a larger sample. However, the finding that the two dementia groups performed alike could theoretically be due to a type II -error. Therefore, we calculated effect sizes for all retrospective memory variables, which revealed that the (nonsignificant) differences between the groups were very small. Thus, we are confident in claiming that the two dementia groups were equally impaired at least in retrospective memory. For prospective memory, the same finding should be treated more cautiously, as the combination of a small sample and a dichotomous memory measure decreases the statistical power.

### 4.5.2 The prospective memory task

The prospective memory task used in this project has a major disadvantage in terms of metric properties. Single, dichotomous measures of prospective memory are more sensitive to measurement noise than continuous prospective memory measures (Maylor, 2008). This can result in (a) less reliable results in general, and (b) a decreased chance of finding existing differences (i.e., type II -errors, as previously discussed). However, this also means that the limitations resulting from a dichotomous task can be compensated by a larger sample (Maylor, 2008). In the studies included in this thesis, we have larger samples in studies III and IV. In the other two studies, the samples of demented participants are small in number although the control groups are large.

As described in the introduction section of this thesis, prospective memory is often difficult to measure in an optimal way. The prospective memory task was designed in order to resemble those prospective memory tasks that are carried out in everyday life.

This increases the ecological validity and the generalizability of the findings. Including many trials in the task, especially within a short time frame, might result in a measure of vigilance rather than of prospective memory. Still, in future research, it is recommended to include a more refined prospective memory task in examining the effects of various age-related disorders.

### 4.5.3 The dementia diagnoses

The physicians had to rely on clinical data and the HIS score in order to make a decision about the presence and subtype of dementia. Unfortunately, no imaging or autopsy data were available. This makes the diagnoses less certain, as we were not able to validate the clinical diagnosis. The differential diagnosis of Alzheimer's disease or vascular dementia is often complicated by the fact that many persons are affected by neurodegenerative and vascular disease at the same time. This pattern is increasingly common in very old age (Aguero-Torres, Winblad, & Fratiglioni, 1999).

However, the uncertainty resulting from the overlap in pathology is at least partly a reflection of reality and not due to the methods adopted. Neurodegenerative and vascular alterations frequently co-occur and contribute to the development of a dementia disorder (Barker et al., 2002; Kalaria & Ballard, 1999). It should also be pointed out that some researchers have suggested that neurodegeneration in Alzheimer's disease is caused by vascular pathology (de la Torre, 2008), which would further attenuate the distinction made between these two disease entities. In the Kungsholmen project, the diagnosis were made independently by at least two physicians, and inter-rater reliability was high (Fratiglioni et al., 1997). In addition, the HIS score was used to improve the accuracy of the differential diagnoses (Hachinski et al., 1975). The sensitivity as well as specificity of the HIS has proved to be high (Moroney et al., 1997).

However, the HIS is a tool developed mainly to distinguish between multi-infarct dementia and Alzheimer's disease. Therefore, we are less likely to capture those persons with vascular dementia that do not have a history of stroke. The fact that the vascular dementia diagnoses mainly included multi-infarct or strategic-infarct dementia has implications for some of the results of this thesis. This applies to Study I, where groups with Alzheimer's disease and vascular dementia are compared, and possibly to Study II, which focuses on early episodic memory impairment in persons that receive an Alzheimer diagnosis up to three years later. The potential effects of the diagnostic procedure have been discussed in a previous section of the discussion. However, it is important to underscore that the generalizability of the findings in Study I are restricted to the subtypes of vascular dementia that occur following stroke.

## 4.6 FUTURE DIRECTIONS

The general aim of this thesis was to explore the effect of health status on cognition in old age. More specifically, we have examined how different aspects of episodic memory are affected by a few common disorders and by subclinical variations in health status. Prospective memory is still a rather new field of research, and little is known about the influence of different health factors on this form of memory. Traditionally, the majority of research studies on episodic memory have focused on retrospective

memory. Still, many questions remain unanswered for retrospective memory as well, such as which health factors have the most pronounced effects, and what specific aspects of retrospective memory are implicated under what circumstances. This thesis has attempted to provide at least partial answers to some of these questions. However, many new questions have also arisen from these and other studies:

One question that arises from Studies I and II is whether prospective memory is affected during the early, preclinical period of vascular dementia. If so, it would be of great interest to compare the time course of prospective memory impairment during vascular dementia and Alzheimer's disease. This would involve following persons from the preclinical to the clinical phases of both disorders.

