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# COGNITIVE PERFORMANCE IN OLD-AGE DEPRESSION

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# Cognitive performance in old-age depression

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To everyone who has experienced or will experience depression,  
and to everyone who knows them.

*“There is no need for temples.  
Our own brain, our own heart is our temple; the philosophy is kindness.”*

Dalai Lama XIV



## ABSTRACT

This thesis investigated factors contributing to the high variability of observed cognitive deficits (Studies I, II, III), and reversibility of cognitive deficits (Studies III, IV), in old-age depression. Dementia-free nondepressed and depressed (unipolar; ICD-10 criteria) participants from the population-based Swedish National study on Aging and Care-Kungsholmen (SNAC-K) who underwent extensive neuropsychological testing formed the basis of the study samples.

**Study I** assessed the influence of depression severity on cognitive performance, while controlling for a range of clinical and demographic factors. Individuals with moderate/severe depression exhibited deficits in multiple cognitive domains, whereas only processing speed was affected in mild depression. **Study II** examined the influence of combined *KIBRA* (CC) and *CLSTN2* (TT) risk alleles on episodic memory performance. Episodic memory deficits were only observed in individuals with both depression and the disadvantageous CC/TT allelic combination. **Study III** investigated the role of psychiatric history on cognitive performance in acute and remitted states of depression. Currently depressed individuals with a psychiatric inpatient history and individuals with late-onset depression performed at the lowest levels, whereas cognitive performance in individuals with self-reported recurrent unipolar depression was intermediate. Individuals with remitted unipolar depression exhibited no cognitive deficits. Physical inactivity, cumulative inpatient days, heart disease burden, and prodromal dementia modulated cognitive performance. **Study IV** assessed cognitive performance in different depression courses (depressed-remitted, remitted-depressed, and nondepressed-late-onset depression) longitudinally over a maximum period of 6 years. Cognitive decline was observed in all groups for multiple domains, although individuals who changed their status from nondepressed to depressed showed exacerbated cognitive decline. In remitted states, only processing speed and attention were affected. However, these deficits were modulated by benzodiazepine intake.

In sum, depression-related cognitive deficits were observed in processing speed, attention, executive function, verbal fluency (Studies I, III, IV), episodic memory (Studies I, II), and semantic memory (Study I). No depression-related deficits were observed in general knowledge, short-term memory, or spatial ability. As multiple factors were found to modulate cognitive performance in dementia-free unipolar old-age depression, and consistent with the notion that depression is a heterogeneous disorder, this may explain why patterns of cognitive deficits in depression vary between studies. Recurrence rates of depression remain high, and cognitive deficits in depression are associated with a poor prognosis and take a longer time to recover than depressive symptoms. This underscores the importance of early detection of cognitive deterioration in depression. Importantly, cognitive deficits in depression seem largely reversible. Thus, they should be regarded as treatment targets rather than as stable vulnerabilities. Combined profiles of psychiatric history, cognitive performance, and health behaviors may provide important information to individualized treatment.

## SAMMANFATTNING

Denna avhandling undersökte faktorer som kunnat bidra till den stora variation som observerats i studier rörande kognitiva nedsättningar hos äldre deprimerade (Studie I, II, III), och deras reversibilitet (Studie III, IV). Icke-deprimerade personer och deprimerade personer (unipolär depression; ICD-10 kriterier) utan demens som deltagit i den populationsbaserade SNAC-K studien och genomgått kognitiv testning, utgjorde grunden för studiernas undersökningsgrupper.

**Studie I** undersökte påverkan av depressionsgrad på kognitiv prestation, när man kontrollerar för kliniska och demografiska faktorer. Personer med måttlig/svår depression uppvisade nedsättningar i flera kognitiva domäner, däremot var endast mental hastighet nedsatt hos personer med mild depression. **Studie II** undersökte påverkan av kombinationen av *KIBRA* (CC) och *CLSTN2* (TT) risk-alleler på prestation i episodiskt minne. Nedsättning i episodiskt minne observerades enbart för personer med både depression och de två risk- allelerna (CC/TT). **Studie III** undersökte påverkan av psykiatrisk historik på kognitiv prestation hos personer som antingen var i en depressiv episod eller återhämtat sig därifrån. Deprimerade personer med psykiatrisk historik, och personer med depressions-debut vid högre ålder presterade sämst kognitivt. Personer med självrapporterad historik av återkommande depressiva episoder presterade på en mellannivå, medan personer som återhämtat sig inte uppvisade några kognitiva nedsättningar. Fysisk inaktivitet, kumulativa sjukhusvistelser, hjärtsjukdom och preklinisk demens modulerade gruppskillnader i kognitiva förmågor. **Studie IV** undersökte kognitiv prestation longitudinellt under olika depressions-faser (deprimerad - återhämtad, återhämtad - deprimerad, icke-deprimerad - depressions debut). Kognitivt åldrande observerades för samtliga grupper i flera kognitiva domäner, däremot försämrades personer som utvecklade depression vid uppföljningen i snabbare takt. Vid återhämtning från depression observerades enbart nedsatt prestation i mental hastighet och uppmärksamhet, men dessa nedsättningar kunde delvis förklaras av intag av benzodiazepiner.

Sammantaget observerades depressionsrelaterade kognitiva nedsättningar i mental hastighet, uppmärksamhet, exekutiva funktioner, verbalt flöde (Studie I, III, IV), episodiskt minne (Studie I, II) och semantiskt minne (ordkunskap; Studie I). Inga kognitiva nedsättningar observerades i kunskapsminne, korttidsminne eller spatial förmåga. Då en rad faktorer modulerade kognitiv prestation hos personer med unipolär depression utan demens, och depression är ett heterogent syndrom, kan detta förklara varför mönster av kognitiva nedsättningar skiljer sig mellan studier. Depressionsåterfall är mycket vanligt, och kognitiva nedsättningar i depression är kopplade till en dyster prognos, och kan ta längre tid att återhämta sig från relativt depressiva symptom. Därför är det av stor vikt att upptäcka depression i ett tidigt skede. Kognitiva nedsättningar i depression verkar i stor utsträckning vara reversibla. De bör därför betraktas som behandlingsbara tillstånd istället för stabila nedsättningar. Kombinerade profiler av psykiatrisk historik, kognitiv prestation och hälsobeteenden kan ge viktig information till en mer individualiserad behandling.

## LIST OF SCIENTIFIC PAPERS

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## LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
CLSTN2	Calsyntenin 2
CPRS	Comprehensive Psychopathological Rating Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Classification of Mental and Behavioural Disorders
IPR	Swedish National Inpatient Register
KIBRA	Kidney and Brain expressed protein
MADRS	Montgomery and Åsberg Depression Rating Scale
MAO	Monoamine Oxidase Inhibitors
MMSE	Mini Mental State Examination
SNAC-K	Swedish National Study on Aging and Care in Kungsholmen
SSRI	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic Agents
TMT	Trail Making Test



# 1 INTRODUCTION

## 1.1 DEPRESSION

Depression has been documented throughout history. In Ancient Greece, disease was thought to result from imbalances of the four bodily fluids (blood, yellow bile, black bile, and phlegm). Hippocrates (460-377 BC) described *melancholia*, which included a broad spectrum of conditions, as a distinct disease caused by excess of black bile from the spleen that affected the brain (Davison, 2006).

Today, there are two major diagnostic manuals of mental disorders: the American Diagnostical and Statistical Manual for Mental Disorders (DSM-5; APA, 2013) and the European International Classification of Mental and Behavioural Disorders (ICD-10; WHO, 1993). However, it was not until 1952 (DSM-I; APA) that the first diagnostic criteria for mental disorders emerged (ICD-8 came in the early 60's). Since then, depression has had several categorizations, including neurosis (DSM-II; APA, 1968) and affective psychosis (ICD-8; WHO, 1965). The variability in conceptualization and diagnostic criteria for depression suggests difficulties in conceptualizing emotional disorders. Today, depression is categorized as affective disorders by ICD-10 (WHO, 1993) and as depressive disorders by DSM-5 (APA, 2013), and consists of multiple types (e.g., unipolar, bipolar, cyclothymia, dysthymia) and specifiers (e.g., mild, moderate, severe, with or without psychotic symptoms).

Unipolar depression (in contrast to bipolar disorders, with occurrence of both depressive and manic episodes) is primarily characterized by low mood, loss of interest and enjoyment (also called anhedonia), and reduced energy leading to diminished activity. The depressive symptoms should represent a change from previous functioning, and should last at least 2 weeks. According to ICD-10 criteria, at least two of the above mentioned symptoms, plus at least two of the following symptoms should be present to diagnose mild depression (4 depressive symptoms): reduced concentration and attention; reduced self-esteem and self-confidence; ideas of guilt and unworthiness; bleak and pessimistic views of the future; ideas or acts of self-harm or suicide; disturbed sleep, and; disturbed appetite. As depressed individuals may exhibit a wide variation in symptoms, depression is considered a heterogeneous disorder (Fava & Kendler, 2000).

Depression is a leading cause of global disease burden (Ferrari et al., 2013), accompanied by emotional and functional disability (APA, 2013), and affects more than 350 million people globally across all ages (WHO, 2005). Depression is not only highly prevalent, but also highly recurrent; the life time risk of depression is higher for women (10-25%) than men (5-12%), and the majority (25-75%) have more than one episode (APA, 2000). Furthermore, rates of recurrence tends to increase with subsequent episodes (APA, 2000), and comorbidity occurs frequently, such as anxiety disorders (Moffitt et al., 2007). The median age of onset for depression is 32 years, and about 10% have their first depressive episode after the age of 55

(APA, 2000). Depression is also related to suicide; about 15% of clinically depressed individuals take their lives (Yen et al., 2003). Thus, for the majority of people with depressive disorders the prognosis is a life-long disorder with multiple recurrences (WHO, 1993; 2005; APA, 2000).

A negative view of the world, oneself, and the future is characteristic of depression (Beck, 1967). This “negative cognitive triad” is related to biases in attention and memory, such that negative information is more easily attended to and recalled (Matthews & MacLeod, 2005). Furthermore, rumination (recycling of negative thoughts) is frequently occurring in depression (Aldao et al., 2010), and prolongs negative mood (Cooney et al., 2010; Scheppes, et al., 2015). Thus, emotion regulation is affected in depression (Sheppes et al., 2015), which in turn affects inhibitory cognitive control (Joorman & Gotlib, 2010; Zetsche et al., 2012).

The etiology of depression is recognized as a complex interplay between nature and nurture (Colman et al., 2014; Pasquini et al., 2014). Thus, biological vulnerabilities are thought to interact with environmental risk factors. There are numerous risk-factors and endophenotypes for depression (see Goldstein & Klein, 2014, for a review), where at least some of the associations appear to be causal: female gender, stressful life events, adverse childhood experiences, and the personality trait neuroticism (Fava & Kendler, 2000). There is an increased risk of depression in first-degree relatives (30-40%; Kendler et al., 2006; Sullivan et al., 2000). However, it seems that the risk for depression arises from multiple susceptibility genes, each of which has a small effect that is neither necessary nor sufficient for development of depression (Lau & Elay, 2010). Stress may be defined as when a person perceives that demands or threats to their well-being are higher than the available resources (Lazarus, 1999). Early exposure to adverse stress (prenatal and childhood) has been linked to cognitive deficits and increased risk of depression in adolescents and adults (Joëls & Baram, 2009; Lupien et al., 2009). Moreover, the majority (80%) of depressive episodes seems to be preceded by stressful life events (Hammen, 2005). The personality trait neuroticism is described as a disposition to report and experience negative emotions (Eysenck, 1967). Not only do depression and neuroticism share susceptibility genes (Lau & Elay, 2010), depressed persons with high levels of neuroticism also have a more chronic course of depression (Mulder, 2002).

