Cognitive Functions in Depression and Anxiety Disorders
Findings from a population-based study

Eija Airaksinen
“Watch your thoughts; they become words.
Watch your words; they become actions.
Watch your actions; they become habits.
Watch your habits; they become character.
Watch your character; it becomes your destiny.”
ABSTRACT

This doctoral thesis examines cognitive functions in depression and anxiety disorders in a population-based sample that includes mostly untreated persons. It is well established that depression is associated with cognitive impairments. However, in spite of the fact that most of the depressed persons are untreated, almost all available evidence in this field is based on in-and outpatient samples. Also, little attention has been paid to cognitive functioning in anxiety disorders. The thesis includes four empirical studies that were based on data from the PART study, an ongoing population-based study of mental health in Stockholm, Sweden.

The specific objectives of Study I were to examine whether there is an association between depression and cognitive abilities including episodic memory, verbal ability, psychomotor speed (TMT-A), and executive function (TMT-B) as well as to examine whether potential cognitive deficits vary as a function of DSM-IV defined depression diagnoses. Similarly, in Study II we aimed to examine the relationship between anxiety disorders and cognitive functioning in the same abilities as in Study I and whether the observed cognitive impairments varied as a function of anxiety diagnosis. In Study III, the major objective was to study cognitive functioning in recovery from depression by following up a sample of depressed persons three years later. Study IV, finally, aimed to investigate premorbid markers of depression with a specific focus on low episodic memory performance. This was accomplished by prospective examination of a cohort of depression-free persons three years after the baseline examination, at which a group of these persons received a depression diagnosis.

Results from Study I indicated that depressive disorder was associated with cognitive dysfunction. Depression-related deficits were observed in tests tapping episodic memory and executive function. Further, we found that persons diagnosed with Major Depressive Disorder and Mixed Anxiety Depressive Disorder showed significant deficits in episodic memory functioning, whereas Dysthymia was associated with impaired executive function. Minor Depressive Disorder was not found to be associated with cognitive dysfunction. The pattern of results in Study II was comparable to the observations in Study I. We found anxiety-related impairments in episodic memory that remained even after controlling for comorbid depression. Specifically, Panic Syndrome (PD), Social Phobia (SP), and Obsessive Compulsive Disorder (OCD) were associated with episodic memory dysfunction, whereas Specific Phobia was not. In addition, we observed executive dysfunction in anxiety and then specifically in persons affected by PD and OCD. However, these deficits were non-significant after controlling for alcohol abuse/dependence, suggesting that excessive alcohol use may explain parts of these findings. Results from Study III demonstrated that the recovered persons suffered a continuous cognitive dysfunction. Results from Study IV suggested that low episodic memory performance, as measured by the sum of free and cued recall, was a significant risk factor for developing depression three years later independently of demographic, clinical and socioeconomic factors.

Taken together, the findings from this thesis extend the picture of cognitive dysfunction in depression and anxiety disorders by including untreated persons sampled from the population. Further, the present findings suggest that episodic memory impairments persist beyond the recovery from depression and that low cognitive performance is present already three years before depression diagnoses. The overall conclusion that can be drawn from the thesis is that depression in particular, but also anxiety, are serious conditions that affect cognitive functioning indicating that these disorders are associated with brain dysfunction. This, in turn, may have a large negative impact, not only for the working and social lives of the persons affected by depression and anxiety, but also for society as a whole.

Key words: depression; anxiety; general population; cognitive functions; episodic memory; recovery; etiology; follow-up studies.
LIST OF PUBLICATIONS

The present doctoral thesis is based on the following four original papers, which will be referred to in the text by their Roman numerals.


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<td>ECA</td>
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INTRODUCTION

Depression and anxiety disorders are the most common psychiatric disorders in the adult population in the Western world. Lifetime prevalence of depressive disorder ranges between 5 to 25% (American Psychiatric Association, 1994), whereas the lifetime prevalence for anxiety disorders is estimated to be even higher, around 29% in the population (Kessler & Zhao, 1999). These disorders are also associated with considerable disability and suffering that is not limited to the affected persons alone, but also includes consequences for close persons such as family members and friends. It is estimated by the World Health Organisation (WHO) that unipolar depression will continue to be one of the leading causes of suffering in the year 2020 (Murray & Lopez, 1997). Further, a strong body of evidence demonstrates the coexistence of depression in many medical illnesses (e.g., cardiovascular disease, stroke, cancer, epilepsy) and presence of depression is reported to considerably worsen medical prognoses (Evans et al., 2005). In addition, suicide is a serious consequence of depression and in the year 2000, approximately one million people died from suicide (WHO. http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/). For these reasons, depression and anxiety disorders can be considered as having a large negative impact on public health.

It is also important to highlight that both depression and anxiety disorders are often unrecognised and untreated in the population. Although effective treatments of mental disorders are available, only 20-30% of the people identified in epidemiological surveys as meeting the criteria for a mental disorder, have met need (Bebbington, Marsden, & Brewin, 1997; Bijl & Ravelli, 2000; Henderson, Pollard, Jacobi, & Merkel, 1992; Kessler et al., 1997).

Depression is not only a mood disorder; it also affects an individual’s cognitive ability. It is evident from conducted research over the past decades that depressive disorders are associated with cognitive dysfunction (e.g., see Austin et al., 2001; Miller, 1975; Veijel, 1997 for a review). In particular, impaired memory function has been observed in depression (e.g., Burt, Zembar, & Niederehe, 1995). However, almost all available evidence addressing cognitive deficits in depression are based on in-and outpatient samples, i.e., studies of persons who have sought treatment for their mental problems. Because most of the depressed persons do not enter the clinics (Christiana et al., 2000), an important research goal is to study cognitive function in the population. Furthermore, most research on this topic has focused on persons affected by Major Depression, leaving other depression diagnoses relatively unexplored. Thus, an important research goal in the present work was to examine cognitive functioning across different depressive disorders. Another neglected research question concerns whether the observed cognitive dysfunction persists with recovery from depression. This is a particularly important question given that evidence from previous research suggests that the hippocampal volume reduction persists beyond recovery from depression (Neumeister et al., 2005). Another important research subject concerns the influence of low memory performance as a premorbid marker of development of depression.
As noted, anxiety represents a group of disorders causing major mental health problems in the population. In contrast with the amount of research that has focused on depressive disorders, little is known regarding the relationship between anxiety disorders and cognitive functions, and the reported observations are inconclusive.

Taken together, the general aim of this thesis is to extend available knowledge on cognitive functioning in depression and anxiety disorders in the population. This was accomplished by examining persons affected by depression and anxiety disorders in a population-based sample that mainly included untreated persons.
BACKGROUND

Depression

The concept of depression includes a wide range of symptoms including normal feelings of depressed mood that affects almost everyone from time to time, to more severe depressive states that meet diagnostic criteria for a depressive disorder. Furthermore, depression shows high rates of relapse and chronicity as reported in several studies (e.g., Howarth, Johnson, Klerman, & Weissman, 1992; Paykel, 1992). Specifically, research indicates that about 50% of those who have experienced one depressive episode will be depressed again within one year and about 70% within two years (Angst & Preisig, 1995a; Angst & Preisig, 1995b). Depression is a complex disorder with a multifactorial genesis. It is well established that depression is approximately twice as common in women as in men and that it affects people of all ages. Moreover, genetics, adverse events in childhood, as well as other stressful events later in life are well-documented risk factors for depression (Levinson, 2006; Kendler, Karkowski, & Prescott, 1999).

Depression diagnoses

Depression is a heterogeneous disorder and may be defined in different ways. In this thesis, we used depression diagnoses based on the criteria established in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994). The DSM-IV is a frequently used classification system in psychiatric research. In general, mood disorders are separated into two categories: unipolar and bipolar disorder. The distinction between these two types is that bipolar disorder is characterised by alternating manic and depressive episodes, whereas unipolar disorder includes only depressive or manic episodes. This thesis only includes unipolar depressive disorders. Below follows a brief description of the depression diagnoses that were focused in this work.

Major Depressive Disorder (MD) is the most severe form of unipolar depression. It is characterized by at least a two weeks period of depressed mood, loss of interest or pleasure almost all of the time, and accompanied by at least four of the following symptoms: significant change in weight or appetite, sleep disturbance, psychomotor disturbance, feelings of guilt or worthlessness, concentration difficulties, fatigue or loss of energy, and suicidal thoughts or suicide attempt. In the DSM-IV, it is also stated that the symptoms should cause clinically significant impairment and should not be a result of substance abuse, somatic illness or bereavement.