Another question is whether other subtypes of vascular dementia than those examined here would show similar or different patterns of cognitive deficits. Vascular brain pathology often affects frontal-subcortical circuits to a large degree, resulting in executive deficits (Cummings, 1993). Prospective memory places high demands on executive functions such as attention and planning (Burgess et al., 2008; McDaniel, Glisky, Rubin, Guynn, & Routhieaux, 1999). It is also known that the frontal lobes are highly involved in prospective remembering (Burgess et al., 2008; Kliegel, Jäger, Altgassen, & Shum, 2008). Thus, it may be hypothesized that the prospective memory impairment would be even more pronounced in subcortical forms of vascular dementia.

In Study III, we replicated previous findings showing a negative association between depressive symptoms and retrospective memory performance. A somewhat unexpected finding was that depressive symptomatology was unrelated to prospective memory performance. It should be noted that previous work on depression and prospective memory has yielded some inconsistencies that remain to be solved. Therefore, future research should examine more closely under what circumstances depression-related prospective memory deficits can be expected. It seems likely that task characteristics are at least part of the explanation, (e.g., the length of the retention interval and the number of prospective memory retrievals required).

Finally, in Study IV we examined the effect of TSH on prospective memory, and found that persons in the upper normal-range interval performed on a superior level. This indicates a non-linear association between TSH and cognition, which has to be further explored. There has been a debate about the correct cut-offs to use in order to distinguish between normal and pathological thyroid functioning. A possible interpretation of the results in study IV is that the previously considered "normal-range" interval should be moved further up, at least when cognition is considered. If so, it is an interesting question whether the same is true for younger adults.

# 5 ACKNOWLEDGEMENTS

First of all, my warmest thanks to my supervisor Lars Bäckman for giving me the opportunity to do research at ARC, for your support and outstanding knowledge.

Thanks also to my co-supervisor Åke Wahlin. You were one of the first persons that I met when I first came to ARC to work as a research assistant. You have always been a great support, and I was very happy to be able to work with you again during this dissertation project.

I would also like to thank my co-authors. To Erika Jonsson-Laukka: thank you for being the perfect mentor as well as a good friend. Many thanks also to Sari Karlsson, for generously sharing your great knowledge and to Anna-Karin Berger for your support and valuable comments.

Thanks to the other persons in the psychology group: Johanna Lovén for your support, knowledge, and the fun we had when teaching together, Yvonne Brehmer and Anna Rieckmann for your advice and for organizing dinners and other nice events, Agneta Herlitz for much appreciated advice on teaching and help with this thesis, thanks to Håkan Fischer, Petra Thilers and Helena Westerberg for your practical help and for always being so friendly and fun to work with, and many thanks also to Jenny Rehnman and Joachim Gavazzeni. Thanks also to all other present and former members of the psychology group.

I would also like to thank Ingemar “Pingo” Kåreholt for statistical advise on study IV, Johan Fastbom for providing advise and data regarding the use of medications in the study sample, and Chengxuan Qiu for help with blood pressure data.

Thanks to all participants and staff working with the Kungsholmen Project, as well as with the new longitudinal research study, SNACK. In addition, thanks to all administrative persons in the house for your great help througout the years: Cecilia Annerholm, Britt-Marie Gulbrandsen, Maria Yohuang, Zoltan Pethö, Maria Wahlberg, Lena Ragert-Blomgren, Christian Lynghaug and to Malin Hallberg, Peter Axelsson, Sofia Österman and Helen Hägglund.

Finally, I would like to thank all leaders as well as all other co-workers at the House of Aging Research. I have had a pleasant feeling when coming to work every morning, and this is thanks to all of you. In addition, I would like to thank Stephanie Paillard-Borg for sharing my enthusiasm, frustrations and sometimes pure panic during the last months before my thesis defense, and Hui-Xin Wang for the strawberry plants and nice chats.

Tack till alla små och stora människor runtomkring, som ger mig möjlighet att tänka också på andra saker än forskning: Östen, Monika, Sofie, Mårten, Jonatan, Ludvig, Anette, Erik-Jan, Rintje, Hanna, Anders, Lovisa, Johan, och alla andra.

Sist av allt, ett alldeles särskilt tack till min familj: TACK till min kära mamma, pappa och lillebror. Och till min Stora Kärlek, Anders, och världens bästa och underbaraste busungar – Isak och Linn.

# 6 REFERENCES


Aguero-Torres, H., Winblad, B., & Fratiglioni, L. (1999). Epidemiology of vascular dementia: Some results despite research limitations. *Alzheimer Disease and Associated Disorders, 13*(Suppl. 3), S15-S20.

Almqvist, O., & Bäckman, L. (1993). Progression in Alzheimer's disease: Sequencing of neuropsychological decline. *International Journal of Geriatric Psychiatry, 8*, 755-763.

Almqvist, O., Fratiglioni, L., Aguero-Torres, H., Viitanen, M., & Bäckman, L. (1999). Cognitive support at episodic encoding and retrieval: Similar patterns of utilization in community-based samples of Alzheimer's disease and vascular dementia. *Journal of Clinical and Experimental Neuropsychology, 21*(6), 816-830.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3 ed.). Washington DC: American Psychiatric Association.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4 ed.). Washington DC: American Psychiatric Association.