Neurobiological alterations are associated with depression (for reviews, see Arnone et al., 2012; Drevets et al., 2000; Nestler et al., 2002). At the neurotransmitter level, multiple studies have shown lowered levels of serotonin, norepinephrine, and dopamine in depression. These neurotransmitters are important regulators of bodily functions and behavior. Serotonin regulates mood, impulse control, as well as social and goal-directed behaviors (Owens & Nemeroff, 1994; Savitz et al., 2009). Norepinephrine is released during situations of experienced danger or fear in the sympathetic nervous system, and regulates attention, concentration, and states of arousal (Ferry et al., 1999). Dopamine regulates motivation, exploratory behavior, learning, and reward-mediated behavior (Nestler & Carlezon, 2006). At the brain-systems level, the amygdala (regulator of fear and danger responses, located in the limbic system in the temporal lobes) is

associated with hyperactivity (Fitzgerald et al., 2008), which in turn is associated with hypervigilance and a high degree of stress (McEwen, 2009), whereas the prefrontal cortex is associated with hypoactivity (Fitzgerald et al., 2008; Ochsner & Gross, 2005). Together, these activity alterations in depression imply that the limbic system is overriding the prefrontal cortex, which regulates functions such as logical thinking, self-control, self-awareness and executive function. This is often referred to as “mood over mind”, so that negative mood may dominate the life situation, as opposed to “mind over mood”. At the connectivity level, impaired fronto-striatal connectivity is a well-documented finding in depression (Arnone et al., 2012; Drevets, 1999). At the volumetric level, atrophy in hippocampus, basal ganglia, and frontal cortex has been observed (Bremner et al., 2000; Lorenzetti et al., 2009). This has consequences for cognitive functioning, including domains such as episodic memory, executive function, processing speed, and verbal fluency (Alvarez & Emory, 2006; de Quervain et al., 2010; Newcomer et al., 1999; Tulving, 2002). Thus, depression is associated with numerous brain alterations, although it remains unclear whether depression is the cause or effect of these changes.

The first antidepressant medications emerged in the 1950's, and guided cellular and molecular theories on depression etiology. The “monoamine hypothesis” rests on the assumption that depression is the result of functional decline in monoamines (e.g., lowered levels of serotonin, norepinephrine and dopamine) in specific brain regions (Prange, 1964; Schildkraut, 1965). The first drugs were tricyclic agents (TCAs, such as Imipramine; Kuhn, 1958), which inhibit reuptake of serotonin and noradrenaline from the synaptic cleft by blocking serotonergic and noradrenergic reuptake transporters, respectively. These compounds are still prescribed, but rarely as first-line agents, as side effects are substantial. Monoamine Oxidase Inhibitors (MAOIs, such as Iproniazid; Baiely et al., 1959) also arrived in the 1950's, and similar to TCAs, they have substantial side effects. Selective Serotonin Reuptake Inhibitors (SSRIs, such as Prozac) were introduced in 1987, and inhibit serotonin reuptake, which in turn increases synaptic serotonin levels, causing increased serotonin receptor activation and enhanced postsynaptic responses. SSRIs are used as first-line agents in depression treatment today (APA, 2010; Socialstyrelsen, 2010). Further development of antidepressants after the SSRIs include serotonin-norepinephrine reuptake inhibitors (SNRIs, such as Venlafaxine), and agents targeting circadian rhythms (e.g., melatonin release; such as Agomelatine). Other antidepressant treatments include transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT; used in severe and suicidal depression), and psychotherapy (e.g., cognitive behavioral therapy (CBT), interpersonal therapy (IP), mindfulness-based stress reduction (MBSR), and acceptance commitment therapy, (ACT)). MBSR has shown good treatment efficacy in recurrent depression (for a review see, Gotink et al., 2015). Despite multiple treatment modalities, recurrence rates of depression are high (APA, 2013), and around 30-40% of depressed persons are classified as non-responders to antidepressant agents (Kuk et al., 2010; Trivedi et al., 2006). Further, there is large variability in treatment response; some persons respond early in the treatment course, whereas others do so much later (Keller et al., 2000; Trivedi et al., 2006);

some persons do not respond to one pharmacological agent, but to another (Rush et al., 2006), other persons do not respond to pharmacological agents at all, but to psychotherapy (Thase et al., 2000), and vice versa; and still other persons may need a combination of pharmacological agents and psychotherapy in order to reach remission (Keller et al., 2000).

Taken together, depression is a commonly occurring, seriously impairing, heterogeneous and recurrent disorder, accompanied by a multifactorial etiology and neurobiological alterations, which is difficult to treat to remission.

## **1.2 DEPRESSION IN OLD AGE**

Depression is common across the lifespan (prevalence ranges of major depressive disorder: children: 0.3-3.0%; youth: 1.9-18.4%; middle-aged: 2-8%; older: 1-9%; Gotlib & Hammen, 2010; APA, 2013). The distribution is typically U-shaped, with the highest prevalence rates among adolescents and older persons (Kessler et al., 1992). Depression is highly distressing in all ages, but can be especially problematic in old age when the symptoms most likely add to other diseases and physical disabilities (Alexopoulos, 2005; Beekman et al., 2002; Gottfries, 2001), such as cardiovascular diseases and loss of hearing and vision. Older persons are less likely to report affective symptoms (i.e. the cardinal symptoms of depression; Brodaty et al., 2001; Gallo et al., 1997) and more likely to report psychosomatic complaints (Hegeman et al., 2012). As a consequence, old-age depression is often both underrecognized and undertreated (Cole et al., 1999; Reynolds et al., 2001). Furthermore, depression in old age has negative impacts on quality of life, global functioning, and physical health (Koenig et al., 2014).

Prevalence of mild depression in older ages in the general population is higher (8-14%) compared to moderate and severe depression (1-9%). Importantly, if mild depression is undetected, and thus left untreated, about 25% will develop moderate depression within 2 years (Alexopoulos, 2005). In the oldest old (85+), depression can affect as many as 29% (Bergdahl et al., 2007), and this is also an age when suicide rates increase (Wang & Blazer, 2015). Furthermore, in hospitalized and nursing home patients depression prevalence may be as high as 40% (Beekman et al., 2002). There are reports that older women are still twice as often affected in comparison to men (Blazer, 2003), but also reports on greatly reduced gender differences in aging (Steffens et al., 2009).

The course of depression in old age is often more chronic as compared to midlife depression, and also more difficult to treat to remission (Beekman et al., 2002; Koenig et al., 2014), due to comorbidity and cognitive deficits (Blazer et al., 2003).

Older persons with depression differ in several respects, particularly in terms of psychiatric history and comorbidity (Taylor, 2014). It is therefore important to distinguish between late-onset (LOD) and early-onset depression (EOD, i.e., recurrent depression). The definition of LOD usually varies between onsets after the age of 50-65 years (Herrmann et al., 2007).

Individuals with LOD have lower rates of family history with depression (Devanand et al., 2004), and higher prevalence of dementia (Alexopoulos, 2003) as compared to those with EOD. Furthermore, comorbidity of medical diseases and other psychiatric disorders may influence the manifestation of depression in an older person's life (Baune et al., 2009).

Increasing age is a well-known risk factor for dementia (Raber et al., 2004), and depression is associated with an increased risk of dementia (Byers & Yaffe, 2011; Saczynski et al., 2010). Also, 30-50% of persons with Alzheimer's disease have significant depressive symptoms (APA, 2000). This is yet another reason why old-age depression differs from depression earlier in life. This makes the study of depression in old age highly important, especially as the proportion of older individuals is increasing all over the world (Christiansen et al., 2009). This population is highly vulnerable due to the frequency of other diseases and physical disabilities, as well as vulnerabilities associated with the aging brain. As such, depression adds to a challenging life situation in senescence.

### 1.3 COGNITION

“*Cogito ergo sum*” – “I think therefore I am.” These highly cited words were stated by the philosopher René Descartes (1596-1650). However, as the neurologist Antonio Damasio suggested in his book *Descartes' error*, it might be more correct to state: “I have a brain, therefore I think” (Damasio, 1995).

The term cognition (derived from the latin verb *cognoscere*, *con* with and *gnosco* know; “to know”) may be described as knowledge-related mental information processing; the way we human beings attend to, work with, store, and retrieve information. Our senses (vision, hearing, taste, smell, touch) are information receivers, but the ability to comprehend information is a complex interplay of brain processes. Cognition includes areas such as planning, decision making, problem solving, reasoning, remembering, and language production, and can be conscious as well as unconscious (or effortful vs. automatic). According to connectionist models, cognition is thought to consist of assemblies of brain connections, where one node is connected to other nodes in large networks (McClelland, 1988). Cognitive abilities are the underlying brain functions that make it possible to think, remember, and learn. Hence, cognitive skills greatly contribute to an individual's ability to function in everyday life.

Below follows an overview of the cognitive domains examined in this thesis, all of which were investigated using emotionally neutral stimuli.

### **1.3.1 Processing speed**

The ability to process information at a speedy rate enables grasping of knowledge faster, and thus, facilitates learning. Processing speed can be described as cognitive efficiency or proficiency; the ease with which something is processed. It has been proposed that age-related differences in cognitive performance to a large part may stem from decreased processing speed (Salthouse, 1992).

### **1.3.2 Attention**

Attention may be described as the ability to attend to some things while ignoring others, and is assumed to be limited in capacity (Pashler et al., 2001). We make a selection of where to direct our awareness, but our attention may also be reflexive, such as when a loud noise disrupts a conversation, and we momentarily look for the source of the noise to evaluate if it is dangerous or not. In other words, attention may be described as how the brain controls its own information processing (Chun et al., 2011). This process may affect how we encode and analyze sensory inputs, and consequently act on it.

### **1.3.3 Executive functioning**

Executive functions, also referred to as cognitive control, involve multiple top-down effortful mental processes (Diamond, 2013). Building on Baddeley and Hitch's (1974) multicomponent model of working memory (see below), Miyake and colleagues (2000), proposed a theory on how the central executive controls the two slave systems (phonological loop and visuospatial sketchpad). Executive control was proposed to be exerted via three core functions: shifting (between tasks or mental sets), updating (refreshing and monitoring of working memory representations), and inhibition (suppression of dominant, automatic or prepotent responses). In this thesis, only shifting was examined.

### **1.3.4 Memory**

Oscar Wilde (1854-1900) eloquently described memory as "*the diary we all carry with us*". Memory involves encoding, storing, and retrieving information. Our sense of self, our identity, we consequently owe to our memory.

Memory consists of process-related systems. The notion of multiple memory systems, and interactions between them, is nowadays widely accepted (Eichenbaum & Cohen, 2001; Squire, 2004). However, there still remains uncertainty about the exact number of memory systems.

A commonly used distinction is that between nondeclarative (not examined in this thesis) and declarative memory (Atkinson & Shiffrin, 1968; Squire 1993). Nondeclarative memory consists of procedural memory (learning of motor skills, such as walking, and riding a bike – behaviors

that after acquisition becomes automatic) and the perceptual representation system (PRS), also referred to as priming. Nondeclarative memories are typically out of reach of conscious awareness (i.e., no mental effort is needed, for example, we do not need to ask ourselves “how is this done?” every time we ride a bike or drive a car). Declarative memory may further be divided into short-term and long-term memory.

#### *1.3.4.1 Short-term memory*

Short-term memory is the retention of information over seconds to minutes (Jonides et al., 2008). This memory system is assumed to be limited, and the number of items that can be retained has been proposed to be  $7 \pm 2$  (Miller, 1956). An example of short-term memory is the retention of a phone number. In addition to storage, working memory, also involves performing mental operations (i.e., manipulations). Baddeley and Hitch (1974) proposed a cognitive framework of a three part working memory system consisting of a central executive function (see above) that controls two subordinate content-specific systems: the phonological loop (rehearsal) and the visuospatial sketch pad (visuospatial information storage). In 2000, an episodic buffer was added to this working memory model (Baddeley, 2000), a component that binds the various content types together.

#### *1.3.4.2 Long-term memory*

Long-term memory is the retention of information over days and years, and is typically subdivided into episodic and semantic memory (Tulving, 1972). Both memory systems involve conscious recollection of stored information, but differs in their content. Episodic memory stores personal events that specifies what, when and where, and has further been described as mental time travelling (Tulving, 2002). An example of an episodic memory is when and where the last vacation was spent, what activities were performed, and other types of contextual information (e.g., persons present, weather conditions, etc.). Episodic memory is highly sensitive to aging (Rönnlund et al., 2005), and among the first cognitive domains affected in dementia (Bäckman et al., 2005). Semantic memory, in turn, concerns the recollection of factual knowledge. Examples of semantic memory are recollections of bird species, reciting a poem, or naming the highest mountains on every continent.

### **1.3.5 Verbal fluency**

Language encompasses abilities such as production of speech, writing text, and comprehension of spoken and written words (Strauss et al., 2006). Verbal fluency may be described as the production of a series of words, and typically also taxes other cognitive domains such as executive functioning and processing speed (Lezak, 2005).

### **1.3.6 Spatial ability**

Spatial ability has been described as the capacity to comprehend and remember spatial relationships among objects (Webb et al., 2007). Spatial skills are important in many areas, such as mathematics and engineering (Wright et al., 2008), and encompasses tasks such as driving a car, building a house, or assembling IKEA furniture.