Dysthymic Disorder (DD) is more chronic in nature than MD. It is defined as a chronic disturbance of mood involving depressed mood for at least two years, during which the condition has not met the criteria for MD. At least two of the following symptoms must be present: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty in making decisions or, feelings of hopelessness.

In addition to the above described established depression diagnoses, this work also comprised two new research diagnoses that were introduced in the 4th edition of the DSM. Minor Depressive Disorder (MinD) involves at least two but less than five symptoms that are identical with MD in duration, but involves less impairment. Depressed mood or loss
of interest must be one of the symptoms. This disorder is relatively common in primary care and in outpatient mental health settings (Banazak, 2000; Rapaport et al., 2002).

Mixed Anxiety-Depressive Disorder (MAD) involves a persistent or recurrent dysphoric mood, lasting for at least one month. At least four of the following symptoms causing significant distress or impairment should be prevalent: concentration or memory difficulties, sleep disturbances, fatigue or low energy, irritability, worry, being easily moved to tears, hyper vigilance, anticipating the worst, hopelessness or pessimism about the future, and low self-esteem or feelings of worthlessness.

It should be noted that several other depression diagnoses are covered in the DSM-IV. Those are not covered here due to low numbers or lack of data to make these diagnoses.

**Anxiety**

Feelings of anxiety affect almost everyone from time to time and may be regarded as a normal part of human life. To consider anxiety as an illness, distress and impaired function should also be present. As is true for depression, anxiety disorders are more common in females, and risk factors for developing the disorder are similar to those of depression. Also, anxiety disorders are strongly associated with depressive illness (Kessler, 1995), and research suggests that an anxiety disorder may precede and increase the risk for developing depression (Bittner et al., 2004; Stein et al., 2001; Wittchen, Kessler, Pfister, & Lieb, 2000).

**Anxiety diagnoses**

Below, a short overview of the DSM-IV defined anxiety disorders included in this thesis is provided (American Psychiatric Association, 1994). It should be noted that not all of the DSM-IV defined anxiety disorders are listed below.

Panic Disorder (PD) is characterized by recurrent panic attacks typically occurring spontaneously which means that it is not associated with a situational trigger (i.e., it occurs “out of the blue”). A panic attack is defined as a discrete period of fear or discomfort that is accompanied by somatic symptoms such as palpitations, sweating, trembling or shaking, sensations of shortness of breath, chest pain, nausea, or dizziness, together with emotional and cognitive symptoms such as fear of “going crazy” or fear of dying.

Agoraphobia is described as anxiety about, or avoidance of, places or situations from which escape might be difficult or in which help may not be available in the event of having a panic attack or panic-like symptoms. Agoraphobic fear typically involves situations that include being outside the home alone, being in a crowd, or standing in a line and leads to avoidance of these situations. Agoraphobia may occur in the context of PD or without PD.

Generalized Anxiety Disorder (GAD) is characterized by excessive anxiety and worry about a number of events or activities for a period of at least six months. The anxiety or worry should be difficult to control and accompanied by at least three of the
following additional symptoms: restlessness, being easily fatigued, difficulty to concentrate, irritability, muscle tension, and disturbed sleep.

Social Phobia (SP) is defined by a marked and persistent fear of social or performance situations in which embarrassment may occur. This leads to that the feared social or performance situations are avoided, a behaviour that significantly interferes with the person’s normal routines, occupational functioning, and social activities.

Specific Phobia is characterized by an unreasonable persistent fear for innocuous stimuli or situations commonly leading to avoidance of the feared object or situation (e.g., flying, heights, and animals, receiving an injection, seeing blood).

Obsessive-Compulsive Disorder (OCD) is defined by intrusive, unwanted thoughts (i.e., obsessions), which cause marked anxiety, and ritualized repetitive behaviours or mental acts (i.e., compulsions) that serve to neutralize anxiety. The obsessions and compulsions cause marked distress and are time-consuming, take more than one hour per day, or may significantly interfere with the person’s life.

**Comorbidity**

It is important to highlight that in “the real world”, the psychiatric diagnoses are not distinct conditions as they are described in the DSM manual. For example, psychiatric comorbidity that refers to the presence of more than one mental disorder occurring in a person at the same time is highly prevalent and this is true for all psychiatric disorders. Depression and anxiety, for example, typically co-occur simultaneously. It is estimated that up to two-thirds of those having a lifetime history of MD in the general population, also have a lifetime history of at least one other psychiatric disorder (Kessler, 2001). Robins, Locke, and Regier (1991) noted even higher proportions of comorbidity in anxiety.

**Cognitive functions**

Cognition may be defined as all mental activities that are involved in acquisition, processing, storage, and retrieval of information. Cognitive functioning includes a variety of skills such as attention, learning, memory, verbal ability, visuospatial skill, logical thinking, and problem solving. The cognitive domains focused in this thesis were selected because previous work indicated that they were particularly affected in depression and anxiety disorders (e.g., Goodwin, 1997). In the following section a short overview of the assessed cognitive domains is provided including memory, verbal fluency, and executive functions.

**Memory**

Memory is not a single process or system, but a collective term for a family of neurocognitive systems that differ in the way they store information and become available to consciousness and behaviour. An overview of the memory systems is portrayed in Figure 1.

Memory can be separated into short-term (STM) and long-term (LTM) memory. STM is characterized by a temporary storage of a limited amount of information dependent on attention for maintenance. The two components of STM are primary memory that reflects relative passive information holding, and working memory referring to active
processing of information in the focus of consciousness (Baddeley, 1992). In contrast, LTM is regarded as more or less permanent and is unlimited with regard to information storage capacity.

Figure 1. An overview of the memory systems (modified after Tulving 1983; Baddeley, 1992; Squire & Zola 1996)

LTM is separated by two fundamentally different memory systems: non-declarative (e.g., procedural memory) and declarative memory (e.g., episodic memory). The former comprises implicit memory and the latter explicit memory referring to unconscious and conscious retrieval, respectively.

Procedural memory involves memory for various types of skills and actions (e.g., riding a bike, playing the piano). The acquisition of most procedural skills is gradual and slow, but once a skill is acquired, retrieval becomes more or less automatic and is relatively resistant to forgetting (e.g., Nilsson, 2003).

The perceptual representation system (PRS) is primarily concerned with improving identification of perceptual objects and words (e.g., instantly knowing - when seeing a telephone - that it is used to make calls with) (Tulving & Schacter, 1990). PRS is involved in priming that refers to an increased ability to identify a stimulus as a result of prior exposure to the same or related item (Schacter, 1987).

Semantic memory involves acquisition and use of factual knowledge (e.g., H₂O is the chemical formula of water; Paris is the capital of France). Semantic memory is typically accessed with tests tapping general knowledge or verbal fluency (e.g., Nilsson, 2003).

Episodic memory refers to our ability to recollect personally experienced events from the past (i.e., yesterday I went to the cinema; remembering all the presents I received when I turned 30). This form of memory is unique for each person and constitutes the only memory system that operates backwards in time at the time of retrieval (e.g., Tulving & Markowsitsch, 1998; Tulving, 2002). Episodic memory involves three successive stages: encoding, storage and retrieval that refers to processes that lead to
the formation of new memory representations, the maintenance of memory representations over time, and accessing stored memory representations, respectively (Cabeza & Nyberg, 2000). In the laboratory setting, episodic memory performance is traditionally tested by providing different amount of support during retrieval (i.e., free recall, cued recall, or recognition). In a free recall test, a person is required to recall the previously presented information (e.g., words, objects) without support, whereas in a cued recall assessment retrieval cues are presented to facilitate recall (e.g., semantic categories of words). In recognition, low cognitive demands are posed in that the target item (i.e., a face, word, odor) is completely re-instated at test.

Neuroimaging studies indicate that different brain areas are involved in encoding and retrieval. Here, research suggests that the left frontal brain areas primarily are involved in encoding of information, whereas retrieval functions primarily are chiefly supported by the right frontal areas of the brain (Cabeza & Nyberg, 2000).

**Verbal fluency**

Verbal abilities such as language, fluency, reading, and writing abilities are typically represented in the left hemisphere of the brain (Kolb & Whishaw, 1996). Verbal fluency is generally assessed by oral production of spoken words from a certain taxonomic category (category fluency or semantic fluency), or words beginning with a given letter (letter fluency or phonemic fluency) (Lezak, 1995). Letter fluency involves development of a strategy to produce words and is thus a measure of executive function and language (Ravnkilde et al., 2002).