Anderson, N. D., & Craik, F. I. M. (2000). Memory in the aging brain. In E. Tulving & F. I. M. Craik (Eds.), *The Oxford handbook of memory* (pp. 411-425). NY: Oxford University Press.

Baddeley, A. (1986). *Working memory*. Oxford: Oxford University Press.

Balota, D. A., Dolan, P. O., & Duchek, J. M. (2000). Memory changes in healthy older adults. In E. Tulving & F. I. M. Craik (Eds.), *The Oxford handbook of memory* (pp. 395-409). NY: Oxford University Press.

Barker, W. W., Luis, C. A., Kashuba, A., Luis, M., Harwood, D. G., Loewenstein, D., et al. (2002). Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. *Alzheimer Disease and Associated Disorders, 16*, 203-212.

Bauer, M., London, E. D., Silverman, D. H. S., Rasgon, N., Kirchheiner, J., & Whybrow, P. C. (2003). Thyroid, brain and mood regulation in affective disorder: Insights from molecular research and functional brain imaging. *Pharmacopsychiatry, 36*(Suppl. 3).

Bhatara, V. S., Tripathi, R. P., Sankar, R., Gupta, A., & Khushu, S. (1998). Frontal lobe proton magnetic-resonance spectroscopy in Graves' disease: A pilot study. *Psychoneuroendocrinology, 23*(6), 605-612.

Biondi, B., & Cooper, D. S. (2008). The clinical significance of subclinical thyroid dysfunction. *Endocrine Reviews, 29*(1), 76-131.

Blazer, D. (2003). Depression in late life: Review and Commentary. *Journal of Gerontology: Medical Sciences, 58A*(3), 249-265.

Braak, H., & Braak, E. (1997). Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiology of Aging, 18*(4), 351-357.

Brooks, B. M., Rose, F. D., Potter, J., Jayawardena, S., & Morling, A. (2004). Assessing stroke patients prospective memory using virtual reality. *Brain Injury, 18*(4), 391-401.

Brown, S. C., & Craik, F. I. M. (2000). Encoding and retrieval of information. In E. Tulving & F. I. M. Craik (Eds.), *The Oxford handbook of memory* (pp. 93-108). NY: Oxford University Press.

Burgess, P. W., Dumontheil, I., Gilbert, S. J., Okuda, J., Schölvinck, M. L., & Simons, J. S. (2008). On the role of rostral prefrontal cortex (area 10) in prospective memory. In M. Kliegel, M. A. McDaniel & G. O. Einstein (Eds.), *Prospective memory: Cognitive, neuroscience, developmental and applied perspectives* (pp. 235-260). NY: Lawrence Erlbaum.

Burt, D. B., Zembar, M. J., & Niederehe, G. (1995). Depression and memory impairment: A meta-analysis of the association, its pattern, and specificity. *Psychological Bulletin, 117*(2), 285-305.

Bäckman, L., & Forsell, Y. (1994). Episodic memory functioning in a community-based sample of old adults with major depression: utilization of cognitive support. *Journal of Abnormal Psychology, 103*(2), 361-370.

Bäckman, L., Hill, R., & Forsell, Y. (1996). The influence of depressive symptomatology on episodic memory functioning among clinically nondepressed older adults. *Journal of Abnormal Psychology, 105*(1), 97-105.

Bäckman, L., Jones, S., Berger, A.-K., Laukka, E. J., & Small, B. S. (2005). Cognitive impairment in preclinical Alzheimer's disease: A meta-analysis. *Neuropsychology, 19*(4), 520-531.

Bäckman, L., & Small, B. J. (2007). Cognitive deficits in preclinical Alzheimer's disease and vascular dementia: patterns of findings from the Kungsholmen Project. *Physiology and Behavior, 92*, 80-86.

Bäckman, L., Small, B. J., & Fratiglioni, L. (2001). Stability of the preclinical episodic memory deficits in Alzheimer's disease. *Brain, 124*, 96-102.

Bäckman, L., & Wahlin, Å. (1995). Influences of item organizability and semantic retrieval cues on word recall in very old age. *Aging and Cognition, 2*(4), 312-325.

Bäckman, L., Wahlin, Å., Small, B. J., Herlitz, A., Winblad, B., & Fratiglioni, L. (2004). Cognitive functioning in aging and dementia: The Kungsholmen project. *Aging Neuropsychology and Cognition, 11*(2-3), 212-244.

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience, 12*(1), 1-47.