## **1.4 COGNITIVE PERFORMANCE IN OLD-AGE DEPRESSION**

Depression frequently presents with cognitive deficits in all ages (for a review on research with younger adults, see Castaneda et al., 2008). Cognitive deficits in depression have been shown to contribute to poor functioning independent of affective symptoms (Jaeger et al., 2006), affecting situations in daily life, such as maintaining household and interpersonal relationships.

Importantly, cognitive deficits in depression are associated with higher rates of recurrence (Fossati et al., 2002; Majer et al., 2004), longer episode durations and reduced remission rates (McCall & Dunn, 2003; Papakostas, 2014), reduced coping abilities and treatment compliance (Dunkin et al., 2000), poorer antidepressant treatment response (Koenig et al., 2014; Morimoto & Alexopoulos, 2015), and greater overall disability (Koenig et al., 2014). Thus, cognitive deficits in depression are associated with poor prognosis.

Underdetection of depression in older ages is a common problem (Cole et al., 1999; Reynolds et al., 2001), as this population is less likely to report mental health symptoms (Brodaty et al., 2001; Gallo et al., 1997), and more likely to report psychosomatic symptoms compared to their younger counterparts (Hegeman et al., 2012). A factor that further complicates diagnosis of depression in older ages is that depressive symptoms may be conceived of as something “normal” in late life (Netuveli et al., 2006). Thus, at a time when spouses and friends may have poor physical health and die, when an older person’s physical body may limit activities that previously were easily accomplished and enjoyed, and when normal cognitive decline is frequently occurring — depressive symptoms may be overlooked rather than attended to — both by the person experiencing them, and by the examining doctor. Furthermore, depression-related cognitive deficits in older ages may mimic dementia-related problems, as episodic memory deficits characterize both dementia and depression (Bäckman et al., 2005; Potter & Steffens, 2007; Veiel, 1997). Thus, persons who should be diagnosed with depression may be wrongly diagnosed with dementia, a phenomenon known as “pseudo dementia” (Fischer, 1996). These problems make it especially important to extend the knowledge on cognitive performance in old-age depression.

### **1.4.1 Cognitive deficits during an acute episode**

Multiple cognitive domains are affected in old-age depression. Deficits have been reported in: processing speed (Beats et al., 1996; Butters et al., 2004; Kramer-Ginsberg et al., 1999; Köhler et al., 2010; Nebes et al., 2000); attention (Ganguli et al., 2009; Thomas et al., 2009); executive functions (Beats et al., 1996; Baudic et al., 2004; Butters et al., 2004; Elderkin-Thompson et al., 2004; 2007; Lockwood et al., 2002; Nebes et al., 2003; Sheline et al., 2006); episodic memory (Bäckman et al., 1994; 1996; Kramer-Ginsberg et al., 1999; Sheline et al., 2006; Veiel, 1997); semantic memory (Bhalla et al., 2006; Sheline et al., 2006; Zakzanis et al., 1998); verbal fluency (Beats et al., 1996); and visuospatial ability (Bhalla et al., 2006; Elderkin-Thompson et al., 2004; Lesser et al., 1996; Thomas et al., 2009). However, there are also numerous reports of lack of cognitive deficits in these domains: processing speed (Boone et al., 1995); executive functions (Baune et al., 2006; Boone et al., 1995; Elderkin-Thompson et al., 2007); episodic memory (Baune et al., 1996); and semantic memory (Butters et al., 2004; Ravdin et al., 2003). Moreover, some reports of complete absence of cognitive deficits also exists (Fisher, et al., 2008; Krogh et al., 2012).

Hence, cognitive deficits in depression differ both between and within studies. The large heterogeneity of cognitive deficits in old-age depression may originate from multiple factors acting as modulators: clinical factors, including age of onset and cumulative illness burden (Hasselbalch et al., 2013), depression severity (McDermott & Ebmeier, 2009), comorbidity (Baune et al., 2009), inpatient versus outpatient status (Lee et al., 2012), medication status (Porter et al., 2003); demographic factors, including gender (Halpern et al., 2007; Miller & Halpern, 2014), education and age (Rönnlund et al., 2005); health behaviors, including exercise (Colcombe & Kramer, 2003); and the presence of risk alleles of cognitively relevant genes (Laukka et al., 2013; Papassotiropoulos, 2006).

Research on the influences of these factors on cognitive performance in old-age depression is scarce. Therefore, it is important to extend our knowledge of the influence of both depression-related factors modulating cognitive performance in old age, as well as the influence of demographic and other factors previously known to affect cognitive performance in nondepressed samples. This is a pertinent issue, as findings on cognitive deficits in old-age depression are mixed, and as cognitive deficits in depression have major implications for treatment and the likelihood of remission.

### **1.4.2 Cognitive deficits during remission**

The heterogeneity of cognitive deficits in depression is extended to remission of depression, although the bulk of findings demonstrate remaining deficits (for reviews, see Bora et al., 2013; Hasselbalch et al., 2011). The majority of evidence on reversibility of cognitive deficits in depression stems from younger samples (Biringier et al., 2005; 2007; Gallagher et al., 2007;

Hammar & Årdal, 2012; Lahr et al., 2007), although there are some reports of reversibility in old-age depression (Barch et al., 2012; Beats et al., 1996; Story et al., 2008).

It has been suggested that cognitive deficits in depression are more trait- (stable deficits in both acute and remitted states) than state-related (fluctuating between acute and remitted states, i.e., somewhat reversible). The most recent review of longitudinal studies, following persons from a depressed state to a remitted state, summarized their findings suggesting that attentional and executive dysfunctions may be trait-related, whereas deficits in other cognitive domains may be state-related (Douglas & Porter, 2009). However, recent findings regarding this question are mixed. For example, studies have shown support for executive dysfunction being trait-related (Årdal & Hammar, 2011; Koenig et al., 2015), whereas other studies have indicated reversibility (Barch et al., 2012; Gorlyn et al., 2015). Furthermore, factors that modulate cognitive performance during a depressed state, as described above, may also modulate performance in a remitted state.

As findings on whether cognitive deficits in depression are state- or trait related have been mixed, further investigation of this research question is warranted. Notably, if cognitive deficits in old-age depression are reversible (i.e., state-related), then they should be regarded as targets for treatment, rather than as stable vulnerabilities.

### **1.4.3 Origins of cognitive deficits**

As noted, cognitive deficits in depression are well-established. Although this research field is relatively young, and cognitive symptoms are described vaguely in the clinical criterion – “*reduced concentration and attention*” – (ICD-10; WHO, 1993), cognitive deficits are now considered a core feature of depression (Köhler et al., 2010).

There are several theories of the origins of cognitive deficits in depression. One of the earliest accounts suggested lack of motivation as the underlying cause (Weingartner et al., 1981). Lack of motivation was thought to be associated with lowered drive, and thus associated with anhedonia (loss of interest and enjoyment). Relatedly, it has been suggested that studying depression is, to some extent, to study reduced motivation (Austin et al., 2001). The typical way to examine lack of motivation was to use tasks measuring lack of response to monetary reward (Richards & Ruff, 1989). Typically, depressed persons were less sensitive to reward as compared to nondepressed.

Another notion is based on the distinction between effortful and automatic processing, where the first category was assumed to be impaired, whereas the other was not (Denny & Hunt, 1992; Hertel & Hardin, 1990). The reason for this pattern was thought to be reduced attentional capacity in depression (Hasher & Zacks, 1979). However, both these theories have been refuted (Austin et al., 1992; 1999; Brown et al., 1994; Kindermann & Brown, 1997), and cognitive

deficits in depression are no longer considered epiphenomena of poor motivation or attentional capacity.

More recent theories on the origins of cognitive deficits in depression include stress. The overdrive of the Hypothalamic-Pituitary-Adrenal axis (HPA), is a well-documented finding in depression (Pariante & Lightman, 2008) and an essential feature of stress (Sapolsky, 2000a). The HPA-axis overdrive leads to excessive levels of cortisol, which in turn may have detrimental effects on episodic memory and other cognitive domains (de Quervain et al., 2010; Howland & Yang, 2008; Newcomer et al., 1999; Schwabe et al., 2010), due to hippocampal atrophy following the cortisol cascade (Sapolsky, 2000b). It has further been shown that the prefrontal cortex is even more sensitive to the negative effects of stress compared to the temporal lobes (Lupien et al., 1999; Young et al., 1999), which may have implications for cognitive domains such as executive function, attention, processing speed, and verbal fluency (Alvarez & Emory, 2006). Thus, elevated and prolonged stress may be a key factor in the origins of cognitive deficits in depression.

As mentioned, there are at least two types of depression in older ages: recurrent depression (EOD) and the development of a first depressive episode (LOD). These two types of depression have been suggested to differ in their neurobiology. LOD has been associated with white-matter lesions, whereas EOD may be more associated with stress-related neurotoxicity resulting in hippocampal atrophy (Janssen et al., 2007; Rapp et al., 2005). Furthermore, the vascular depression hypothesis formulated, by Alexopoulos and colleagues (1997; 2006), states that cerebrovascular disease and white-matter hyperintensities often precedes LOD (for a review, see Herrmann et al., 2008). LOD has been associated with higher prevalence rates of dementia (Alexopolous, 2003), and LOD also has weaker genetic link to depression than EOD (Devanand et al., 2004). The pattern of cognitive deficits in EOD and LOD may differ, as there might be neurobiological differences exerting differential effects on cognitive performance. Specifically, LOD has been suggested to have pronounced executive dysfunction (Alexopolous, 2003; Rapp et al., 2005), whereas EOD has been suggested to have pronounced episodic memory deficits (Jansen et al., 2007; Rapp et al., 2005; Salloway et al., 1995).



## 2 AIMS

The overall aim of the present thesis was to investigate cognitive performance in unipolar depression in older dementia-free persons ( $\geq 60$  years). We examined a range of factors that might contribute to the high variability of observed cognitive deficits in old-age depression (Studies I, II, and III), and which cognitive deficits may be reversible upon remission from a depressive episode (Studies III and IV). The specific research aims were:

*Study I:* To assess the influence of depression severity on cognitive deficits in dementia-free older persons with unipolar depression, while controlling for a range of clinical (psychiatric comorbidity, antidepressant medications, prodromal dementia) and demographic (age, gender, education) factors that may influence cognitive performance.

*Study II:* To examine the role of the combination of *KIBRA* and *CLSTN2* risk alleles on episodic memory performance in dementia-free older persons with unipolar depression.

*Study III:* To investigate the effects of psychiatric history (in- and outpatient), including psychiatric comorbidity, on cognitive performance in dementia-free older persons during acute and remitted states of depression.

*Study IV:* To assess level and change in cognitive performance in dementia-free older persons in three courses of unipolar depression (from depressed to remitted; from remitted to depressed, and from a nondepressed state to late-onset depression) over a maximum period of 6 years.



## 3 MATERIALS AND METHODS

### 3.1 THE SNAC-K STUDY

All studies in this thesis were based on SNAC-K, which is a longitudinal population-based study comprising an extensive medical, social, and psychological data base. The overall aim of SNAC-K is to increase the understanding of aging processes and to identify potential preventive strategies to improve health and care for older adults.

Participants were randomly selected (based on birth dates) from elderly persons ( $\geq 60$  years) registered as residents in the Kungsholmen municipality of Stockholm, Sweden. At baseline, between 2001 and 2004, there were 4590 eligible participants. In total, 3363 persons completed baseline assessments. Reasons for non-participation included: refusal: 25%; refusal by relative: 1%; and disrupted examination: 0.004%. Data were collected using clinical examinations and structured interviews, self-report questionnaires, and administration of an extensive neuropsychological test battery. Altogether, the examinations (physician, nurse, and psychologist) take approximately 6 hours at each data collection wave.

At baseline, 2848 participants completed neuropsychological testing. Reasons for non-participation included: refusal: 12%; Mini Mental State Examination (MMSE; Folstein et al., 1975)  $< 10$ : 3%; death: 0.3%; and other reasons: 0.3%.

All participants belong to pre-specified age cohorts (60, 66, 72, 78, 81, 84, 87, 90, and 90+ years). Younger cohorts (60-72 years) are re-examined at 6-year intervals and older cohorts ( $\geq 78$  years) at 3 year-intervals. In total, 1960 persons (68.8%) completed neuropsychological testing at follow-up after 3 or 6 years. Reasons for non-participation at follow-up included death: 13.8%; refusal: 13.2%; moved/no contact: 2.8%; MMSE  $< 10$ : 1.2%; and other reasons: 0.1%.