**Executive functions**

Executive functions include abilities such as formulating goals, planning, initiating and carrying out tasks, and self-monitoring and regulation of behavior to meet desired goals (Lezak, 1995). In this thesis, executive function is assessed with the trail-making test (TMT) that is given in two parts, A and B. On the TMT-A, the task is to draw lines to connect consecutively numbered circles, thus demanding rapid visuospatial scanning and identification. On the TMT-B, the task is to draw lines alternating between consecutively numbered and alphabetized circles, a task which poses demands on mental flexibility by requiring managing of more than one stimulus category at a time and ability to shift the course of ongoing activity. TMT-B also draws on other working memory and semantic functions.

**Cognitive functioning in depressive disorders**

Impaired memory function is presumably the most consistent finding in studies examining cognitive functioning in depression. However, not all forms of memory are affected by depression. Several studies suggest a specific episodic memory dysfunction (den Hartog, Derix, van Bemmelen, Kremer, & Jolles, 2003; Fossati et al., 2004a; Ilsley, Moffoot, & O’Carroll, 1995; Wolfe, Granholm, Butters, Saunders, & Janowsky, 1987), but spared functions in semantic memory (Zakzanis, Leach, & Kaplan, 1998), implicit memory (Bazin, Perruchet, De Bonis, & Feline, 1994; Danion, Kauffmann-Muller, Grangé, Zimmermann, & Greth, 1995; Hertel & Hardin, 1990), and short-term memory (Ilsley et al., 1995) have been reported. Two meta-
analyses reported a significant stable association between depression and impairments in episodic memory for both younger (Burt et al., 1995) and older adults (Kindermann & Brown, 1997), although the negative effect of depression on memory was greater among younger individuals. A possible explanation for this discrepancy is that several factors may explain age-related deficits in episodic memory (e.g., speed of processing, working memory deficits, health, selective attrition) whereas at a young age, depression may account for most of the cognitive variance. In addition, some studies have reported impairments in working memory (Elliot et al., 1996; Rose & Ebmeier, 2006). However, it is important to note that some investigators have failed to find a negative association between depression and episodic memory performance (e.g., Fossati, Amar, Raoux, Ergis, & Allilaire, 1999; Grant, Thase, & Sweeney, 2001; Wang et al., 2006). Possible explanations for the inconsistent findings may be differences across studies in the selection of participants, depression subtypes and treatment settings. Other potential sources of the mixed results are differences in the material used to measure memory performance (e.g., visual vs. verbal), retention interval, and the amount of cognitive effort posed during encoding and retrieval (e.g., recall vs. recognition) (Burt et al., 1995).

With regard to other cognitive domains, available research presents a mixed pattern of findings. Significant negative effects of depression have been observed for attention (Porter, Gallagher, Thompson, & Young, 2003; Sweeney, Wetzer, Stokes, & Kocsis, 1989), executive functions (Elliott et al., 1996; Fossati et al., 1999; Grant et al., 2001), motor speed and attention set-shifting (Porter et al., 2003; Purcell, Maruff, Kyrious, & Pantelis, 1997), psychomotor speed (Austin et al., 1992; Ilsley et al., 1995), verbal fluency (Elliott et al., 1996; Landro, Stiles, & Sletvold, 2001; Porter et al., 2003), and mental flexibility (Austin et al., 1992). However, others have failed to support these observations. It is also important to note that most of the available evidence on the impact of depression on cognitive functions is based on individuals suffering from MD, and little is known as to whether other depressive disorders also are related to cognitive dysfunction.

**Why cognitive deficits in depression?**

Early studies proposed that depression-related cognitive deficits might be associated with a failure to process effort-demanding information as opposed to tasks posing lower cognitive demands that draw on more automatic processes (Hartlage, Alloy, Vázquez, & Dykman, 1993; Hasher & Zacks, 1979; Roy-Byrne, Weingartner, Brierer, Thompson, & Post, 1986; Tancer et al., 1990; Weingartner, Cohen, Murphy, Martello, & Gerdt, 1981). Thus, this perspective embraces the notion that depression is related to significant capacity reductions in adequate processing of cognitively demanding/effortful information (Hartlage et al., 1993). However, not all research supports the effortful-automatic hypothesis (Golinkoff & Sweeney, 1989; den Hartog et al., 2003; Ilsley et al., 1995). For example, den Hartog and colleagues (2003) recently speculated that cognitive dysfunction in depression may be caused by cognitive slowness (i.e., reduction in mental speed) rather than by a reduced ability to process information that poses higher demands of effortful and elaborative processing.

Some studies have also argued that the cognitive deficits may stem from poor motivation (Miller, 1975) while other studies disagree (Ilsley et al., 1995; Richards & Ruff, 1989).
Also, evidence indicates that depressed persons may have a memory bias for emotionally negative information as compared to positive or neutral information (Denny & Hunt, 1992). This observation is in contrast to observations indicating a memory bias in both depressed and healthy persons for all emotional material (i.e., negative and positive), but not for neutral material (Danion et al., 1995). These findings are typically explained by the mood congruity hypothesis referring to the tendency to recall more information about events that are congruent with the current mood. Further, the memory bias for negative information has been reported to be present for explicit but not for implicit memory tasks (Roediger & McDermott, 1992), but with some conflicting findings (Watkins, Mathews, Williamson, & Fuller, 1992). Also, it is worth noting that some researchers suggest that mood congruent memory may play a role in the maintenance of depression (Teasdale, 1983). Here, it is speculated that negative thinking may both have a causal role in producing symptoms of depression as well as being a symptom of depression. This reciprocal relationship between depression and cognition may form the basis of a vicious cycle, which may fuel the maintenance of depression once it is established.

In addition, there are observations suggesting that cognitive deficits are prevalent only in individuals with recurrent depression and not in persons who experience their first depressive episode (Basso & Bornstein, 1999; Fossati et al., 2004a). However, it is worth noting that the pattern of memory impairments observed differs across studies. For example, Basso and Bernstein (1999) reported impairments of both free and cued recall in recurrent depression presumably reflecting an encoding deficits and medial temporal lobe dysfunction. In contrast, Fossati and colleagues (2004a) found impaired free recall, but normal cued recall and recognition performance suggesting retrieval rather than encoding deficits and the presence of prefrontal dysfunction. Despite the different memory impairment patterns, it may be hypothesized that recurrent depression is associated with an increasing cerebral dysfunction. As proposed by Post (1992), fundamental neurochemical changes occur as a function of successive depressive episodes. As a consequence of these changes, cerebral dysfunction increases for each episode, which may in turn decrease the threshold for onset of subsequent depressive episodes.

**Neurobiology of depression**

An increasing amount of evidence indicates that cognitive dysfunction is directly related to the neurobiology of depression. The development of different brain imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) has opened new possibilities to gain new knowledge regarding the neural correlates of depression-related cognitive deficits. Indeed, neurobiological findings suggest that depressive disorders are associated with structural and functional brain changes. For example, brain imaging studies demonstrate an association of depressive disorder with reductions in the metabolic activity of the prefrontal cortex (Dolan et al., 1992; Drevets, 2000), as well as neural atrophy in the prefrontal cortex (Bremner et al., 2000; Drevets, 2000), and limbic structures such as the hippocampus (Bremner et al., 2000; Frodl et al., 2002; McEwen & Magarinos, 2001) and amygdala (Sheline, Gado, & Price, 1998). The hippocampal atrophy in depression may be explained by the toxic effects of hypersecretion of glucocorticoids that results from an over-activation of the hypothalamic-pituitary-adrenal (HPA) axis that typically occur in depression (McEwen, 1999; Sapolsky,
In addition, there is growing evidence linking depression with dysfunction in the frontal lobes; the latter being involved in executive cognitive functions. For example, PET studies performed with persons affected by depression have shown changes in areas including the left anterior cingulate and the left dorsolateral prefrontal cortex, subserving executive functioning (Fossati et al., 2004b).

**Cognitive functioning in recovery from depression**

What happens with the observed cognitive dysfunction in recovery from depression? This is an important research topic that has as yet received relatively limited attention. Most research addressing this issue has focused on the effects of antidepressant treatment on cognitive functioning in the elderly. This research indicates continuous cognitive dysfunction following successful antidepressant treatment in depressed geriatric patients (Butters et al., 2000; Nebes et al., 2003) and in middle-aged remitted patients (Deuschle et al., 2004; Neu et al., 2005) as compared to healthy controls. In a similar vein, results from a cross-sectional study comprising young and middle-aged patients with MD in remission suggested a persistent impairment in cognitive functioning (Weiland-Fiedler et al., 2004). Further, Paradiso, Lamberty, Garvey, and Robinson (1997) reported that male patients with a history of chronic depression exhibited cognitive impairment also in the non-symptomatic phases of depression. Taken together, available evidence suggests that cognitive dysfunction may persist also after recovery from depression.