Campbell, S., Mariott, M., Nahmias, C., & MacQueen, G. M. (2004). Lower hippocampal volume in patients suffering from depression: A meta-analysis. *The American Journal of Psychiatry, 161*(4), 598-607.

Christensen, H., Griffiths, K., Mackinnon, A., & Jacomb, P. (1997). A quantitative review of cognitive deficits in depression and Alzheimer-type dementia. *Journal of the International Neuropsychological Society, 3*, 631-651.

Cohen, J. D., & O'Reilly, R. C. (1996). A preliminary theory of the interactions between prefrontal cortex and hippocampus that contribute to planning and prospective memory. In M. Brandimonte, G. O. Einstein & M. A. McDaniel (Eds.), *Prospective memory: Theory and applications* (pp. 267-295). Mahwah, NJ: Lawrence Erlbaum.

Craik, F. I. M., & Mansini, P. A. (1969). Age and intelligence differences in coding and retrieval of word lists. *British Journal of Psychology, 60*, 315-319.

Crawford, J. R., Smith, G., Maylor, E. A., Della Sala, S., & Logie, R. H. (2003). The Prospective and Retrospective memory Questionnaire (PRMQ): Normative data and latent structure in a large non-clinical sample. *Memory, 11*(3), 261-275.

Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *Neurological Review, 50*, 873-880.

de la Torre, J. C. (2008). Pathophysiology of neuronal energy crisis in Alzheimer's disease. *Neurodegenerative diseases, 5*, 126-132.

Dixon, R. A., Wahlin, Å., Maitland, S. B., Hultsch, D. F., Hertzog, C., & Bäckman, L. (2004). Episodic memory change in late adulthood: Generalizability across samples and performance indices. *Memory and Cognition, 32*(5), 768-778.

Drevets, W. C. (2000). Neuroimaging studies of mood disorders. *Biological Psychiatry, 48*(8), 813-829.

Duchek, J. M., Balota, D. A., & Cortese, M. (2006). Prospective memory and Apolipoprotein E in healthy aging and early stage Alzheimer's disease. *Neuropsychology, 20*(6), 633-644.

Einstein, G. O., & McDaniel, M. A. (1990). Normal aging and prospective memory. *Journal of Experimental Psychology: Learning, Memory and Cognition, 16*(4), 717-726.

Einstein, G. O., & McDaniel, M. A. (1996). Retrieval processes in prospective memory: Theoretical approaches and some new empirical findings. In M. Brandimonte, G. O. Einstein & M. A. McDaniel (Eds.), *Prospective memory: Theory and applications* (pp. 115-141). Mahwah, NJ: Lawrence Erlbaum.

Elias, M. F., Beiser, A., Wolf, P. A., Au, R., White, R. F., & D´Agostino, R. B. (2000). The preclinical phase of Alzheimer disease. A prospective study of the Framingham cohort. *Archives of Neurology, 57*(6), 808-813.

Ellis, J. A., & Freeman, J. E. (2008). Ten years on: Realizing delayed intentions. In M. Kliegel, M. A. McDaniel & G. O. Einstein (Eds.), *Prospective memory: Cognitive, neuroscience, developmental and applied perspectives* (pp. 1-27). NY: Lawrence Erlbaum.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189-198.

Fratiglioni, L., Viitanen, M., Bäckman, L., Sandman, P.-O., & Winblad, B. (1992). Occurence of dementia in advanced age: The study design of the Kungsholmen project. *Neuroepidemiology, 11*(Suppl. 1), 29-36.

Fratiglioni, L., Viitanen, M., von Strauss, E., Tontodonati, V., Herlitz, A., & Winblad, B. (1997). Very old women at highest risk of dementia and Alzheimer's disease: Incidence data from the Kungsholmen Project, Stockholm. *Neurology, 48*(1), 132-138.

Fukui, T., Hasegawa, Y., & Takenaka, H. (2001). Hyperthyroid dementia: Findings and response to treatment. *Journal of the Neurological Sciences, 184*, 81-88.

Giles, A. F. (1982). An improved method for the radioimmunoassay of free thyroxine in serum dialysates. *Clinical Endocrinology, 16*, 101-105.

Gottfries, C.-G. (2001). Late life depression. *European Archives of Psychiatry and Clinical Neuroscience, 251*(Suppl. 2), II57-II61.

Graf, P., & Uttl, B. (2001). Prospective memory: A new focus for research. *Consciousness and Cognition, 10*(4), 437-450.

Graf, P., Uttl, B., & Dixon, R. (2002). Prospective and retrospective memory in adulthood. In P. Graf & N. Ohta (Eds.), *Lifespan development of human memory*. Cambridge, MA: The MIT Press.

Griffin, M. A., & Solomon, D. H. (1986). Hyperthyroidism in the elderly. *Journal of the American Geriatrics Society, 34*, 887-892.