Participants not belonging to the target group (i.e. depression) were used as reference groups for Study I and II. The comparison groups were screened for dementia, psychiatric disorders, antidepressant medications, and MMSE  $< 24$ . Thus, participants with any of these factors were excluded. For Study III and IV, thoroughly screened healthy control groups were created. This was done in a two-step procedure. First, dementia-free, nondepressed participants were screened for self-reported history of other psychiatric disorders, as well as for psychiatric inpatient history, stroke, cancer, Parkinson's disease, diabetes, and medications that may influence cognitive performance (psychotropics, opioids, antiepileptics, glucocorticoids, anticholinergics), MMSE  $< 24$  and prodromal dementia. Second, from the screened healthy participants a random sample was selected. For Study IV, an additional step was taken: The screened healthy participants were also matched on age, gender, education, and follow-up time to the depressed groups.

### **3.2 DEPRESSION DIAGNOSIS**

ICD-10 criteria (WHO, 1993) were used to diagnose unipolar depression. The same procedure was applied for both baseline and follow-ups, by the same geriatric psychiatrist. The diagnosis was made using a three-step procedure. First, the examining physician assessed depressive symptoms using the Comprehensive Psychopathological Rating Scale (CPRS; Åsberg et al., 1978). The CPRS is a rating scale of current psychiatric symptoms such as low mood, anhedonia, low self-esteem, pessimistic view of the future, and suicidal ideation. The CPRS has been validated for research and shown to be reliable and sensitive (Amati, et al., 1978; Montgomery et al., 1978a; 1978b; Perris, 1979). Furthermore, the CPRS has been successfully employed in elderly samples (Bäckman et al., 1996; Berger et al., 1998). As a second step, a geriatric psychiatrist, external to the medical examination, diagnosed unipolar depression, including mild, moderate and severe depression. Severity of depression was assessed using both number of symptoms (mild: 4; moderate: 5-7; severe: 8+), and reported intensity of the specific symptoms (ranging from 0-6). Indicative of pathology, only severity ratings of 2 and above were used (Åsberg et al., 1978). Thyroid function was assessed via peripheral blood samples (TSH: 0.4-4.0 µU/ml; total T4: 4.7-13.5 µg/dl; free T4: 0.8-1.9 ng/dl). Information was also collected via self-report questionnaires (including potential bereavement). Persons with abnormal thyroid function and/or bereavement were not diagnosed with depression. Third, in case of disagreement between different sources of information, a senior geriatric psychiatrist was consulted to confirm or reject the initial diagnosis. The psychiatrists were blind to general health status, medical and psychiatric history, as well as to pharmacological treatment.

### **3.3 DEMENTIA DIAGNOSIS**

DSM-IV criteria (APA, 2000) were used to diagnose dementia. The same three-step procedure was applied for both baseline and follow ups. First, a preliminary dementia diagnosis was made by the examining physician. Second, an independent diagnosis was made based on computerized data by a physician who did not meet with the participant. This diagnosis was compared to the first diagnosis, and in case of disagreement, a third senior physician was consulted to make the final diagnosis. MMSE, the Clock test (Manos & Wu, 1994), and cognition-related questions regarding orientation, memory, interpretation of proverbs, executive functioning, and problem solving were used for diagnostic purposes. The physicians were blind to the results of the neuropsychological testing.

For all studies in this thesis, participants with dementia were excluded. Participants who were non-demented at baseline, but diagnosed with dementia during the follow-up period were considered to be in a prodromal dementia phase at baseline. For Study IV, where longitudinal assessment was carried out, all persons (healthy controls and depressed) with a dementia diagnosis at follow-up were also excluded.

### 3.4 NEUROPSYCHOLOGICAL TEST BATTERY

The neuropsychological test battery was designed in three different versions in order to minimize practice effects, and administered according to two different test orders. Trained psychologists administered the neuropsychological test battery following a standardized procedure, and total testing time was approximately 1.5 hours.

*Processing speed* was assessed by pattern comparison and digit cancellation. For pattern comparison (Salthouse & Babcock, 1991), participants were presented with 30 pattern combinations and asked to, as fast as possible, determine whether these patterns were exactly the same or not. The outcome score was the average number of correct responses across two trials, each lasting 30 seconds. For digit cancellation (Zazzo, 1974), participants were presented with a paper with eleven rows of digits in random order (1-9), and asked to cross out the target digit (4) as fast as possible. The outcome score was the total number of correct responses within 30 seconds.

*Short-term memory* was assessed with digit span (WAIS III; Wechsler, 1981). For digit span forward, participants were asked to verbally repeat the digit sequences that the test leader read aloud, whereas for digit span backwards, participants were asked to verbally repeat the digit sequences backwards. The outcome scores were number of correct repetitions for forward and backward span, respectively.

*Attention and executive function* were assessed with the Trail Making Test (TMT; Lezak, 2004). TMT-A was used to assess attention, and TMT-B assessed executive function (shifting). Both parts consisted of 13 circles with equal distances between the circles. For TMT-A, participants were required to connect the encircled digits in numerical order (1, 2, 3, etc.), whereas for TMT-B participants were required to connect the encircled digits and letters in alternating order (1-A, 2-B, 3-C, etc.). The test administrator corrected the first mistake, which did not result in a lower score (correction time was not included in completion time), and one careless connection (>2 mm) was allowed. The outcome scores were completion times for participants with 12 correct connections.

Letter and category fluency (Lezak, 2004) assessed *verbal fluency*. Letter fluency required oral generation of as many words as possible during 60 seconds beginning with the letters F and A, respectively. The same procedure was used for category fluency, with occupations and animal names serving as taxonomic categories. The outcome scores were the total number of generated words divided by two.

Tests of free recall and recognition were used to assess *episodic memory*. A standard list of 16 unrelated nouns (e.g. carrot, ring, fork) was read aloud by the test leader, and participants were asked to verbally repeat as many of the words as possible within 2 minutes. The free recall outcome score was number of correctly recalled nouns. Immediately following the free recall test, 32 nouns were presented (16 targets, 16 lures) and the participants' task was to determine whether or not the words had been presented previously (yes or no). The outcome score for the recognition task was number of hits minus number of false alarms.

*Semantic memory* was assessed by a vocabulary test and a test of general knowledge. For the vocabulary task, participants were asked to select synonyms for 30 words out of 5 alternatives (SRB:1; Dureman, 1960; Nilsson et al., 1997). The outcome score was number of correctly selected synonyms within 7 minutes. The general knowledge test (Dahl et al., 2009) consisted of 10 moderately difficult questions (e.g., what is the name of the capital of Uruguay?) with two response alternatives, one of which was correct. The outcome score was number of correct answers.

*Spatial ability* was assessed with a test of mental rotations, a simplified 10-item version of the Shepard-Metzler test (1970; Rehnman & Herlitz, 2006; Vandenberg & Kuse, 1971). A target figure was presented and the participants' task was to decide, within 45 seconds, which of three other rotated figures equaled the target. The outcome score was number of correctly selected figures.

### **3.5 THE SWEDISH NATIONAL INPATIENT REGISTER**

The Swedish National Inpatient Register (IPR) was used for Study III (basis for group formation of psychiatric history) and IV (screening of psychiatric history) and entails information on ICD diagnoses requiring hospitalizations. The IPR became national in 1969, and from 1987 Swedish physicians are required to report to the register, which has been validated for research purposes (Ludvigsson et al., 2011). SNAC-K participants were matched to the IPR with personal identity numbers. Thereafter, information on primary psychiatric diagnoses was obtained from 1969 to baseline examination (2001-2004), thus covering up to a maximum of 35 years. The ICD-8 and -9 primary psychiatric diagnoses were converted into ICD-10 categories. All persons with F00-F09 diagnoses (dementia) were excluded.

### **3.6 MEDICATION**

Participants were asked to bring a list of currently used medications (prescription and over-the-counter drugs) to the medical examination. Information from patient journals was also used when participants were living in elderly homes. Information on antidepressant medication, including tricyclic agents (TCAs), selective serotonin re-uptake inhibitors (SSRIs), and others (e.g. Venlafaxin, Mirtazapin) were used for all studies in this thesis. For Studies III and IV, information on medications for psychiatric disorders, other than unipolar depression, was also used: lithium, benzodiazepines, and antipsychotics. Additional analyses controlling for medications that may have negative effects on cognition (psychotropics, opioids, antiepileptics, glucocorticoids, anticholinergics) were applied in Study I. For Study III and IV, healthy control groups were screened for these medications.

### **3.7 ADDITIONAL BACKGROUND VARIABLES**

Mini Mental State Examination (MMSE; Folstein et al., 1975) was used in all studies for assessment of global cognitive functioning. For Study III, a number of variables that may modulate cognitive performance were used: cardiovascular disease burden (composite score, ranging from 0-3, of heart failure, ischemic heart disease, and atrial fibrillation); cardiovascular risk burden (composite score, ranging from 0 to 5, of hypertension stage 2, diabetes, obesity, current smoking, and high cholesterol); physical inactivity (never physically active or < 2-3 times per month); and cerebrovascular disease (e.g., stroke). Montgomery and Åsberg Depression Rating scale (MADRS; Montgomery & Åsberg, 1979) was used in Studies III and IV for assessment of residual depressive symptoms in remission.

### **3.8 STATISTICAL ANALYSES**

All statistical analyses were conducted in SPSS (IBM SPSS 22). Analyses of variance (ANOVAs) and  $\chi^2$  tests were used to assess group differences in background variables. One-two- and three factor, and mixed analyses of covariance (ANCOVAs), were used to assess group differences, interaction effects, and change in cognitive performance. For Studies I and II, age, gender, and education were used as covariates, and for Studies III and IV, age, and gender were used. The rationale behind used covariates were presence of significant group differences for these variables. Regression analyses were used in Study III to examine contributions from clinical and health indicators that may modulate cognitive performance. Additionally, calculations of effect sizes (Cohen's *d*, Cohen, 1992) of group differences in cognitive performance were conducted in Studies III and IV.

### **3.9 ETHICAL CONSIDERATIONS**

The ethical committee at the Karolinska Institutet approved the SNAC-K study for baseline examinations, and the regional ethical review board approved the follow-up examinations. The Helsinki declaration of ethical guidelines was followed throughout all parts of the project. Informed consent was obtained from all participants, and all participants were informed that they could drop out at any time. If, during examination, the participant expressed anguish or discomfort, the interview was terminated. In case of cognitive impairment, informed consent was obtained from next-of-kin.

## 4 RESULTS AND OVERVIEW OF STUDIES

Characteristics of participants in Study I to Study IV are summarized in Table 1, and an overview of effect sizes of cognitive deficits are presented in Table 2.

### 4.1 STUDY I

Previous studies have shown considerable variability with regard to which cognitive domains are affected during a depressive episode in older ages. These inconsistencies may be a function of clinical and demographic sample characteristics. Therefore, the rationale behind the study was to assess the influence of depression severity in unipolar depression in dementia-free older persons, while controlling for a range of potential confounders.

*Participants:* Dementia-free participants completing neuropsychological testing at baseline examination were screened for antidepressant medication intake and comorbid psychiatric disorders (psychotic and bipolar disorders), leaving a study sample of 2486 persons, of whom 89 were depressed (mild:  $n=48$ ; moderate/severe:  $n=41$ ).

*Main results:* Persons with moderate/severe unipolar depression exhibited deficits in processing speed, attention, executive functioning, verbal fluency, episodic memory and vocabulary. Persons with mild depression displayed a deficit in processing speed. No depression-related deficits were observed for short-term memory, general knowledge, or spatial ability. The observed cognitive deficits were not confounded by dementia or prodromal dementia, use of antidepressants, psychiatric comorbidities, use of medication that may have a negative effect on cognition (psychotropics including benzodiazepines; opioids; antiepileptics; glucocorticoids; and anticholinergics), age, education, or gender.

*Main conclusions:* Moderate/severe unipolar depression in old age was associated with cognitive deficits in a range of domains, also when controlling for multiple clinical and demographic factors that influence cognitive performance. Mild depression was only associated with a deficit in processing speed. These findings clearly show that depression severity influences the magnitude of cognitive deficits.