**Low cognitive function as a premorbid marker of depression**

As noted earlier, depression is a multifactorial disorder with both genetic and environmental factors contributing to the development of the disease. To our knowledge, no previous study has investigated specifically whether cognitive functions are affected also in the premorbid course of depressive illness.

**Cognitive functioning in anxiety disorders**

As indicated earlier, the impact of anxiety on cognitive functioning is much less explored than the impact of depression. A review of the literature indicates that most work has focused on OCD, which is the least prevalent anxiety disorder but probably more severe than the other DSM-IV defined anxiety disorders. Previous research on cognitive abilities suggests that OCD has the largest negative effects on tasks tapping non-verbal memory and selective executive functions (Boldrini et al., 2005; Dirson, Bouvard, Cottraux, & Martin, 1995; Kuelz, Hohagen, & Voderholzer, 2004; Penades, Catalán, Andrés, Salamero, & Gastó, 2005; Savage et al., 1996), although verbal memory deficits have been reported (Savage et al., 2000; Zitterl et al., 2001). In contrast, other work suggests normal executive functioning in OCD (Boone, Ananth, Philpott, Kaur, & Djenderdjian, 1991; Christensen, Won Kim, Dysken, & Maxwell Hoower, 1992; Zielinski, Taylor, & Juzwin, 1991). Also, available evidence provides a mixed pattern of findings regarding deficits (Christensen et al., 1992; Deckersbach et al., 2004; Schmidtke, Schorb, Winkelmann, & Hohagen, 1998) or preserved verbal fluency abilities in OCD (Abbruzzese, Ferri, & Scarone, 1995; Boone et al., 1991).

Few studies have assessed cognitive abilities in other DSM-IV defined anxiety disorders, and the results from these investigations are inconsistent. Lucas, Telch, and
Bigler (1991) reported reliable impairments in visual but not verbal memory in persons affected by PD. In addition, Boldrini and colleagues (2005) reported spatial learning impairment in patients affected by PD with agoraphobia. In contrast, an earlier study by Asmundson, Stein, Larsen, and Walker (1995) reported impairments of verbal learning and memory in both PD and SP, although persons with PD performed as well as controls in visual memory tasks. In addition, some research has found significant executive dysfunction in PD (Cohen et al., 1996). In contrast to these observations, other investigators found no evidence for an episodic memory dysfunction in PD, and this was true for both verbal and visual stimuli (Gladsjo et al., 1998). Also, Purcell, Maruff, Kyrios, and Pantelis (1998) compared samples of OCD, PD, and MD patients with healthy controls across a number of cognitive domains. The results indicated that only OCD patients exhibited impairments in executive functioning, attention, and episodic memory, whereas the PD and MD samples performed as well as healthy controls. As noted above, it is highly likely that the inconsistent findings are the result of methodological differences between studies regarding selection of participants, patient status, material used in memory tasks, and memory performance assessment (e.g., recall vs. recognition).

It is important to note that a substantial body of research has focused on memory bias in anxiety disorders (for review see Coles & Heimberg, 2002). This research lends support specifically for explicit memory biases for threat-relevant information in PD and OCD, particularly when information has been deeply encoded. However, this is not observed in SP or GAD. In addition, some degree of support for implicit memory biases has been demonstrated for each of the anxiety disorders. However, this research is not further reviewed here since it is not the focus of the present work.

Neurobiological anxiety research suggests that the medial temporal and frontal lobe structures are affected in anxiety disorders. For example, research suggests dysfunction of prefrontal cortical and striatal regions in OCD patients (Kwon et al., 2003; Saxena, Bota, & Brody, 2001). Further, a magnetic resonance imaging study reported smaller temporal lobe volume in patients with PD whereas the hippocampal volume was not different from normal controls (Vythiligam et al., 2000). In addition, PET studies demonstrate an involvement of the hippocampal and parahippocampal areas in PD (Bisaga et al., 1998), and an abnormal blood flow in the medial temporal lobe including the amygdala and hippocampus among symptom-provoked SP patients (Tillfors et al., 2001).
AIMS OF THE THESIS

The overall objective of this doctoral thesis is to extend the present knowledge of cognitive functioning in depression and anxiety disorders in the general population comprising mostly untreated persons.

The specific aims of the studies included in the thesis are:

- To examine cognitive functioning in depression (Study I) and anxiety disorders (Study II) and to determine whether cognitive performance varies as a function of diagnostic subgroup.
- To examine cognitive functioning in recovery from depression (Study III).
- To investigate premorbid markers of impending depression (Study IV). In particular, the role of low episodic memory performance was investigated.
MATERIAL AND METHODS

The PART study

Data used in this thesis were collected in the ongoing PART project, a longitudinal epidemiological study of mental health, work, and relations in Stockholm County. The general aims of PART are to identify conditions associated with the onset of mental disorders, prognoses and consequences of such disorders. So far, two phases of data collection, with a three-year inter-test interval, have been accomplished. See Figure 2 for a description of the study design.

Figure 2. Overview of the study design of the PART study.
Baseline examination

Participants
The initial study population included 19,742 randomly selected Swedish citizens aged 20-64 years, residing in Stockholm County 1998-2000. The population register of Stockholm County was used to identify participants on five occasions. The samples were of approximately equal size and drawn at regular intervals. To minimize language problems only Swedish citizens were included. In 1998-2000, there were approximately 858,000 inhabitants in Stockholm County that fulfilled the sampling criteria.

Questionnaire
At the baseline assessment, a comprehensive questionnaire was mailed to the participants. The questionnaire covered demographic data and circumstances reported to be either risk or protective factors for mental illness. Screening scales converting psychiatric symptoms, harmful alcohol use, and social disability due to psychiatric or psychological symptoms were also included. The questionnaire took about one hour to complete. In total, 10,441 (53%) of the 19,742 randomly selected persons participated. Of the respondents, 4,643 were men and 5,798 were women. Extensive analyses of non-participation using official registers (i.e., The Hospital Discharge Register 1987-1998, The Register on Income and Wealth 1998, and The Disability Pension Register 1971-August 2000) have been completed (Lundberg, Damström Thakker, Hällström, & Forsell, 2005). These analyses showed that male sex, being below 50 years, low income, low education level, living alone, and country of origin outside the Nordic countries, were strong determinants of non-participation. The associations between age, gender, income, country of origin, sick leave and in-patient hospital care due to psychiatric diagnosis were calculated for participants and the entire target population. The odds ratios (OR’s) for these associations were similar for participants and non-participants (Lundberg et al., 2005).

Psychiatric interview
Of those who responded to the questionnaire, 1,367 persons were randomly selected for a psychiatric interview that was conducted within 2 weeks of receiving the questionnaire. Of the total of 1,093 persons who completed the interview, 884 screened positive (i.e., reported many psychiatric symptoms in the questionnaire) and 209 screened negative (i.e., reported no psychiatric symptoms). Non-participation (274 individuals) was mostly due to lack of time. There were no differences between participants and non-participants in terms of gender, country of origin, welfare allowance, unemployment benefits, sick leave or income (Forsell, 2005).

Schedules for Clinical Assessments in Neuropsychiatry (SCAN, version 2.1, 1998) was used as interview instrument, a semi-structured clinical interview schedule for clinician’s assessment of the symptoms and course of adult mental disorders. SCAN was developed from the Present State Examination (PSE) by Wing, Nixon, Mann, and Leff (1977) and later revised by the WHO (Wing et al., 1990). All interviewers were clinically experienced, most of them were psychiatrists and one was psychologist. The interviewers underwent a one-week introductory course from one of the WHO-designated trainers and they also received regular supervision by an assistant professor.
in psychiatry during the study. Inter-rater reliability was improved by using videotaped interviews.

In addition to the SCAN interview, complementary information regarding treatment needs and heredity was obtained, blood samples were collected and a brief cognitive test battery was administered.