Hachinski, V., Illiff, L. D., Zilkha, E., Du Boulay, G. H., McAllister, V. L., Marshall, J., et al. (1975). Cerebral blood flow in dementia. *Archives of Neurology, 32*, 632-637.

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science, 297*, 353-356.

Harris, L. M., & Menzies, R. G. (1999). Mood and prospective memory. *Memory, 7*(1), 117-127.

Henry, J. D., MacLeod, M. S., Phillips, L. H., & Crawford, J. R. (2004). A meta-analytic review of prospective memory and aging. *Psychology and Aging, 19*(1), 27-39.

Herlitz, A., & Viitanen, M. (1991). Semantic organization and verbal episodic memory in patients with mild and moderate Alzheimer´s disease. *Journal of Clinical and Experimental Neuropsychology, 13*(4), 559-574.

Hughes, C. P., Berg, L., Danzinger, W. L., Cohen, L. A., & Martin, R. L. (1982). A new clinical scale for stageing of dementia. *British Journal of Psychiatry, 140*, 566-572.

Hultsch, D. F. (1975). Adult age differences in retrieval: Trace-dependent and cue-dependent forgetting. *Developmental Psychology, 11*, 197-201.

Huppert, F. A., & Beardsall, L. (1993). Prospective memory impairment as an early indicator of dementia. *Journal of Clinical and Experimental Neuropsychology, 15*(5), 805-821.

Huppert, F. A., Johnson, T., & Nickson, J. (2000). High prevalence of prospective memory impairment in the elderly and in early-stage dementia: Findings from a population-based study. *Applied Cognitive Psychology, 14*(7), S63-S81.

Ingles, J. L., Boulton, D. C., Fisk, J. D., & Rockwood, K. (2007). Preclinical vascular cognitive impairment and Alzheimer's disease: Neuropsychological test performance 5 years before diagnosis. *Stroke, 38*, 1148-1153.

Jacobs, D. M., Sano, M., Dooneief, G., Marder, K., Bell, K. L., & Stern, Y. (1995). Neuropsychological detection and characterization of preclinical Alzheimer´s disease. *Neurology, 45*, 957-962.

Johnson, M. H., & Magaro, P. A. (1987). Effects of mood and severity on memory processes in depression and mania. *Psychological Bulletin, 101*(1), 28-40.

Jones, S., Laukka, E. J., & Bäckman, L. (2006). Differential verbal fluency deficits in the preclinical stages of Alzheimer's disease and vascular dementia. *Cortex, 42*, 347-355.

Jones, S., Laukka, E. J., Small, B. J., Fratiglioni, L., & Bäckman, L. (2004). A preclinical phase in vascular dementia: Cognitive impairment three years before diagnosis. *Dementia and Geriatric Cognitive Disorders, 18*, 233-239.

Kalaria, R. N., & Ballard, C. (1999). Overlap between pathology of Alzheimer disease and vascular dementia. *Alzheimer Disease and Associated Disorders, 13*(Suppl. 3), S115-S123.

Kim, D. H., Payne, M. E., Levy, R. M., MacFall, J. R., & Steffens, D. C. (2002). APOE genotype and hippocampal volume change in geriatric depression. *Society of Biological Psychiatry, 51*, 426-429.

Kim, J. J., & Diamond, D. M. (2002). The stressed hippocampus, synaptic plasticity and lost memories. *Nature Reviews Neuroscience, 3*, 453-462.

Kindermann, S. S., & Brown, G. G. (1997). Depression and memory in the elderly: A meta-analysis. *Journal of Clinical and Experimental Neuropsychology, 19*(5), 625-642.

Kliegel, M., & Jäger, T. (2006). The influence of negative emotions on prospective memory: A review and new data. *International Journal of Computational Cognition, 4*(1), 1-17.

Kliegel, M., Jäger, T., Altgassen, M., & Shum, D. (2008). Clinical neuropsychology of prospective memory. In M. Kliegel, M. A. McDaniel & G. O. Einstein (Eds.), *Prospective memory: Cognitive, neuroscience, developmental, and applied perspectives* (pp. 283-308). NY: Lawrence Erlbaum.

Kliegel, M., & Martin, M. (2003). Prospective memory research: Why is it relevant? *International Journal of Psychology, 38*(4), 193-194.

Kramer, J. H., Rosen, H. J., Du, A.-T., Schuff, N., Hollnagel, C., Weiner, M. W., et al. (2005). Dissociations in hippocampal and frontal contributions to episodic memory performance. *Neuropsychology, 19*(6), 799-805.

Larrabee, G. J., Youngjohn, J. R., Sudilovsky, A., & Crook, T. H. (1993). Accelerated forgetting in Alzheimer-type dementia. *Journal of Clinical and Experimental Neuropsychology, 15*(5), 701-712.