**Table 1.** Background variables across all study samples.

	<b>Mild depression</b>	<b>Age</b>		<b>Women</b>	<b>Education</b>		<b>MMSE</b>		<b>Medications</b>	
	<i>n</i>	<i>%</i>	<i>M</i>	<i>(SD)</i>	<i>%</i>	<i>M</i>	<i>(SD)</i>	<i>M</i>	<i>(SD)</i>	<i>(%)</i>
<b>Study I</b>		53.9								<i>Antidepressants</i>
Mild depression	48		78.6	(10.3)	68.8	10.7	(4.2)	27.9	(2.3)	-
Moderate/severe depression	41		75.9	(9.0)	58.5	10.5	(3.4)	27.9	(2.1)	-
Nondepressed	2397		72.6	(10.1)	60.7	12.1	(4.3)	28.9	(1.4)	-
<b>Study II</b>		53.2								
Depressed, CC/TT	27		77.8	(9.0)	63.0	11.5	(4.1)	27.7	(2.1)	-
Depressed, CC/any C	7		75.6	(5.2)	85.7	10.3	(3.9)	28.7	(1.7)	-
Depressed, any T/TT	31		77.4	(10.7)	67.7	9.7	(3.4)	27.6	(2.5)	-
Depressed, any T/any C	14		76.1	(10.1)	50.0	10.8	(4.9)	28.9	(1.9)	-
Nondepressed, CC/TT	707		72.5	(9.8)	59.1	12.2	(4.2)	28.9	(1.4)	-
Nondepressed, CC/any C	225		71.7	(10.2)	66.7	12.1	(4.3)	29.0	(1.3)	-
Nondepressed, any T/TT	885		72.4	(10.1)	59.9	12.2	(4.4)	28.9	(1.4)	-
Nondepressed, any T/any C	280		72.6	(10.3)	61.4	12.6	(4.3)	28.8	(1.4)	-
<b>Study III</b>		52.0								<i>Psychiatric</i>
Depressed, no history	49		80.3	(8.2)	65.3	10.6	(3.8)	27.6	(2.2)	6.1
Depressed, self-reported history	52		74.5	(10.9)	76.9	10.6	(3.8)	28.5	(1.7)	32.7
Depressed, inpatient history, mixed diagnoses	20		71.8	(9.8)	55.0	11.1	(4.6)	27.9	(2.5)	65.0
Remitted, inpatient history, unipolar	38		68.3	(7.9)	60.5	12.0	(3.9)	28.8	(1.5)	39.5
Healthy controls	96		71.3	(9.9)	58.3	11.7	(4.0)	29.1	(1.3)	0
<b>Study IV*</b>		T1: 40.6 T2: 77.0								
Depressed-Remitted	32		71.8	(9.8)	68.8	11.9	(4.7)	28.7	(1.5)	28.1
Remitted-Depressed	45		71.2	(9.7)	68.9	12.2	(3.7)	29.2	(1.0)	42.2
Nondepressed-Depressed	29		76.5	(7.8)	75.9	12.2	(3.8)	29.2	(1.1)	3.5
Matched healthy controls	106		72.0	(9.5)	73.6	12.7	(3.9)	29.1	(1.0)	0

*Note.* M=Mean; SD=Standard Deviation; MMSE=Mini-Mental State Examination; Antidepressant medications: tricyclic agents, selective serotonin reuptake inhibitors; and others such as Mirtazapin, Venlafaxin; Psychiatric medications: antidepressants, antipsychotics, lithium, benzodiazepines; \*=baseline values

**Table 2.** Effect sizes (Cohen's *d*) of significant cognitive deficits across all studies.

	Processing speed		Attention	Executive function	Verbal fluency		Episodic memory		Semantic memory
	Pattern	Digit	TMT-A	TMT-B	Letter	Category	Free recall	Recognition	Vocabulary
<b>Study I</b>									
Mild depression	0.58								
Moderate/severe depression	0.57	0.64	0.55	0.45	0.42	0.76	0.63	0.51	0.46
<b>Study II*</b>									
Depressed, CC/TT							0.94	0.74	
Depressed, CC/any C									
Depressed, any T/TT									
Depressed, any T/any C									
<b>Study III</b>									
Depressed, no history	1.13	1.00	0.61	0.59	0.66	0.80			
Depressed, self-reported history	0.50								
Depressed, inpatient history, mixed	0.63	0.50		0.85	0.66	0.88			
Remitted, inpatient history, unipolar									
<b>Study IV</b>									
Depressed-Remitted, T1		0.63		0.45					
Depressed-Remitted, T2		0.49 <sup>a</sup>	0.35 <sup>b</sup>						
Remitted-Depressed, T1		0.31							
Remitted-Depressed, T2		0.59	0.53	0.31 <sup>c</sup>					
Nondepressed-Depressed, T1				0.63					
Nondepressed-Depressed, T2		0.58	0.71	0.62		0.85			

Note. \*=only episodic memory was assessed; controlled for use of benzodiazepines; <sup>a</sup>=*d*=0.40; <sup>b</sup>=n.s., *d*=0.23; <sup>c</sup>=n.s., *d*=0.14.

## 4.2 STUDY II

Kidney and brain expressed protein (*KIBRA*, rs7070145, a C > T substitution), and Calsyntenin 2 (*CLSTN2*, rs6439886, a T > C substitution) have both been identified as episodic memory-related genes. Research on these genes has yielded mixed results, including performance advantages in episodic memory of the *KIBRA* T-allele and *CLSTN2* C-allele, respectively, as well as non-associations. Furthermore, the potentially added performance advantage of the *KIBRA* T-allele in combination with the *CLSTN2* C-allele has also shown mixed findings. The resource-modulation hypothesis postulates that loss of resources (i.e., due to aging), may magnify effects of allelic variation on cognitive performance.

Furthermore, reports of episodic memory deficits in old-age depression are common.

Therefore, it was hypothesized that the combination of disadvantageous *KIBRA* and *CLSTN2* alleles in persons with old-age unipolar depression would lead to especially poor episodic memory performance.

*Participants:* Dementia-free participants who had completed neuropsychological testing at baseline and been genotyped for *KIBRA* and *CLSTN2* were screened for antidepressant intake and comorbid psychiatric disorders (psychotic and bipolar disorders), leaving a study sample of 2170, of whom 79 were depressed. Participants were grouped according to depression status (yes/no) and genotype combinations (*KIBRA*: CC, any T; *CLSTN2*: TT, any C), resulting in eight groups (nondepressed/depressed; *KIBRA/CLSTN2* carriers of: CC/TT; CC/any C; any T/TT; and any T/any C).

*Main findings:* Three-way interaction effects of depression x *KIBRA* x *CLSTN2* for both free recall and recognition showed that the combination of disadvantageous alleles (*KIBRA*: CC, *CLSTN2*: TT) was associated with poorer episodic memory performance only in depressed older persons; depressed CC/TT carriers consistently performed at the lowest levels.

*Main conclusions:* The finding of impaired episodic memory performance only in depressed older persons carrying risk alleles of *KIBRA* and *CLSTN2* supports the notion that effects of genetic polymorphisms on cognitive performance may be most easily disclosed at suboptimal levels of cognitive ability, such as in old-age depression. These results show that memory-related genes influence cognitive performance in depression, and that this effect may be exacerbated in older ages.

*Implications:* Older depressed persons carrying disadvantageous memory-related alleles are more likely to present with cognitive deficits. This further underscores the importance of early detection of depression.

### 4.3 STUDY III

Cognitive deficits in old-age depression vary as a function of multiple factors, such as depression severity, inpatient status, and cumulative illness burden. The heterogeneity of cognitive deficits present during acute versus remitted states has raised the question of whether these deficits are state- (fluctuating with clinical state) or trait-related (stable vulnerabilities). A limitation of previous research is short follow-up time, which may partly explain findings of remaining cognitive deficits. The objective of this study was to assess the influence of psychiatric history on cognitive performance in dementia-free older persons during acute and remitted states of depression. Inpatient history was obtained from the IPR, covering up to 35 years, and self-reported history was obtained during the SNAC-K medical examination.

*Participants:* Four groups were identified, based on psychiatric history and current depression status: (1) late-onset unipolar depression, no history; (2) recurrent unipolar depression, self-reported history; (3) depressed with a recurrent mix of psychiatric disorders, inpatient history; and (4) remitted unipolar depression, inpatient history. These four groups were compared to a group of randomly selected healthy controls.

*Main results:* Depression-related cognitive deficits were observed in processing speed, attention, executive function, and verbal fluency among currently depressed persons. Currently depressed with a psychiatric inpatient history and persons with late onset depression performed at the lowest levels, whereas cognitive performance in persons with self-reported recurrent unipolar depression was intermediate. Remitted unipolar depression exhibited no cognitive deficits, possibly due to the extended time since their last admission (m=15.6 years). Physical inactivity, cumulative inpatient days, heart disease burden and prodromal dementia modulated the observed group differences in cognitive performance.

*Main conclusions:* Currently depressed persons displayed deficits in multiple cognitive domains, and those with a psychiatric inpatient history, or late-onset depression performed at the lowest levels. Cumulative psychiatric illness may account for the poor cognitive performance of the former group, whereas for the latter, heart disease burden and prodromal dementia were shown to modulate cognitive performance. Cognitive recovery may take longer time as compared to recovery of depressive symptoms. Taken together, the present data suggest that cognitive deficits in depression may be more state- than trait-related. Thus, cognitive deficits in depression seem reversible.

*Implications:* Relapse rates in depression remain high, and cognitive deficits are associated with poor prognosis, and may take longer time to recover. Therefore, combined profiles of psychiatric history, cognitive performance, and health behaviors may provide important clues for more individualized treatments.

#### 4.4 STUDY IV

The episodic nature of depression makes repeated assessments of cognitive performance important in order to investigate which deficits are state- (fluctuating with clinical state) or trait-related (stable vulnerabilities). Previous studies have shown mixed findings regarding which cognitive deficits are present during acute and remitted states, and a limitation is that most studies are cross-sectional. The rationale of this study was to investigate state- versus trait-related aspects of cognitive deficits in old-age depression with repeated assessment of cognitive performance across the same persons over a maximum period of 6 years.

*Participants:* Dementia-free participants who had completed neuropsychological testing at both baseline (T1) and follow-up (T2) formed the basis of the study sample. Participants were grouped according to depression status at T1 and T2, and three groups were identified: (1) depressed-remitted; (2) remitted-depressed; and (3) nondepressed-depressed. These three groups were compared to matched (age, gender, education, and follow-up time) healthy controls.

*Main results:* Depression-related cognitive deficits were observed for processing speed, attention, executive function, and category fluency. The general pattern showed that participants deteriorated cognitively. Significant decline was observed for: processing speed, executive function, and category fluency, as well as for episodic and semantic memory. Persons who changed their status from nondepressed to depressed tended to show exacerbated cognitive decline. In remitted states, only processing speed and attention were affected. However, these deficits were modulated by benzodiazepine intake.

*Main conclusions:* The results support the notion that cognitive deficits in depression are more state- than trait-related. Few cognitive deficits were observed in remission. Furthermore, persons who at baseline were nondepressed or in a remitted state and later developed a depressive episode at follow-up tended to show steeper cognitive decline.

*Implications:* As degree of reversibility of cognitive deficits is likely to diminish with age and cognitive deficits are likely to be exacerbated with each successive episode, early detection of depression is highly important. The findings of this study imply that cognitive deficits in old-age depression may be reversible. This further suggests that cognitive deficits should be viewed as potential treatment targets, rather than as irreversible vulnerabilities. Along these lines, repeated assessments of cognitive performance may provide an additional marker of treatment response.

## 5 DISCUSSION

Taken together, the findings of this thesis show that multiple factors influence cognitive deficits in dementia-free unipolar old-age depression: depression severity (Study I); disadvantageous alleles of memory-related genes (Study II); and psychiatric history (Study III). In addition, several other factors, such as cumulative inpatient days, prodromal dementia, comorbidity of psychiatric disorders, comorbidity of heart disease, physical inactivity, and benzodiazepine drug intake were found to modulate group differences in cognitive performance. The complexity of these observed patterns indicate the existence of multiple, rather than one “true” manifestation of cognitive deficits in old-age depression. Consistent with the notion that depression is a heterogeneous disorder, these factors have likely contributed to the high variability of cognitive deficits observed in old-age depression in previous research.

This thesis has furthermore shown that cognitive deficits in depression are more state- than trait-related (Study III and IV), and that time spent in remission seems to be a key factor for reversibility of cognitive deficits. This finding suggests that cognitive deficits in depression should be regarded as treatment targets rather than as stable vulnerabilities.