**Cognitive assessment**

As noted, all subjects invited to the SCAN interviews were asked to complete a brief cognitive test battery tapping episodic memory, verbal fluency, psychomotor speed, and executive functioning. These tests were specifically selected because previous research had shown that the cognitive domains tapped by these tests might be particularly affected by depression and anxiety. The participants were tested individually in one session that always took place before the SCAN interview and lasted approximately 25 minutes. The test session started with a questionnaire concerning health status. The examiner gathered information regarding sensory functioning (vision and hearing), neurological diseases, migraine, sleep apnoea, concussion of the brain, epilepsy, meningitis, and tick-borne encephalitis (TBE). Information regarding drug intake and mother tongue was also collected.

**Diagnostic procedures**

DSM-IV diagnostic criteria for Axis I disorders were strictly followed and diagnoses according to Appendix B criteria were included (APA, 1994). Diagnoses were first made by the interviewer and then by a senior psychiatrist. In case of disagreement another senior psychiatrist made the final decision. The SCAN algorithm was used, but diagnosis was also allowed for persons having an ongoing successful treatment and Appendix B diagnoses.

A detailed description of the first phase of the PART study can be found in Hällström, Damström Thakker, Forsell, Tinghög, and Lundberg (2003).

**Follow-up examination**

At the second phase of the PART study that took place between 2001-2003, all individuals who participated at baseline (n=10,441) received a questionnaire comprising almost the same questions as in the initial screening by mail. Altogether, 8,613 persons responded (84.5%). Of the respondents, 3,635 were men and 4,978 were women. Moreover, persons who at the baseline interview were diagnosed with depression or alcohol dependence/abuse according to the DSM-IV criteria (n=308) were followed up with a new SCAN interview. Clinically experienced psychiatric nurses, psychotherapists or psychologists performed the interviews. As in phase I, the interviewers in phase II were initially trained in the use of SCAN by a WHO designated trainer and provided regular tutoring by a senior psychiatrist. In addition to the SCAN interview an identical cognitive test battery as that used at the baseline examination was administered.
Psychiatric measures

Depression diagnoses (Study I, III, and IV)
Depression diagnoses (i.e., MD, DD, MAD, MinD) were based on information collected from the SCAN interviews in Studies I and III. In Study IV, the SCAN defined diagnoses were used in order to exclude persons affected by depression including MD, DD, MAD from the study sample whereas the diagnoses used to determine the dependent variable (i.e., depressed/not depressed) were based on self-reported information collected from the questionnaire by using the Major Depression Inventory screening scale (MDI; Bech & Wermuth, 1998).

Anxiety diagnoses (Study II)
Anxiety diagnoses (i.e., PD with and without agoraphobia, SP, GAD, OCD, Specific Phobia) were based on information from the SCAN interview.

Control group (Study I and II)
In order to compare the cognitive test performance in persons affected by depression (study I) or anxiety (Study II) and controls, a comparison group comprised of persons who screened negative in the SCAN interview was used (n=208). A closer inspection of this sample revealed that 30 of the controls had obtained psychiatric diagnoses in the SCAN interviews. These were excluded together with one severely somatic ill person. Thus, the final control group included 175 healthy persons.

Cognitive indicators

Episodic memory (Study I, II, III, and IV)
Episodic memory was assessed by means of free and cued recall of 32 organizable words belonging to 8 taxonomic categories (e.g., vehicles, toys, kitchen utensils) with four subordinates each (e.g., train, doll, spoon). The items used were highly typical of their category, according to norms established by Nilsson (1973). Participants were instructed to remember as many words as possible but were not informed about the possibility to organize the words. The examiner read aloud the words in a rate of one word every three seconds. Immediately following the presentation of the last word, the participant was asked to free recall the words during three minutes. The examiner recorded all the responses verbatim. The cued recall test was followed using the category names as retrieval cues. For each of the eight categories, 20 seconds were allowed for retrieval. Also here, all responses were recorded word for word by the examiner. Maximum score in both tests was 32. Four different presentation orders for the words were used. For the cued recall test two different presentations orders were used. These eight combinations were randomly distributed among the participants.
Verbal fluency (Study I and II)
The Word Association Test was used to assess verbal fluency (Benton & Hamsher, 1989). The test consists of three word-naming trials using the letters F, A, and S. The participants were instructed to generate as many words as possible excluding proper names in one minute, beginning with each of the target letters. The sum of all correct words for each letter and the total sum of words were used in the analyses.

Psychomotor speed and executive function (Study I and II)
The Trail-Making Test (TMT) was used to assess perceptual-motor speed and executive function (Reitan, 1959; Reitan & Davidson, 1974), and was given in two parts, A and B. For both parts, subjects were presented with a white sheet of paper on which circles were distributed. In part A, the circles were numbered from 1 to 25 and participants were asked to draw lines to connect the 25 circles in the correct order (i.e., 1-2-3…25). In part B, the 25 circles contained numbers from 1 to 13 and letters from A to L. The subjects were instructed to connect the consecutively numbered and alphabetically lettered circles, by alternating between the two sequences (i.e., 1-A-2-B….L-13). In both tests, subjects were requested to connect the circles as fast as they could. The examiner immediately pointed out the first error observed, and the subject was required to correct the error. Thereafter the subject could continue in the proper sequence. From the second error onward the subject was not corrected, and performance time was unlimited. For both parts, the examiner recorded accuracy scores and completion time. Maximum score for both TMT-A and TMT-B was 24.

Background variables

Demographic factors (Study I, II, III, and IV)
Age, gender, and educational level were considered in all four studies. Age was treated as a continuous variable in all studies with the exception of Study IV, where age was divided into three categories: 20-34, 35-49, and 50-64 years. Education was treated as a categorical variable in all four studies, and was divided into three categories: primary (i.e., education up to and including 9 years), secondary (i.e., education spanning between 10 to 16 years), and university (i.e., graduated from university >16 years).

Alcohol use (Study II, III, and IV)
In Study II, DSM-IV defined alcohol diagnoses, including alcohol dependence and alcohol abuse, were used. In Study III and IV the Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993), which was developed for early detection of hazardous and harmful alcohol use, was administered. The scale includes 10 items. In PART, only those who had consumed at least one glass of alcohol during the past 12 months were asked to answer the AUDIT questions. The scores ranged from 1 to 40. High scores indicated more harmful alcohol use. The used cut-off point for non-harmful/ harmful alcohol use was eight (Saunders et al., 1993).
Psychopharmacological drug use (Study I, II, and III)

In connection with the cognitive testing, self-reported information regarding psychopharmacological drug use was collected. The drugs considered in the present work were antidepressants, anxiolytics, sleep medication, and neuroleptics. The drug use across Studies I, II, and III is displayed in Table 1.

Table 1. The psychopharmacological drug use in Studies I, II, and III.

<table>
<thead>
<tr>
<th>Study</th>
<th>Depressed</th>
<th>Anxiety</th>
<th>Depressed / Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study I</td>
<td>Study II</td>
<td>Study III</td>
</tr>
<tr>
<td></td>
<td>n=187</td>
<td>n=112</td>
<td>Baseline (T1) Follow-up (T2)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>31</td>
<td>17</td>
<td>7/5</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>13</td>
<td>6</td>
<td>6/3</td>
</tr>
<tr>
<td>Sleep medication</td>
<td>17</td>
<td>7</td>
<td>7/3</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>6</td>
<td>2</td>
<td>1/2</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>23</td>
<td>13/7</td>
</tr>
</tbody>
</table>

Anxiety (Study II, III, and IV)

In Study II and IV, the anxiety diagnoses as defined by the DSM-IV were used. In Study III, information on anxiety symptoms was collected from the SCAN interview.

Social disability (Study III)

Social disability due to psychiatric or psychological symptoms was assessed with a 5-item Role Disability scale selected from the WHO’s Brief Disability Questionnaire (BDQ; Ormel et al., 1999). The included items concern daily activities (i.e., leisure activities, daily routines, work motivation, personal efficiency, and social relations) that may have been affected or limited by personal or psychological problems during the past 30 days. Answers to each question were coded from 1 (indicating no impairment) to 4 (completely impaired).

Social support was assessed with a single statement collected from the scale developed by Undén and Orth-Gomèr (1989); “Besides from those at home, there are persons I can turn to, easily meet, and get help from when I am in difficulties”. The answers ranged from 1) “agree completely” 2) “agree quite well” 3) “agree not that well” to 4) “disagree”. The answers were divided into two categories where answer 3 and 4 were classified as “low social support”.