Laukka, E. J., Jones, S., Small, B. J., Fratiglioni, L., & Bäckman, L. (2004). Similar patterns of cognitive deficits in the preclinical phases of vascular dementia and Alzheimer's disease. *Journal of the International Neuropsychological Society, 10*(3), 382-391.

Laukka, E. J., Karlsson, S., MacDonald, S. W. S., & Bäckman, L. (2009). Cognitive functioning in vascular dementia before and after diagnosis. In L.-O. Wahlund, T. Erkinjuntti & S. Gauthier (Eds.), *Vascular cognitive impairment in clinical practice* (pp. 46-57). NY: Cambridge University Press.

Looi, J. C. L., & Sachdev, P. S. (1999). Differentiation of vascular dementia from AD on neuropsychological tests. *Neurology, 53*, 670-678.

Manji, H. K., Drevets, W. C., & Charney, D. S. (2001). The cellular neurobiology of depression. *Nature Medicine, 7*(5), 541-547.

Maylor, E. A. (2008). Commentary: Prospective memory through the ages. In M. Kliegel, M. A. McDaniel & G. O. Einstein (Eds.), *Prospective memory: Cognitive, neuroscience, developmental, and applied perspectives* (pp. 217-233). NY: Lawrence Erlbaum.

Maylor, E. A., Smith, G., Della Sala, S., & Logie, R. H. (2002). Prospective and retrospective memory in normal aging and dementia: An experimental study. *Memory & Cognition, 30*(6), 871-884.

McDaniel, M. A., & Einstein, G. O. (2000). Strategic and automatic processes in prospective memory retrieval: A multiprocess framework. *Applied Cognitive Psychology, 14*, S127-S144.

McDaniel, M. A., Glisky, E. L., Rubin, S. R., Guynn, M. J., & Routhieaux, B. C. (1999). Prospective memory: A neuropsychological study. *Neuropsychology, 13*(1), 103-110.

McDaniel, M. A., Guynn, M. J., Einstein, G. O., & Breneiser, J. (2004). Cue-focused and reflexive-associative processes in prospective memory retrieval. *Journal of Experimental Psychology: Learning, Memory and Cognition, 30*(3), 605-614.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-

ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology, 34*, 939-944.
Meacham, J. A., & Singer, J. (1977). Incentive effects in prospective remembering. *Journal of Psychology, 97*, 191-197.
Moroney, J. T., Bagiella, E., Desmond, D. W., Hachinski, V. C., Mölsä, P. K., Gustafson, L., et al. (1997). Meta-analysis of the Hachinski Ischemic Score in pathologically verified dementias. *Neurology, 49*(4), 1096-1105.
Moscovitch, M. (1992). Memory and working-with-memory - A component process model based on modules and central systems. *Journal of Cognitive Neuroscience, 4*, 257-267.
Moscovitch, M., & Melo, B. (1997). Strategic retrieval and the frontal lobes: Evidence from confabulation and amnesia. *Neuropsychologia, 35*(7), 1017-1034.
Munte, T. F., Radamm, C., Johannes, S., & Brabant, G. (2001). Alterations of cognitive functions induced by exogenous application of thyroid hormones in healthy men: A double-blind cross-over study using event-related brain potentials. *Thyroid, 11*(4), 385-391.
Mäntylä, T. (2003). Assessing absentmindedness: Prospective memory complaint and impairment in middle-aged adults. *Memory and Cognition, 31*(1), 15-25.
Mäntylä, T., & Nilsson, L.-G. (1997). Remembering to remember in adulthood: A population-based study on aging and prospective memory. *Aging, Neuropsychology and Cognition, 4*(2), 81-92.
Nilsson, L.-G. (1973). *Category norms for verbal material* (No. 135). Sweden: Uppsala: University of Uppsala, Department of Psychology.
Nilsson, L.-G. (2003). Memory function in normal aging. *Acta Neurologica Scandinavica, 107*(Suppl. 179), 7-13.
Nyberg, L., & Tulving, E. (1996). Classifying human long-term memory: Evidence from converging dissociations. *European Journal of Cognitive Psychology, 8*(2), 163-183.
Paykel, E. S., & Priest, R. G. (1992). Recognition and management of depression in general practice: Consensus statement. *British Medical Journal, 305*, 1198-1202.
Phillips, L. H., Henry, J. D., & Martin, M. (2008). Adult aging and prospective memory: The importance of ecological validity. In M. Kliegel, M. A. McDaniel & G. O. Einstein (Eds.), *Prospective memory: Cognitive, neuroscience, developmental, and applied perspectives* (pp. 161-185). NY: Lawrence Erlbaum.
Qiu, C., De Ronchi, D., & Fratiglioni, L. (2007). The epidemiology of dementias: An update. *Current Opinion in Psychiatry, 20*, 380-385.
Roman, G. C., Tatemichi, T. K., Erkinjuntti, T., Cummings, J. L., Masdeu, J. C., Garcia, J. H., et al. (1993). Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN international workshop. *Neurology, 43*, 250-260.
Rude, S. S., Hertel, P. T., Jarrold, W., Covich, J., & Hedlund, S. (1999). Depression-related impairments in prospective memory. *Cognition and Emotion, 13*(3), 267-276.
Rönnlund, M., Mäntylä, T., & Nilsson, L.-G. (2008). The prospective and retrospective memory questionnaire (PRMQ): Factorial structure, relations to global