### 5.1 DEPRESSION-RELATED COGNITIVE DEFICITS

The present studies range among only a few to date which investigate cognitive performance in old-age depression according to ICD-10 criteria, which allows for distinctions between mild, moderate and severe depression. DSM criteria (APA, 2000; 2013) of major depression (MDD; five depressive symptoms must be present) are more commonly used. This is an important contribution to the literature, because mild depression is not only more rarely investigated, it is also more prevalent in older ages. This was reflected by the high proportion of mild depression across the four studies. Hence, this thesis extends current knowledge on cognitive deficits, including those observed in mild depression. Had DSM-IV criteria been used, multiple cases of mild depression would have been neglected (baseline:  $n=95$ , 52.7%).

Across the four studies included in this thesis, depression-related cognitive deficits were observed in processing speed, attention, executive function, verbal fluency, episodic memory, and semantic memory (vocabulary). These findings are in line with previous research on cognitive deficits in old-age depression (Bäckman et al., 1994; Baudic et al., 2004; 1996; Beats et al., 1996; Bhalla et al., 2006; Butters et al., 2004; Elderkin-Thompson et al., 2004; 2007; Ganguli et al., 2009; Kramer-Ginsberg et al., 1999; Köhler et al., 2010; Lesser et al., 1996; Lockwood et al., 2002; Nebes et al., 2000; 2003; Sheline et al., 2006; Thomas et al., 2009; Veiel, 1997).

A semantic memory deficit (vocabulary) was only observed for moderately and severely depressed persons (Study I). No general knowledge deficits were observed in any of the four studies, in line with some previous reports (Butters et al, 2004; Herrmann et al., 2007;

McDermott & Ebmeier, 2009; Ravdin et al., 2003), but in contrast to others (Bhalla et al., 2006; Sheline et al., 2006). A possible explanation for the lack of general knowledge deficits may be that education was controlled for.

Cognitive deficits observed in Study I and II were not influenced by antidepressant medication, as all participants on any such medications were excluded. The proportion of dementia-free depressed persons who completed cognitive testing at baseline and used any antidepressant medication was low (17.7%). This may be a reflection of underdetection of depression in older ages, as SSRIs are first-line treatments (APA, 2010; Socialstyrelsen, 2010). In Study III and IV, depressed persons on antidepressant medication were included, and for these studies, episodic memory deficits were lacking. This finding may partially be explained by SSRI medication, as a potential mechanism of action is thought to result from increased neurogenesis and HPA-axis reregulation, which may have stabilized neurobiological alterations in the temporal lobes (Maglite et al., 2008; Mahar et al., 2014; Wilner et al., 2013). Tasks assessing cognitive domains that draw on the prefrontal lobes (processing speed, attention, executive function, and verbal fluency) were negatively affected across all four studies. This finding is in line with previous research showing that the prefrontal lobes are more sensitive to stress compared to the temporal lobes (Lupien et al., 1999; Ochsner & Gross, 2005; Young et al., 1999).

Depression severity was further shown to influence cognitive deficits, as more severe depression was associated with more severe cognitive deficits (Study I; see Table 2 for effect sizes). In a group of mildly depressed persons, processing speed was the only cognitive domain affected. This is an important finding, as mild depression is likely to develop into more severe depression if left untreated (Alexopoulos, 2005), and thus also increases the likelihood of exacerbated cognitive deficits. This in turn underscores the importance of early detection of depression.

Importantly, the observed cognitive deficits were not associated with dementia-related pathology, as participants with a dementia diagnosis were excluded from all studies. However, excluding persons in a prodromal dementia phase showed that the episodic free-recall deficit was more related to prodromal dementia than depression (Study I). Excluding persons with prodromal dementia also attenuated other cognitive deficits (processing speed, attention, executive function and verbal fluency), although group differences were still significant for these domains. Additionally, prodromal dementia modulated the attention deficit in Study III. This underscores the importance of controlling for dementia-related pathology when investigating patterns of cognitive deficits in old-age depression, as there is a plethora of research showing cognitive deficits in both dementia (Mathias & Burke, 2009) and in its prodromal phase (Bäckman et al., 2005; Laukka et al., 2004). The exclusion of persons with a dementia diagnosis may explain the total lack of deficits in short-term memory and spatial ability across all studies; findings that contrast with some of previous reports (Bhalla et al., 2006; Elderkin-Thompson et al., 2004; Lesser et al., 1996; Thomas et al., 2009). Further reasons for this discrepancy include: (1) the tests used to measure short-term

memory (digit span forward and backward) were not sensitive enough to pick up on depression-related deficits; and (2) the mental rotation task used to assess spatial ability primarily draws on parietal brain areas (Tagaris et al., 1996; Wendt & Risberg, 1994) rather than fronto-temporal regions, which other measurements of spatial ability such as pattern recognition and object assembly, are dependent on (Lezak, 2004).

Disadvantageous alleles of cognition-related genes may exert negative influences on performance (McLearn, 2006; Plomin et al., 1994). These effects have been proposed to be magnified in aging (Lindenberger et al., 2008; Papenberg et al., 2013; 2015). This assertion rests on the assumption that the relationship between genetic variations and brain resources are non-linear, so that genetic effects on cognition increase as resources recede from optimal levels (e.g., as is the case in aging; Bäckman et al., 2000; Raz et al., 2005). Depression might represent an additional vulnerability factor acting on structural integrity of the brain. Indeed, disadvantageous alleles of the episodic memory-related genes *KIBRA* and *CLSTN2* were linked to episodic memory deficits only in depressed older persons (Study II). This effect was not observed in depressed persons without these alleles, reflecting that genetic influences on cognitive performance were more pronounced in old-age depression. As such, this makes older depressed persons carrying disadvantageous memory-related alleles even more likely to present with cognitive deficits.

Previous research has shown that recurrent episodes of depression exert a negative impact on cognitive performance (Robinson & Sahakian, 2008; Stordal et al., 2004; Takami et al., 2007). The underlying assumption is that cognitive and depressive symptoms worsen with each successive depressive episode. In Study III, it was shown that inpatient history and comorbidities of bipolar, psychotic, and anxiety disorders, had a larger negative influence on cognitive performance during a current depressive episode. Specifically, cumulative load of inpatient days exerted negative effects on processing speed and executive function. In addition, inpatient history had a greater degree of negative influence than outpatient history on cognitive performance, as the group without inpatient history outperformed the group with inpatient history in both processing speed and verbal fluency. These findings extends our knowledge on cognitive performance in recurrent depression, showing differential patterns of deficits as a function of psychiatric history.

Physical activity is known to have positive effects on cognitive performance in healthy (Barnes, 2015), and older (Carvalho et al., 2014; Colcombe & Kramer, 2003) persons, and further to have antidepressant effects (Greer & Trivedi, 2009; Hallgren et al., 2015; Wegner et al., 2014). The underlying mechanisms are thought to originate from decreased levels of damaging effects from oxidative stress, including increased anti-inflammatory processes, positive immune function effects, lowered cortisol levels, increased levels of serotonin and dopamine, endorphins, and Brain-Derived-Neurotrophic Factor (BDNF; Eyre & Baune, 2012; Knochel et al., 2012; Meeusen, 2014). As such, physical activity may exert a protective influence on the same pathways mediating oxidative stress and inflammation (Munhoz et al., 2008), making the bodily response from exercise rewarding. Recently, a specific mechanism

was discovered in stress-induced depressed rats; during exercise the muscle activity produces an enzyme, KAT, which turns the harmful kynurenine molecule into the non-harmful kynurenic acid (Agudelo et al., 2014). Thus, the muscle during exercise can be compared to the detoxifying work of the liver. Ergo, exercise supposedly has neuroprotective properties. In line with this view, physical inactivity had negative effects on cognitive performance in depressed persons (Study III). Hence, depressed older persons not engaging in physical activity are more likely to present with cognitive deficits. This point is reinforced by the finding that remitted persons with higher proportions of physical activity displayed a total lack of cognitive deficits.

## **5.2 RECURRENT DEPRESSION VS. LATE-ONSET DEPRESSION**

Previous research has suggested that early-onset depression (EOD; i.e., recurrent) and late-onset depression (LOD; i.e., first depressive episode in older age) may differ both in their etiology and neurobiology. Consequently, they have also been suggested to differ in their patterns of cognitive deficits.

Executive dysfunction (Alexopoulos, 2003; Rapp et al., 2005) has been suggested to be a hallmark feature of LOD as compared to EOD, which may be related to altered white-matter integrity (Herrmann et al., 2008) and frontostriatal abnormalities (Sheline et al., 2006). In contrast, EOD has been suggested to be linked to episodic memory deficits (Jansen et al., 2007; Rapp et al., 2005; Salloway et al., 1995), which are thought to originate from hippocampal atrophy due to stress from recurrent depressive episodes (Bell-McGinty et al., 2002; Lampe et al., 2003; Sheline et al., 1999). Findings from Study III and IV are not entirely consistent with these assertions; deficits in executive function were observed for both LOD and EOD, whereas none of the groups exhibited deficits in episodic memory. However, Study IV showed that only in LOD, the observed executive function deficit further exacerbated upon depression onset, when also deficits in processing speed, attention and category fluency were developed.

LOD and the EOD group with psychiatric inpatient history exhibited similar patterns of cognitive deficits, whereas an EOD group without inpatient history was relatively unimpaired, only exhibiting a processing speed deficit (Study III). This processing speed deficit was replicated in Study IV for both EOD groups, where they were additionally found to exhibit deficits in attention and executive function. Thus, the patterns of cognitive deficits for LOD and EOD differed across the two studies.

Although observed patterns of cognitive deficits in groups of EOD and LOD stand in contrast to some previous research (Alexopoulos, 2003; Rapp et al., 2005; Salloway et al., 1995), a more recent meta-analysis (Herrmann et al., 2007), showed that both EOD and LOD displayed deficits in executive function, processing speed, and episodic memory, and that LOD exhibited larger effect sizes relative to EOD, with the largest effect size for executive function. Thus, in line with our research, executive dysfunction was pronounced in LOD,

however, pronounced episodic memory deficits in EOD were not seen in our findings. A potential explanation for the lack of episodic memory deficits in EOD in Study III and IV may include a dementia-free sample, and the combination of high proportions of mild depression (McDermott & Ebmeier, 2009) and antidepressant medication intake (Wilner et al., 2013).

The observed cognitive deficits in the two LOD groups, may also largely reflect dementia-free samples, which may have confounded previous research. Although the attentional deficit in LOD (Study III) was modulated by prodromal dementia, the other deficits were modulated by heart disease burden, consistent with the notion that LOD may be preceded by cerebrovascular disease (Alexopoulos et al., 1997; 2006). Furthermore, prodromal dementia may have exerted a larger influence on LOD deficits observed in Study IV, but information on future dementia diagnosis was not yet available. Factors speaking in favor of this scenario are: (1) marked MMSE decline in this group; (2) presence of an executive deficit before depression onset; and (3) the fact that the executive function deficit was more pronounced in LOD relative to both EOD groups. Even so, episodic memory deficits were absent for all groups in both Study III and IV, a domain known to be one of the first affected in prodromal dementia (Bäckman et al., 2005).

Taken together, these findings suggest that even though EOD and LOD have etiological and neurobiological differences, their patterns of cognitive deficits may be both similar and different. Specifically, patterns of cognitive deficits in both EOD and LOD seem to vary as a function of multiple factors, including psychiatric history, prodromal dementia, and comorbid medical diseases.

### **5.3 COGNITIVE AGING AND DEPRESSION**

Cognitive decline was observed in processing speed, executive function, and category fluency, as well as in episodic and semantic memory for three depression courses (depressed-remitted, remitted-depressed, nondepressed-depressed), as well as for healthy controls in Study IV.

Steeper trajectories of cognitive decline were displayed by persons going from a remitted to a depressed state than those going from a depressed state to a remitted state. This finding is in line with previous research showing “scarring” from previous depressive episodes (Robinson & Sahakian, 2008; Stordal et al., 2004). As normal aging entails deteriorating processes of cognitive abilities and brain integrity (Nyberg et al., 2012; Raz et al., 2005), older persons suffering from recurrent depression may be especially vulnerable to progressive cognitive decline upon entering yet another depressive episode.

LOD also displayed marked cognitive decline (see Table 2). Potential explanations include older mean age and potential prodromal dementia. Depressed-remitted persons displayed cognitive decline only in short-term memory and processing speed, possibly reflecting slower aging upon entering a remitted state in recurrent old-age depression.