Financial strain (Study IV)

Financial strain was assessed with the question “Would you be able to obtain 14 000 Swedish kronor (approximately 2000 US dollar) within a week if you had to?” The answers ranged from 1) “Yes, definitely”, 2) “Yes, probably”, 3) No, “Probably not” to 4) “No” and were dichotomised into two categories where answers 3 and 4 were classified as “financial strain”.

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Statistical analyses

All statistical analyses were carried out by using the statistical package SPSS for Windows (SPSS inc., version 11.5-14; Chicago, IL). Univariate analyses of variance (ANOVAs), and Chi-squares for categorical data, were used for comparisons between groups on the demographic variables (Study I and II). Univariate analyses of covariance (ANCOVAs) with gender as covariate in Study I, and chronological age, sex and education as covariates in Study II, were performed on the separate cognitive functions data.

In Study III, both the cross-sectional and longitudinal data were analysed with ANOVAs. Across all measures, raw data were used for the cross-sectional data-analyses, whereas standardized residual scores that were obtained by regressing the follow-up data on the baseline data were used for the analyses of longitudinal change.

In Study IV, the longitudinal data were analysed by hierarchical logistic regression. Demographic factors (age, sex, and education), clinical factors (anxiety and alcohol diagnoses), and episodic memory performance (high vs. low) were considered as predictors of depression.

Ethical considerations

Informed consent was obtained from all the participants. The PART study was approved by the ethical committee at Karolinska Institutet: registration numbers: 96-260; 01-218. Due to ethical reasons all persons with suicidal ideation were offered an interview. No treatments were given, but persons that suffered from serious psychiatric problems were provided support in order to seek help.
OVERVIEW OF THE STUDIES

An overview of the study samples and the cognitive tasks across Study I-IV is provided in Table 2.

Table 2. Study samples and the cognitive tasks across Study I-IV

<table>
<thead>
<tr>
<th>Study samples</th>
<th>Study design</th>
<th>Cognitive measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study I</strong></td>
<td>Cross-sectional</td>
<td>Free recall, Cued recall, Verbal fluency, TMT-A, TMT-B</td>
</tr>
<tr>
<td>Depression group  n=187</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD n=68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD n=28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAD n=25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MinD n=66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls n=175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety group     n=112</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD n=33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP n=32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAD n=7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCD n=16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific phobia   n=24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls n=175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered         n=35</td>
<td>Cross-sectional</td>
<td>Free recall, Cued recall</td>
</tr>
<tr>
<td>Still depressed   n=41</td>
<td>Longitudinal</td>
<td></td>
</tr>
<tr>
<td><strong>Study IV</strong></td>
<td>Longitudinal</td>
<td>Sum of free and cued recall</td>
</tr>
<tr>
<td>Study sample 1    n=400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study sample 2    n=386</td>
<td></td>
<td>Free recall</td>
</tr>
<tr>
<td>Study sample 3    n=442</td>
<td></td>
<td>Cued recall</td>
</tr>
</tbody>
</table>

In the first two studies, we examined cognitive functioning in persons affected by DSM-IV defined depression and anxiety disorders by using cross-sectional data from the baseline examination of the PART study. As noted earlier, depression and anxiety disorders commonly occur together. This was also true in the PART study. The overlap of depressed and anxiety samples as well as the number of persons who used psychopharmacological drugs are illustrated in Figure 3. Study III followed a cohort of depressed persons with regard to cognitive and social functioning by using both cross-sectional baseline and follow-up data in combination with longitudinal data. Finally, by using longitudinal data Study IV examined whether low episodic memory performance may serve as a premorbid marker of impending depression.
Many studies have demonstrated an association between depression and cognitive dysfunction (e.g., Austin et al., 2001; Elliott, 1998). However, as noted earlier, most of the previous work in this context is based on in- and outpatient samples, although a majority of depressed persons do not seek treatment (Christiana et al., 2000; Wang et al., 2005a; Wang et al., 2005b). In addition, relatively little is known about the effects of depression on cognition in other depression diagnoses than MD. The main purpose of this study, therefore, was to examine the effects of depressive disorders on cognitive functioning in a population-based sample. Of particular interest was to determine whether cognitive performance varied as a function of depression subgroup. Population-based samples, aged 20-64 years, with MD (n=68), Dysthymia (n=28), MAD (n=25), and MinD (n=66) were compared with a control group of non-depressed, healthy persons (n=175) across a variety of cognitive tasks tapping episodic memory, verbal fluency, psychomotor speed (TMT-A), and executive functions (TMT-B). The data were analyzed in two parts. First, in order to examine whether depressive disorder in general exerts negative effects across cognitive functions, we compared the total group of depressive persons with the non-depressive control group. This was followed by separate analyses for each of the depression subgroups. Also, in order to examine whether psychopharmacological drug use (i.e., antidepressants, anxiolytics, sleep medication, or neuroleptics) affected the obtained results, we divided the total group of depressed into those who used psychopharmacological medication and those who did not. Gender was entered as covariate in all analyses.

The results revealed that the total group of depressed individuals showed impairments in tasks tapping episodic memory and executive function. Of more interest, however, was the observation that the pattern of these impairments varied as a function of depression subgroup: MD and MAD groups exhibited memory dysfunction, whereas individuals with dysthymia showed pronounced difficulties in executive functions.
Our results showed that verbal fluency and perceptual-motor speed were not affected by depression. In addition, MinD did not affect cognitive performance. Additional analyses regarding drug use did not affect the results on episodic memory performance. However, the analyses of TMT-B completion time showed that medicated depressed persons were slower than unmedicated individuals, who in turn were slower than the group of non-depressed controls.

The main conclusion drawn from this study was that persons affected by depression from the general population exhibit cognitive impairments in tasks tapping episodic memory and mental flexibility and that cognitive impairments varies as a function of depressive disorder.

**Study II (Airaksinen, Larsson, & Forsell, 2005)**

As mentioned in the introduction, little attention has been paid to potential cognitive impairments in anxiety disorders. The general objective of this study was to examine the effects of anxiety disorders on cognitive functioning. Population-based samples comprising individuals affected by PD with and without Agoraphobia or Agoraphobia only (n=33), SP (n=32) GAD (n=7), OCD (n=16), and Specific Phobia (n=24) were compared with non-anxious healthy controls (n =175) in cognitive performance. The cognitive test battery included the same tests as in Study I. In the first analysis, we compared the total group of persons affected by anxiety (n=112) with healthy controls. This was followed by separate analyses for each anxiety group. Also, we examined whether concomitant depression or alcohol abuse/dependence and psychopharmacological drug use affected the results. Age and gender variations were statistically controlled for in all analyses.

The results revealed that the total anxiety disorder group exhibited significant impairments in episodic memory and executive functioning as compared with healthy controls. Separate analyses of the respective subgroup indicated that PD and OCD were related to impairments in both episodic memory and executive functioning. In addition, SP was associated with episodic memory dysfunction. Verbal fluency and psychomotor speed were not affected by anxiety. Specific Phobia and GAD did not affect cognitive functioning. In a similar vein, comorbid depression or alcohol diagnoses did not affect the obtained results regarding episodic memory, whereas the significant effects disappeared after exclusion of participants with alcohol abuse/dependence on the OCD and PD samples. Psychopharmacological drug use did not affect episodic memory, whereas the analyses of TMT-B showed that drug users used more time to complete the TMT-B as compared with non-users and controls.

Taken together, this study extends previous research by indicating that anxiety disorders are associated with reliable impairments in episodic memory and executive functions in population-based samples.
Table 3. Cognitive performance across study groups in Study I and Study II.

<table>
<thead>
<tr>
<th></th>
<th>MD n=68</th>
<th>DD n=28</th>
<th>MAD n=25</th>
<th>MinD n=66</th>
<th>Dep n=187</th>
<th>Anx n=112</th>
<th>PD n=33</th>
<th>SP n=32</th>
<th>GAD n=7</th>
<th>OCD n=16</th>
<th>SpcP n=24</th>
<th>Cont n=175</th>
</tr>
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<td>13.1*</td>
<td>12.9***</td>
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MD= Major Depression  
DD=Dysthymic Disorder  
MAD=Mixed Anxiety Depressive disorder  
MinD=Minor Depressive Disorder  
Dep=the total group of depressive disorder  
Anx= the total group of anxiety disorder  
PD=Panic Disorder with or without Agoraphobia  
SP=S Social Phobia  
GAD=Generalised Anxiety Disorder  
OCD=Obsessive-Compulsive Disorder  
SpcP=Specific Phobia  
Cont=control group  
FAS=the sum of word beginning with F, A, and S  
TMT=trail-making test  
* p<0.05; ** p<0.01; *** p<0.001; +p<0.1
Study III (Airaksinen, Wahlin, Larsson, & Forsell, 2006)

The main aim of Study III was to examine social and cognitive functioning in recovery from depression. This was accomplished by a three-year follow-up examination of a cohort of persons (n=187), who at baseline were diagnosed with depression according to DSM-IV (i.e., MD, DD, MAD, and MinD). From this sample we excluded persons diagnosed with MinD (n=62), since our findings from Study I indicated that MinD was not associated with cognitive dysfunction. A total of 43 persons dropped out of the study and six persons were excluded because of neurological diseases, language problems, and missing cognitive data. Of the remaining 76 depressed persons at baseline, 41 fulfilled, and 35 did not fulfil the depression criteria at the follow-up examination three years later. These two groups were compared with respect to social functioning and episodic memory performance (free and cued recall) at baseline (T1), at follow-up (T2), and change across time (i.e., by examination of residual change scores). Background data concerning demographics, anxiety level, alcohol and psychopharmacological drug use were considered.