subjective memory ratings, and Swedish norms. *Scandinavian Journal of Psychology, 49*, 11-18.

Seth, J., Kellett, H. A., Caldwell, G., Sweeting, V. M., Beckett, G. J., Gow, S. M., et al. (1984). A sensitive immunoradiometric assay for serum thyroid stimulating hormone: A replacement for the thyrotropin releasing test? *British Medical Journal, 289*, 1334-1336.

Small, B. J., Fratiglioni, L., Viitanen, M., Winblad, B., & Bäckman, L. (2000). The course of cognitive impairment in preclinical Alzheimer disease: Three and 6-year follow-up of a population-based sample. *Archives of Neurology, 57*(6), 839-844.

Smith, A. D. (1980). Age differences in encoding, storage and retrieval. In L. W. Poon, J. L. Fozard, L. S. Cermak, D. Arenberg & L. W. Thompson (Eds.), *New directions in memory and aging*. Hillsdale, NJ: Erlbaum.

Smith, G., Della Sala, S., Logie, R. H., & Maylor, E. A. (2000). Prospective and retrospective memory in normal ageing and dementia: A questionnaire study. *Memory, 8*(5), 311-321.

Squire, L. R. (1986). Mechanisms of memory. *Science, 232*, 1612-1619.

Squire, L.R. (1992). Memory and the hippocampus: A synthesis from findings with rat, monkeys and human. *Psychological Review, 99*, 195-231.

Steffens, D. C., Byrum, C. E., McQuoid, D. R., Greenberg, D. L., Payne, M. E., Blitchington, T. F., et al. (2000). Hippocampal volume in geriatric depression. *Society of Biological Psychiatry, 48*, 301-309.

Tierney, M. C., Szalai, J. P., Snow, W. G., Fisher, R. H., Nores, A., Nadon, G., et al. (1996). Prediction of probable Alzheimer's disease in memory-impaired patients: A prospective longitudinal study. *Neurology, 46*, 661-665.

Tulving, E. (1983). *Elements of episodic memory*. Oxford: Oxford University Press.

Tulving, E. (2002). Episodic memory: From mind to brain. *Annual Review of Psychology, 53*, 1-25.

Tulving, E., & Pearlstone, Z. (1966). Availability versus accessibility of information in memory for words. *Journal of Verbal Learning and Verbal Behavior, 5*, 381-391.

Uttl, B., Graf, P., Miller, J., & Tuokko, H. (2001). Pro- and retrospective memory in late adulthood. *Consciousness and Cognition, 10*(4), 451-472.

Wahlin, Å., Bunce, D., & Robins Wahlin, T.-B. (2005). Longitudinal evidence of the impact of normal thyroid stimulating hormone variations on cognitive functioning in very old age. *Psychoneuroendocrinology, 30*(7), 625-637.

Wahlin, Å., Bäckman, L., & Winblad, B. (1995). Free recall and recognition of slowly and rapidly presented words in very old age: A community based study. *Experimental Aging Research, 21*, 251-271.

Wahlin, Å., Robins Wahlin, T.-B., Small, B. J., & Bäckman, L. (1998). Influences of Thyroid Stimulating Hormone on cognitive functioning in very old age. *Journal of Gerontology: Psychological Sciences, 53 B*, 234-239.

van der Flier, W. M., van den Heuvel, D. M. J., Weverling-Rijnsburger, A. W. E., Bollen, E. L. E. M., Westendorp, R. G. J., van Buchem, M. A., et al. (2002). Magnetization transfer imaging in normal aging, mild cognitive impairment, and Alzheimer´s disease. *Annals of Neurology, 52*(1), 62-67.

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Van Paesschen, W., & Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science, 277*, 376-380.

West, R. (2008). The cognitive neuroscience of prospective memory. In M. Kliegel, M. A. McDaniel & G. O. Einstein (Eds.), *Prospective memory: Cognitive, neuroscience, developmental, and applied perspectives* (pp. 261-282). NY: Lawrence Erlbaum.

Videbech, P., & Ravnkilde, B. (2004). Hippocampal volume and depression: A meta-analysis of MRI studies. *The American Journal of Psychiatry, 161*(11), 1957-1966.