Taken together, persons going from a nondepressed state to a depressed state showed the largest cognitive decline. Hence, depression in old age seems to exacerbate cognitive aging.

#### **5.4 ORIGINS OF COGNITIVE DEFICITS IN DEPRESSION AND THEIR REVERSIBILITY**

Stress is suggested to be a key factor in the etiology of depression. Early exposure to adverse stress (prenatal and childhood) has been shown to trigger long-term changes in adolescents and adults, involving cognitive deficits, increased risk of depression, and compromised regulation of the HPA-axis (Joëls & Baram, 2009; Lupien et al., 2009). Moreover, it has been suggested that the majority (80%) of depressive episodes are preceded by stressful life events (Hammen, 2005). A potential explanation for this include that early adverse life-events alter gene expression involved in bodily responses to threat, injury and infection. Thus, stress-induced epigenetic mechanisms (i.e., interactions between nature and nurture) have been suggested to mediate vulnerability to depression, and other psychiatric disorders (Dudley et al., 2011). As such, origins of cognitive deficits in depression may also be stress-related.

The physiology of stress is a complex interplay of several systems, including endocrine, immune, and neurotransmitter systems. In response to stress, the neuroendocrine system is activated, specifically the HPA-axis (McEwen, 2009), and hyperactivity of the HPA-axis is also a well-known finding in depression (Pariante & Lightman, 2008.) As the HPA-axis is activated, corticotrophin releasing factor (CRF) is released from the hypothalamus which stimulates the pituitary gland to produce adrenocorticotrophic hormone (ACTH). This in turn stimulates the adrenal cortex to release glucocorticoids (cortisol) into the blood circulation. Glucocorticoids are important regulators of metabolism and the immune system, and thus important for homeostasis. Thus, HPA-axis hyperactivity is a well-known feature during both stress and a depressive episode.

Prolonged stress may induce a vicious neurotoxic circle, which in turn makes coping with stress even more difficult. And reduced coping and poor emotion regulation is associated with depression (Aldao et al., 2010; Joorman & Gotlib, 2010; Sheppes et al., 2015; Zetsche et al., 2012). Furthermore, rumination has also been shown to be stressful and associated with increased levels of cortisol (Woody et al., 2015; Zoccola & Dickerson, 2012).

Both acute and chronic stress are known to activate the immune system inducing pro-inflammatory states (Munhoz et al., 2008), and inflammation is frequently occurring in depression (Maes et al., 2009). High levels of glucocorticoids stimulate the release of pro-inflammatory cytokines, such as interleukin-6, which further stimulates the HPA-axis (Cassidy & O'Keane, 2000; Zunszain et al., 2011). Furthermore, inflammatory cytokines have been associated with learning and memory (McAfoose & Baune, 2009). As pro-inflammatory cytokines can activate neuroendocrine processes, and vice versa, HPA-axis

hyperactivity and inflammatory processes may be part of the same stress-induced processes (Zunszain et al., 2011).

The depression-related neurotransmitters serotonin, dopamine, and norepinephrine (lowered in depression; Ferry et al., 1999; Nestler & Carlezon, 2006; Owens & Nemeroff, 1994; Savitz et al., 2009; Southwick et al., 2005), and stress-related cortisol and CRF, all act in brain regions important for cognitive functioning (Alvarez & Emory, 2006; Tulving, 2002) and emotion regulation (McEwen, 2009; Ochsner & Gross, 2005). Cortisol, CRF, dopamine and serotonin are active in the prefrontal cortex; cortisol and CRF further act in hippocampus, amygdala, and hypothalamus; serotonin is active in hippocampus; and dopamine and serotonin are both active in the amygdala (McEwen, 2009; McEwen & Morrison, 2013; Southwick et al., 2005). Stress is also known to affect regions in prefrontal cortex, including the insula and dorsal anterior cingulate cortex, which are involved in self-control, self-awareness and executive function; and these regions are also known to be affected in depression (Arnone et al., 2002; Drevets et al., 2000; Nestler et al., 2002). As such, these prefrontal regions could slow down the hyperactivity of the HPA-axis and the amygdala in the temporal lobes, but when affected these brakes are less efficient. Depression is furthermore associated with atrophy in the prefrontal cortex, basal ganglia and hippocampus (Bremner et al., 2000; Lorenzetti et al., 2009). Thus, both stress and depression are associated with similar neurobiological alterations. As tasks assessing cognitive domains that draw on the prefrontal lobes (processing speed, attention, executive function, and verbal fluency) were negatively affected across the four studies in this thesis, this finding is in line with previous research showing that the prefrontal lobes are more sensitive to stress compared to the temporal lobes (Lupien et al., 1999; Ochsner & Gross, 2005; Young et al., 1999).

Taken together, there is pervasive evidence that both stress and depression are linked to cognitive deficits; they seem to use similar pathways and affect similar brain regions. If cognitive deficits in depression is partly a function of the neurotoxic effects of stress, they should show some degree of reversibility when stress is discontinued, and when homeostasis is somewhat restored (McEwen & Morrison, 2013). As this thesis was able to demonstrate reversibility of cognitive deficits (executive function) in depression (Study IV), one possibility is that the observed cognitive deficits were related to stress.

Another finding in support of reversibility of cognitive deficits in dementia-free unipolar old-age depression is that cognitive deficits were absent in long-term remission of recurrent depression (Study III). This suggests that cognitive deficits may be reversed if sufficient time is spent in remission. Further support for this reasoning is that physical activity influences the same pathways as oxidative stress and inflammation, but in a neuroprotective way. Consistent with this notion, physical inactivity exerted negative effects on cognitive performance in depressed persons (Study III). This is further supported by the finding that more physically active remitted persons displayed complete absence of cognitive deficits. As such, these findings do not support the suggestion that deficits in attention and executive function in

depression are trait-related (Douglas & Porter, 2009), but rather that cognitive deficits in depression are largely reversible (i.e., state-related).

Numerous factors may modulate brain plasticity, age being a critical one (Coillard-Depres et al., 2011). As the aging brain is vulnerable (Bäckman et al., 2000; Raz et al., 2005), reports of remaining cognitive deficits during remission in old-age depression (Bhalla 2006; Nebes et al., 2003; Portella et al., 2003) may not be surprising. Also, other pathways to cognitive deficits in depression, such as dementia and prodromal dementia, may lead to limited reversibility. Consequently, studies not controlling for dementia may be more likely to support the trait hypothesis.

In sum, previous findings of persistent cognitive deficits in remitted old-age depression (Bhalla et al., 2006; Nebes et al., 2003; Portella et al., 2003) may partly be accounted for by: (1) dementia-related pathology; (2) insufficient time spent in remission; and (3) reduced plasticity. This is consistent with the observation that most evidence for reversibility of cognitive deficits in depression originate from younger samples (Biringier et al., 2005; 2007; Gallagher et al., 2007; Hammar & Årdal, 2012; Lahr et al., 2007).

## 5.5 CONCEPTUALIZATION OF DEPRESSION

*“Why is it that when we are talking to God we’re praying,  
but when God talks to us we’re schizophrenic?”*

(Psychiatrist Thomas Szaz, 1963)

Throughout history, conceptualization of depression and other psychiatric disorders has presented itself with challenges. In contrast to many medical diseases, mental disorders do not have clear physical criteria that may be measured in an objective way. Diagnostic criteria of depression, and most psychiatric disorders, rely on reported symptoms, and thus are descriptive in nature. For example, we cannot draw a blood sample and from that conclude that a person has depression or not, as is the case for a person with diabetes. Instead, psychiatric disorders are essentially syndromes, something that Owens (2014) explains as: “constellations of signs and symptoms that tend to occur together”. For the new edition of DSM-5 in 2013, there was hope that neuroscience would have progressed to the point that psychiatric categories could be defined by biomarkers, but this has not yet been realized (e.g., Nesse & Stein, 2012). At this point in history, we still face conceptual challenges, as knowledge on etiology and biological mechanisms of depression and other psychiatric disorders remain insufficient.

Several theories have tried to explain the etiology of depression: the monoamine hypothesis (Prange, 1964; Schildkraut, 1965); cognitive and behavioral theories (vulnerability-stress

models; Beck et al., 1979; Bower, 1981); HPA-axis dysfunction theory (Dinan, 1994; Pariante & Lightman, 2008); the neurogenesis hypothesis (Jacobs et al., 2005; Petrik et al., 2012); the inflammatory or cytokine theory (Maes et al., 2009). None of these theories has so far been sufficient to explain the etiology of depression. This is reflected in suboptimal treatment; 30-40 per cent of depressed individuals do not respond to antidepressant treatments (Kuk et al., 2010; Trivedi et al., 2006), and augmented or sequenced treatment alternatives have also shown poor remission rates (Rush et al., 2006). Despite prolific treatment alternatives, including antidepressant medication, psychotherapies (e.g., CBT, IP, ACT, MBSR), ECT and TMS, recurrence rates of depression are still high (APA, 2013). To date, depression etiology is recognized as a complex interplay between biological predispositions and stressors (Pasquini et al., 2014; Southwick et al., 2005). Thus, all of the above mentioned theories trying to explain depression etiology might provide valid contributions, rather than just one having the “ultimate” answer.

Modern psychiatry tries to distinguish between spectra of normal-abnormal and function-dysfunction (Kendler et al., 2006; Stein, 2013; Stein et al., 2013), but has also been criticized for labeling normal variation as pathologic (Wakefield, 2013; Wakefield et al., 2013). For each successive edition of both ICD and DSM, the number of possible psychiatric diagnoses has increased. Although this growth of psychiatric categories, disorders and specifiers may help the diagnostic procedure, it may also add complexity. This is, for example, reflected in the number of pages: DSM-I consisted of 152 pages (1952, APA), whereas DSM-5 covers more than 800 pages. Moreover, the potential combinations of depressive symptoms alone are above 1000.

Depressive symptoms have also been reported to be etiologically heterogeneous (Fried et al., 2013). This “symptomatic heterogeneity” reflects that depression may be viewed as a spectrum disorder, or consist of a continuum, ranging from of a few depressive symptoms to a maximum of 10, where each of these individual symptoms may also vary in their intensities.

DSM and ICD conceptualizations of depression have faced substantial criticism. For example, Holtzheimer and Mayberg stated: “*it has lost its utility*” (2011, p.1). They suggested to focus on the core symptoms of depression – depressed mood, anhedonia, worthlessness or guilt, poor concentration, and suicidal ideation – rather than including the highly variable somatic/vegetative symptoms (appetite, sleep, psychomotor activity, fatigue), which makes the definition of depression too broad. A new depression definition was proposed: “*the inability to disengage from a negative mood state and the tendency to re-enter this state inappropriately*” (p.1), and that the depressive state “*reflects an etiologically non-specific response to stress/distress that includes a stereotypical set of emotional, cognitive-behavioral and somatic responses*” (p.6). This conceptualization of depression argues that depression is a function of stress/distress, and that symptomatic heterogeneity in turn is a function of variation in stress responses. This may be especially true, as variability also exist in treatment response; some persons respond early in the treatment course, whereas others do so much

later (Keller et al., 2000; Trivedi et al., 2006); some persons do not respond to one pharmacological agent, but to another (Rush et al., 2006), other persons do not respond to pharmacological agents at all, but to psychotherapy (Thase et al., 2000), and vice versa; and other persons need a combination of pharmacological agents and psychotherapy in order to reach remission (Keller et al., 2000).

Although the conceptualization of depression as a stress-induced disorder, or a subtype of depression, also face challenges, such as establishing cause and effect between stressful events and neurobiological alterations (Baune et al., 2009), there is also substantial evidence linking stress and depression (as described in section 5.4). Further support for stress playing a key role in the development in depression is that cortisol levels are higher in women than in men (Heuser et al., 1994; Laughlin & Barret-Connor, 2000), and depression prevalence is higher in women compared to men. In line with this reasoning, gender differences in depression prevalence emerge in puberty at the ages of 12-13, when sex hormones are increasing (Gotlib & Hammen, 2010), and animal studies have shown that ovarian steroids increase HPA-axis activity (Kirschbaum et al., 1996; Roy et al., 1999). Moreover, MBSR, a therapy that targets stress has shown good treatment efficacy in recurrent depression (for review, see Gotink et al., 2015).