The results revealed that the groups did not differ in any of the examined background variables at baseline whereas the still depressed group experienced higher levels of anxiety at follow-up. The groups did not differ on social functioning at baseline whereas the recovered group experienced decreased social disability between T1 and T2 as compared to the still depressed group. In addition, the groups did not differ in episodic memory performance either at T1, T2, or in the residual change scores.

To conclude, depression was associated with a continued cognitive dysfunction that goes beyond functional and symptomatic recovery, at least in a three-year perspective. This outcome suggests that depression may cause long-standing cognitive deficits and thus may be considered as a serious disorder also in population-based samples.

Study IV (Airaksinen, Wahlin, Forsell, & Larsson, in press)

The results from Study III raised the question whether persons affected by depression have a lower cognitive performance to start with. The main focus of Study IV was to investigate whether low episodic memory performance predicts later development of depression. This was accomplished by creating three separate study groups that were defined according to three measures of episodic memory (i.e., free + cued recall, free recall, and cued recall) in order to examine whether the risk varies as a function of test among depression-free persons at baseline (n=708). To maximize the cognitive variance, only those who performed in the 25% highest and 25% of the lowest range of the episodic memory tests in the respective groups were included. The three groups comprised of 400, 386, and 442 persons respectively. The data were analysed by hierarchical logistic regressions. Demographic variables (i.e., gender, age, and education), socioeconomic variables (i.e., social support and financial strain), clinical variables (i.e., anxiety and alcohol diagnoses), and cognitive variables (low/high
episodic memory performance) were entered in the regression analysis. Three separate analyses were performed, one for each of the three study groups.

The main result from this study showed that low episodic memory defined as the sum of free and cued recall was a reliable premorbid marker for depression. Importantly, this was true after statistical control of the demographic, socioeconomic, and clinical variables. As noted above, the persons included at baseline were non-depressed. However, a closer inspection of the study sample revealed that 37 of them had had a previous episode of depression. In order to investigate whether recurrent depression may exhibit a significant influence on the results reported above, these individuals were excluded from the analyses. In total, 18, 19, and 20 persons were excluded from the first, second, and the third study groups respectively. However, the exclusion of the persons with a history of depression only altered the results to a minor extent, such that the significant contribution of low episodic memory changed to a marginally significant trend in the second set of the analyses.

Taken together, these findings indicate that low episodic memory performance may serve as a premorbid marker of depressive illness.
DISCUSSION

The overall aim of the present thesis was to extend present knowledge on cognitive functioning in depression and anxiety disorders in the general population. The empirical studies in this thesis were based on a random sample of persons aged 20-64 years collected from the population. As noted above, most previous evidence focusing on depression and cognition is based on in- and outpatient samples. However, reports indicate that a majority of the persons affected by depression or anxiety do not seek help and hence are untreated. This discrepancy is important to highlight, since it is most likely that clinical and population-based samples of depressed persons are different. For example, it is reasonable to assume that depressed in- and outpatient samples include more severely ill persons. Naturally, they also use psychopharmacological drugs to a greater extent than depressed persons in the population. As is true for the depressive disorders, anxiety disorders are also typically untreated in the population.

Similar cognitive impairments in depression and anxiety disorders

Studies I and II examined cognitive functioning in persons from a population-based sample affected by depression and anxiety disorders according to the DSM-IV. The results indicated that both depression and anxiety were associated with cognitive deficits. It is of interest to note that the pattern of cognitive impairments was similar for both disorders. Both were found to be associated with a reliable episodic memory dysfunction with deficits in both free and cued recall of verbal information. Also, our results suggested an executive dysfunction (TMT-B) in both disorders. In contrast, verbal fluency and psychomotor speed (TMT-A) were not affected either by depression or by anxiety (see Table 3 for an overview of the results).

Episodic memory

Depression and anxiety were associated with an overall episodic memory dysfunction. However, the ability to utilize semantic cues was intact in both depression and anxiety disorders although overall performance level was lower. The magnitude of the gain from free to cued recall was of equal size across both depression and anxiety subgroups and controls. This pattern of results suggests that both depression and anxiety-related deficits are associated with encoding impairments rather than with retrieval failures. The observation that persons with depression and anxiety did not selectively improve their recall performance when retrieval cues were provided suggests that episodic memory deficits occur during acquisition rather than at retrieval. Also, it is worth noting that our results do not support the effortful-automatic hypothesis given that depression and anxiety-related effects were present in both the less effortful cued recall task and the more effortful free recall task. Likewise, the present results may not be due to poor motivation since it is reasonable to assume that if poor motivation underlies the observed cognitive impairments, deficits should be consistent across all cognitive domains.
The findings from Study I are also in line with most previous clinical research suggesting that both mild and severe forms of depression are associated with cognitive impairments (e.g., Austin et al., 2001; Miller, 1975; Veijel, 1997).

As indicated earlier, knowledge on cognitive functioning in anxiety disorders, with a possible exception of OCD, is sparse and provides a mixed pattern of findings. Results from Study II replicated some previous observations suggesting impaired episodic memory performance for verbal information in PD and SP (Asmundson et al., 1995; Savage et al., 2000). Also, in accordance with previous findings, our results indicate that OCD is associated with episodic memory deficits (Savage et al., 2000; Zitterl et al., 2001). It is important to note that both depression and anxiety-related effects on episodic memory proficiency remained also after controlling for psychopharmacological drug intake. Also, statistical control of comorbid psychiatric diagnoses in anxiety did not alter the effects on episodic memory. This outcome strongly suggests that both disorders exhibit a unique negative influence on episodic memory functioning.

However, episodic memory dysfunction is not exclusive to depression and anxiety disorders. Impaired episodic memory is a known sensitive cognitive marker of a number of conditions that affect the brain, such as aging (e.g., Schönknecht, Pantel, Kruse, & Schröder, 2005), dementia (e.g., Hodges, Erzinclioglu, & Patterson, 2006), and psychoses (e.g., Kuperberg & Heckers, 2000). The vulnerability of episodic memory is most likely related to the complexity of its underlying neural correlates, including medial-temporal regions, the frontostriatal circuitry, anterior cingulate, distinct parietal and temporal regions and the cerebellum. Thus, the integrity of episodic memory depends on both younger and older brain regions (e.g., Cabeza & Nyberg, 2000). This is in contrast with the phylo- and ontogenetically older memory systems such as procedural memory and priming for which the neuroanatomical correlates are more localized (Tulving & Schacter, 1990).

An important topic that needs to be considered when discussing the obtained cognitive abnormalities in anxiety populations concerns whether the findings reflect state rather than stable trait anxiety. Thus, it is likely that the anxiety population is predisposed to test-taking anxiety, and presenting them a huge list of words to be recollected is likely to trigger anxiety. It is reasonable to assume that particularly persons affected by social phobia are experienced test-related anxiety to a greater extent since social and performance situation are critical in triggering anxiety in persons affected by social phobia. Studies that follow persons affected by anxiety in the population beyond the recovery are needed in order to investigate this topic further.