Yamaguchi, H., Sugihara, S., Ogawa, A., Oshima, N., & Ihara, Y. (2001). Alzheimer B Amyloid deposition enhanced by ApoE 4 gene precedes neurofibrillary pathology in the frontal association cortex of nondemented senior subjects. *Journal of Neuropathology and Experimental Neurology, 60*(7), 731-739.

Yuspeh, R. L., Vanderploeg, R. D., & Kershaw, D. A. J. (1998). Validity of a semantically cued recall procedure for the Mini-Mental State Examination. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 11*(4), 207-211.

Åsberg, M., Montgomery, S. A., Perris, C., Schalling, D., & Sedvall, G. (1978). A comprehensive psychopathological rating scale. *Acta Psychiatrica Scandinavica, 271*, 132-138.

# 7 APPENDIX

List of dissertations from the Aging Research Center and the Stockholm Gerontology Research Center, 1991-2008.

**1991**

**Herlitz Agneta.** Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

**1992**

**Borell Lena**. The activity life of persons with a dementia disease.

**1993**

**Fratiglioni Laura.** Epidemiology of Alzheimer's disease. Issues of etiology and validity.

**Almkvist Ove.** Alzheimer's disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

**Basun Hans.** Biological markers in Alzheimer's disease. Diagnostic implications.

**1994**

**Grafström Margareta.** The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)

**Holmén Karin.** Loneliness among elderly - Implications for those with cognitive impairment.

**Josephsson Staffan.** Everyday activities as meeting-places in dementia.

**Stigsdotter-Neely Anna.** Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

**Forsell Yvonne.** Depression and dementia in the elderly.

**1995**

**Mattiasson Anne-Cathrine**. Autonomy in nursing home settings.

**Grut Michaela**. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

**1996**

**Wahlin Åke.** Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.

**Wills Philippa**. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

**Lipinska Terzis Beata.** Memory and knowledge in mild Alzheimer's disease.

**1997**

**Larsson Maria.** Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

**Almberg Britt.** Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

**1998**

**Agüero-Eklund Hedda.** Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

**Guo Zhenchao.** Blood pressure and dementia in the very old. An epidemiologic study.

**Björk Hassing Linda.** 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)

**1999**

**Almberg Britt.** Family caregivers caring for relatives with dementia – Pre- and post-death experiences.

**Robins Wahlin Tarja-Brita.** Cognitive functioning in late senescence. Influences of age and health.

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

**2000**

**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)

**von Strauss Eva.** Being old in our society: Health, functional status, and effects of research.

**2001**

**Jansson Wallis.** Family-based dementia care. Experiences from the perspective of spouses and adult children.

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

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

**2002**

**Fahlander Kjell.** Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.

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

**2003**

**Jönsson Linus.** Economic evaluation of treatments for Alzheimer's disease.

**2004**

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

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

**Qiu Chengxuan.** The relation of blood pressure to dementia in the elderly: A community-based longitudinal study

**Palmer Katie.** Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.

**Larsson Kristina.** According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

**2005**

**Derwinger Anna.** Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.

**De Ronchi Diana.** Education and dementing disorders. The role of schooling in dementia and cognitive impairment.

**Passare Galina.** Drug use and side effects in the elderly. Findings from the Kungsholmen Project.

**Jones Sari.** Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.

**Karp Anita.** Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.

**Nilsson Jan**. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

**2006**

**Klarin Inga.** Drug use in the elderly – are quantity and quality compatible.

**Nilsson Erik.** Diabetes and cognitive functioning: The role of age and comorbidity.

**Ngandu Tiia.** Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.

**Jonsson Laukka Erika**. Cognitive functioning during the transition from normal aging to dementia.

**2007**

**Ferdous Tamanna.** Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)

**Westerbotn Margareta.** Drug use among the very old living in ordinary households - Aspects on well-being, cognitive and functional ability.

**Rehnman Jenny.** The role of gender in face recognition. (Stockholm University)

**Beckman Gyllenstrand Anna.** Medication management and patient compliance in old age.

**Nordberg Gunilla.** Formal and informal care in an urban and a rural population. Who? When? What?

**2008**

**Gavazzeni Joachim.** Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)

**Marengoni Alessandra.** Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.

**Rovio Suvi**. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

**Xu Weili**. Diabetes mellitus and the risk of dementia. A population-based study.

**Meinow Bettina**. Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)

**Agahi Neda**. Leisure in late life. Patterns of participation and relationship with health.

**Haider Syed Imran**. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

**2009**

**Thilers Petra**. The association between steroid hormones and cognitive performance in adulthood.

**Rana AKM Massud**. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.

**Paillard-Borg Stephanie**. Leisure activities at old age and their influence on dementia development.