While both ICD-10 and DSM-5 criteria suffer from some shortcomings mentioned above, ICD-10 criteria was chosen for depression diagnosis in this thesis in an effort to accommodate some of these challenges. The reason for this was two-fold: (1) ICD-10 criteria offers distinctions between mild, moderate and severe depression, to reflect the view of a spectrum disorder; (2), depression in old age frequently presents with milder forms of depression, so that this population is underrepresented in the major depressive disorder prevalence of DSM-IV and DSM-5.

## **5.6 LIMITATIONS**

As all studies in this thesis derived from the population-based SNAC-K study, there is some overlap of participants. Thus, the results from the four studies cannot be entirely viewed upon as independent from each other, but are rather interconnected. Furthermore, the Kungsholmen municipality, where all SNAC-K participants derive from, is not fully representative of the whole Swedish population, as this area is relatively affluent, and persons living here are generally healthier and have received more education compared to other parts of Sweden (Lagergren et al., 2004; Welmer et al., 2013).

Not all SNAC-K participants ( $n=3363$ ) underwent neuropsychological testing (refusals:  $n=515$ , 15.3% at baseline examinations). Furthermore, out of 180 persons with depression, 39 persons (21.7%) refused cognitive testing. These persons were older than the depressed persons who did undergo neuropsychological testing, but they did not differ in rate of dementia diagnoses, MMSE performance, years of education, or depression severity.

Although the cognitive test battery used in SNAC-K is extensive and examines multiple cognitive domains, there was only one test measuring attention and executive functions, respectively. Multiple measurements of these cognitive domains could have further strengthened the results of Study III and IV, concerning the state-trait aspects of cognitive deficits in depression.

Persons with psychiatric disorders are less likely to participate in research studies (Knudsen et al., 2010), which is reflected in the low baseline prevalence of persons with severe depression (0.25%,  $n=9$ ). This makes it likely that many persons with severe depression were missed in the current studies. This, together with the relatively higher refusal rate for neuropsychological testing, is also reflected in rather small sample sizes of depressed participants, which in turn affected statistical power.

To study depression in a large population-based study presents both opportunities and challenges. Designed for healthy and dementia-related aging, some depression-related information was lacking (e.g., data on neurotrophic factors, pro-inflammatory factors, and stress-related factors, such as repeated cortisol measurements). Although a relatively large subsample of SNAC-K participants underwent Magnetic Resonance Imaging (MRI;  $n=555$ ), unfortunately the number of depressed participants who did MRI was small ( $n=16$ ). Although clinically relevant information such as comorbidity of other psychiatric disorders, number of hospitalizations and cumulative inpatient days could be derived from the IPR, specific data on these variables were lacking, such as age of depression onset, number and duration of depressive episodes, as well as amount of time spent in remission. Also, information on treatments received during hospitalizations was lacking.

## 5.7 IMPLICATIONS

Cognitive deficits in depression are associated with longer episode durations and reduced remission rates (McCall & Dunn, 2003; Papakostas, 2014), higher rates of recurrence (Fossati et al., 2002; Majer et al., 2004), reduced coping abilities (Dunkin et al., 2000), poorer antidepressant treatment response (Koenig et al., 2014; Morimoto & Alexopoulos, 2013; Morimoto et al., 2015), greater overall disability (Koenig et al., 2014), reduced quality of life and high distress (Pandina et al., 2009; Shimuzu et al., 2013). Hence, cognitive deficits in depression are associated with a poor prognosis. This makes early detection of depression highly important as cognitive deficits are likely to exacerbate from mild through moderate to severe depression (Study I), as well as with recurrent episodes (Robinson & Sahakian, 2008; Stordal et al., 2004).

Combined profiles of psychiatric history, cognitive performance and health behaviors may add important relevant information to individualized treatment. This is especially so, as about 30-40% of depressed persons do not respond to antidepressant medication (Kuk et al., 2010; Trivedi et al., 2006), and as multiple factors have been shown to modulate patterns of cognitive deficits in old-age depression (Study I: depression severity; Study II:

disadvantageous alleles of memory-related genes; Study III: psychiatric history, cumulative inpatient days, prodromal dementia, comorbidity of psychiatric disorders and heart disease, physical inactivity; Study IV: benzodiazepine drug intake).

This thesis provides evidence that cognitive deficits in depression are more state- than trait-related (Study III and IV). Thus, cognitive deficits in depression seem more reversible than stable, but may take longer time to remit as compared to other depressive symptoms. The finding of reversibility suggests that cognitive deficits in depression should be regarded as treatment targets rather than stable vulnerabilities. Thus, measuring changes in cognitive performance may provide an additional marker of treatment response. However, it needs to be taken into account that degree of reversibility is likely to diminish with age, when co-occurring aging processes are taking place and the brain's capacity for plasticity is declining (Coillard-Depres et al., 2011).

Taken together, these implications are especially important as the older population is increasing (Christiansen et al., 2009), is less likely to report cardinal symptoms of depression such as sad mood (Brodaty et al., 2001; Gallo et al., 1997), and the depressive symptoms most likely add to other diseases and physical disabilities frequently occurring in old age (Alexopoulos, 2005; Beekman et al., 2002; Gottfries, 2001).

## **5.8 CONCLUSIONS**

Depression is a heterogeneous disorder, and likewise the patterns of cognitive deficits in this condition seem to vary. Specific cognitive deficits in dementia-free unipolar old-age depression were shown to vary as a function of multiple factors, including: (1) depression severity; (2) disadvantageous alleles of memory-related genes; (3) psychiatric history and cumulative inpatient days; (4) prodromal dementia; (5) comorbidity of psychiatric disorders and heart disease; (6) physical inactivity, and; (7) benzodiazepine drug intake. This indicates that there is not one clear pattern of cognitive deficits in depression, but rather multiple patterns.

Mild depression was more prevalent than moderate and severe depression in old age, and also underdetected, as reflected by the low proportions of antidepressant medication. This underscores the importance of early detection of depression, especially as untreated depression is likely to develop into moderate and severe depression (Alexopoulos, 2003), and thus linked to exacerbated cognitive deficits.

Cognitive deficits in dementia-free unipolar old-age depression seem to be largely reversible. As such, this finding suggests that cognitive deficits in depression should be regarded as potential treatment targets.

Taken together, in order to provide the best treatment, and thus increase the likelihood of remission for depressed older persons, it would be valuable to combine profiles of psychiatric

history, cognitive performance, and health behaviors. Moreover, the assessment of combined profiles should preferably be repeated during different depression courses.

## 5.9 FUTURE RESEARCH

Ideally, a large-scale longitudinal study, following participants from young to old age investigating different depression courses, with repeated assessments of cognitive performance in combination with neuroimaging methods (MRI, fMRI, PET, ERP) biological (BDNF, cortisol, inflammatory markers, serotonin, norepinephrine, dopamine, glutamate, GABA), psychological (emotion regulation, inner-talk, coping strategies), and social (social activities, support, coping strategies) factors and health behaviors (exercise, nutrition, sleep) would be carried out. Such a design allows for comparisons of combined profiles of healthy persons prior to depression onset to the combined profiles during depression and in remission. This in turn can provide important knowledge on neurobiological markers of depression and its etiology, thereby guiding treatment options. Once a participant received a depression diagnosis, different treatment interventions may take place (antidepressant medication, CBT, MBSR, exercise and nutrition programs). When participants are nonresponsive to one treatment, they should be followed up and the treatment should be modified or augmented. This may give important knowledge on what makes one depressed person respond to one kind of treatment as opposed to another, and thus potentially further elucidate some of the heterogeneity in depression. Furthermore, important knowledge could also be obtained to design preventive interventions in healthy persons, in an attempt to increase resilience, and potentially reduce the incidence of depression in the future. For example, school children could be taught appropriate coping strategies, as well as emotion regulation.

In the more immediate future, research should establish causal links between stress and depressive symptomatology, including cognitive deficits. Further insight into the degree of reversibility of cognitive deficits in depression is highly warranted. Multiple factors could be investigated here, including: (a) establishing factors that modulate reversibility; (b) do the modulating factors exert different degrees of influence in different stages of stress? (e.g., first onset vs. recurrent depression) and in different courses of depression (nondepressed-depressed; depressed-remitted; remitted-depressed; depressed-depressed); and (c) what are the modulating factors' influence on neurobiological changes (before depression onset, during depression and in remission for stress- and depression-related neural pathways and structures).

Furthermore, deepened knowledge on the temporal aspect of reversibility of cognitive deficits is highly warranted, as little is known about this topic and cognitive deficits in depression are associated with poor prognosis. For example, how much more time is required in remission to reverse cognitive deficits in comparison to recovery from core symptoms of depression, and which factors regulate this process?

We still do not have sufficient knowledge about the heterogeneous depression disorder, reflected by high prevalence and recurrence rates, as well as by poor treatment responses. As such, there is no shortage of potential future studies that hopefully can elucidate the etiology of this disorder, its biological markers, and treatment responses.

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What place may a mountain ridge (*Aiguille du Midi, Chamonix, France*) have on a thesis cover? Well, early in life I fell in love with mountains: Their grandeur, presence, beauty, and ability to induce a feeling of absolute freedom. To me, mountains are like life – an exploration with inevitable ups and downs. The ascent of a mountain summit is effortful, but only half of the journey. One also needs strength for a safe descent. There is no summit experience without an ascent. One has to expect change.

The mountain pose (*Tadasana or Samastahiti*), is the pose from which all yoga asanas are derived. The basis and centerpiece of the standing sequences. In yoga breath leads, body follows, mind observes. When engaging in high-altitude climbing, hypoxia may struck as oxygen levels decreases. If one cannot inhale and exhale smoothly, your body is saying it has had enough. Many a mountaineer with summit-fever pushed on and did not have a safe descent. Mountains demand and require calibration of our abilities for balance and reflection – knowing when to push on and when to let go; and to pay attention to what we are doing, how we are doing it, and why we are doing it.

Mountains offer tremendous perspective; miles and miles of remarkable nature and animals. It is all connected. Things that seemed so big and heavy, become small and light. Mountains, more or less, stand unprovoked by storms, thunder, and snow hail. No matter their surroundings or weather changes, they remain a foundation. They stand tall and resilient. In contrast, a small vulnerable human being needs to bring layers of clothes, equipment, and experience in order to survive in their presence; life just like weather can be unpredictable and challenging.

Mountains provide nourishment and energy to body and mind, offer perspective and clarity of mind, remind me of the beautiful wonders in nature, and above all – that we all are small and vulnerable at times. Even the most experienced mountaineer will face vulnerable states, and will be in need of a helping hand. When someone is more vulnerable than ourselves, it is always possible to offer support and compassion. For me, this included trying to understand as many aspects of depression as possible. I have learned much, but there is still much to learn. This is my motivation, and the reason why this thesis is dedicated to everyone who has suffered or will suffer from depression, and to everyone who knows them.



*Namasté!*

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## 8 APPENDIX

List of dissertations from the Aging Research Center and the Stockholm Gerontology Research Center, 1991-2015.

### 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 Alzheimers' disease. Issues of etiology and validity.

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

**Basun Hans.** Biological markers in Alzheimers' 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.** 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.

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

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

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

## 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.

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

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

**Livner Åsa:** Prospective and retrospective memory in normal and pathological aging.

**Atti Anna-Rita.** The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

## 2010

**Fors Stefan.** Blood on the tracks. Life-course perspectives on health inequalities in later life.

**Keller Lina.** Genetics in dementia. Impact in sequence variations for families and populations.

## 2011

**Schön Pär.** Gender matter. Differences and changes in disability and health among our oldest women and men.

**Caracciolo Barbara.** Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.

**Rieckmann Anna.** Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

## 2012

**Haasum Ylva.** Drug use in institutionalized and home-dwelling elderly persons.

**Mangialasche Francesca.** Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.

**Lovén Johanna.** Mechanisms of women's own-gender bias and sex differences in memory for faces.

## 2013

**Hooshmand Babak.** The impact of homocysteine and B-vitamins on Alzheimer's disease, cognitive performance and structural brain changes.

**Rizzuto Debora.** Living longer than expected: protective and risk factors related to human longevity.

## 2014

**Sjölund Britt-Marie.** Physical functioning in old age: Temporal trends and geographical variation in Sweden.

**Wastesson Jonas.** Unequal drug treatment: age and educational differences among older adults.

## 2015

**Sköldunger Anders.** Dementia and use of drugs: Economic modelling and population-based studies.

**Craftman Åsa Gransjön.** Medicine management in municipal home care; delegating, administrating and receiving.

**Svärd Joakim.** Emotional facial processing in younger and older adults.

**Wang Rui.** Cardiovascular risk factors, brain structure, and cognitive decline in old age.