Executive function

In addition to episodic memory impairments, the results from Study I and II also demonstrated that both depression and anxiety exert negative influences on executive function as measured by the TMT-B. This observation is in agreement with previous findings in depressed samples (Austin et al., 1992; Ravnkilde et al., 2002) and in OCD (Aronowitz et al., 1994; Martinot et al., 1990; Veale, Sahakian, Owen, & Marks, 1996). It is important to note, however, that the effects of both depression and anxiety on executive function disappeared after controlling for psychopharmacological drug use. In a similar vein, the observed effects of anxiety on executive function disappeared after controlling for comorbid psychiatric diagnoses (i.e., depression, alcohol
dependence/abuse). However, the corresponding analyses for episodic memory did not alter the obtained effects. This pattern of findings indicates that executive function as measured by the TMT-B, is more susceptible to the negative repercussions of psychopharmacological drug use and psychiatric comorbidity than episodic memory. One possible explanation for the contradictory findings between episodic memory and executive functions may be that the prefrontal brain areas that are chiefly involved in executive functions, are more affected by psychopharmacological drugs and comorbid psychiatric conditions than are the medial temporal regions, key structures for episodic memory functioning.

**Cognitive dysfunction in depression and anxiety subgroups**

The relatively large sample of persons affected by depression and anxiety in the PART study allowed us to further investigate the specificity of cognitive impairments in subgroups of depressive and anxiety disorders. As noted earlier, most of previous research on cognitive functions in depression and anxiety disorders is based on individuals suffering from MD and OCD respectively.

Interestingly, we found a variation of cognitive performance across the different subgroups of persons affected by depression and anxiety. For depression, MD and MAD were associated with the largest episodic memory impairments, whereas DD was associated with deficits in executive functions as measured by the TMT-B. In contrast, all anxiety subgroups were associated with episodic memory dysfunction with the exception of Specific Phobia and GAD. However, the absence of a significant effect on episodic memory in the GAD group is most likely due to the small sample size (n=7). Mean memory performance in both free and cued recall was comparable with the other subgroups that comprised larger samples and who exhibited significant influence on episodic memory. Furthermore, the results indicated an executive dysfunction in both the OCD and PD groups, although none of the subgroups were associated with impairments in verbal fluency or psychomotor speed (TMT-A).

The comparable findings in depression and anxiety may be understood from the perspective that both types of disorder exhibit similar risk factors and gender distribution (Pélassolo & Lépine, 2001). Also, persons affected by depression and anxiety share several common symptoms such as fatigue, concentration difficulties, sleeping problems, loss of appetite, and loss of interest/pleasure in normal activities. All are potential risk factors for cognitive dysfunction, even though the underlying causes of these symptoms may vary. For example, concentration difficulties in depression are characteristically related to a lack of energy and slowing of the mind, whereas concentrations difficulties in anxiety may be related to typical monitoring of own anxiety symptoms. In addition, both depression and anxiety are susceptible to the same pharmacological treatment, suggesting that the underlying biochemical dysfunction is of similar nature in both disorders (den Boer, Slaap, & Bosker, 2001). It is also worth noting that the same temporal lobe regions including the hippocampus and the amygdala as well as the frontal lobes are affected in both disorders (den Boer et al., 2001)
Cognitive dysfunction after recovery from depression

An intriguing research question regarding cognitive dysfunction in depression concerns whether the observed cognitive impairments represent state effects of a depressive disorder or if the cognitive impairments persist beyond recovery from other symptoms. To put it in another way: is the observed cognitive dysfunction reversible? From a clinical point of view it is important to localize markers for prognosis and cognitive dysfunction may constitute one potential factor to take into account.

Consequently, in Study III, we followed up a group of depressed persons over a period of three years with respect to cognitive and social functioning. We found that social functioning recovered concurrently with the symptomatic recovery, whereas episodic memory performance was unaffected by recovery. This outcome suggests that episodic memory dysfunction persists over a three-year period in spite of a symptomatic and other functional recovery. This is a somewhat remarkable finding given that it would be assumed that cognitive recovery would follow a general recovery from depression, especially in population-based samples that include more untreated and probably less severely depressed persons as compared to in- and outpatient samples.

Our results concerning social recovery replicated earlier observations by showing that social functioning recovered to normal levels concomitant with symptomatic recovery (Judd et al., 2000; Ormel, Oldehinkel, Brilman, & van den Brink, 1993; Spjiker et al., 2004; Von Korff, Ormel, Katon, & Lin, 1992).

Our observation regarding continuous cognitive dysfunction is consistent with some studies reporting a persistent cognitive dysfunction also after a successful antidepressant therapy in geriatric and middle-aged clinical samples (Butters et al., 2000; Neu et al., 2005). One explanation for the persistent episodic memory problems may be that depression is associated with an atrophy of the hippocampus, a critical structure for learning and memory (Campbell et al., 2004; Videbech & Ravnkilde, 2004). Recently, Neumeister and colleagues (2005) reported a reduction of the hippocampal volume in a group of unmedicated remitted patients with a major depressive disorder. Provided that depression is associated with hippocampal volume reduction, our data suggest that at least in a three-year perspective, depression-related cognitive deficits are slower to recover than social disability. In line with this observation, Deuschle and colleagues (2004) reported slow gradual improvements in declarative memory function, and cognitive recovery was observed 12 months after symptomatic recovery of depression had taken place.

Low episodic memory functioning as a premorbid marker of depression

So far, in Study I we had demonstrated an association between depression and cognitive dysfunction, specifically in episodic memory functioning that, as demonstrated in Study III, persists after symptomatic and social recovery. Thus, cognitive dysfunction may be considered as a consequence of depressive illness. However, these findings raised an interesting question of whether cognitive dysfunction also may be present before a depression diagnosis. This perspective
indicates that cognitive dysfunction may be regarded as a course or precursor rather than as an effect of depressive illness. This hypothesis was examined in Study IV by following up a sample of depression-free persons. To the best of our knowledge, our study was the first attempt to examine this topic in younger samples. Our results suggested that low episodic memory performance, defined as the sum of free and cued recall, was present already three years prior to the depression diagnoses independently of demographic, socioeconomic, and clinical factors. This outcome indicates that low episodic memory performance may serve as a premorbid marker of depression. As has been indicated earlier, episodic memory dysfunction is prevalent in depression (Burt et al., 1995), and depression is associated with structural abnormalities in the hippocampus (Campbell et al., 2004; Videbech & Ravnkilde, 2004). Hippocampal volume reduction has been reported already in patients with a first episode of depression indicating that hippocampal atrophy may play a crucial role in the pathogenesis of depression (Frodil et al., 2002). Provided that hippocampal atrophy is associated both with episodic memory dysfunction and depression, our finding increases to some extent the understanding regarding these complex associations by showing that low memory performance at baseline, as compared to high memory performance, and in the absence of depression, significantly increases the risk to develop depression three years later. A straightforward interpretation of the results is that because of the brain structures critical in both depression and for episodic memory performance, preclinical phases of depression will be detected in sensitive episodic memory tests.

It is also important to take into consideration that a closer examination of the data revealed that 37 out of the 400 persons in fact had had previous depressive episodes. To examine this further, we excluded these persons from the analyses. However, this altered the results only to a minor extent. In these analyses the previously significant effect of low episodic memory as a predictor of incipient depression was altered to a marginally significant result. This outcome suggests that low episodic memory performance may be a premorbid marker of depression over and above the deficits typically resulting from depression.

Methodological issues

There are some methodological considerations that need to be highlighted in the interpretation of the findings. First, I will provide issues relevant for all of the four studies. Next, this is followed by study-specific considerations.

General considerations

Prevalence rates in PART

In the PART study the one-month prevalence of MD was found to be 3.7%, which is somewhat higher than the corresponding rates of 2.7% found in the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (Bijl, Ravelli, & van Zessen, 1998), and the one-month prevalence rates ranging between 1.6 and 2.9 found in the Epidemiologic Catchment Area (ECA) study investigating prevalence across five sites in the USA (Reiger et al., 1988). Other community surveys using other forms of
structured interviews have reported higher rates ranging from 4.6% in Finland to 7.4% in Athens (Lehtinen et al., 1990; Mavreas & Bebbington, 1988). The prevalence of all depressive disorders was around 10%. This group included DSM-IV research diagnoses (i.e., MAD and MinD) as well as bipolar disorder, which make it difficult to compare with other studies.

Due to low numbers, no subdivision was made of the anxiety disorders and the overall one-month prevalence rate was estimated to be around 7%, which is somewhat lower than reported in the ECA study (8.5%), and in the NEMESIS study (9.7%) (Bijl et al., 1998; Reiger et al., 1988).

High non-participation rate
It is important to consider the high non-participation rate in the PART study. Only 52% of those who were randomly sampled to the study participated. The main reasons for non-participation might be due to the subject of the investigation, since many of those approached refused participation for that reason. The questionnaire took approximately one hour to complete and it is also possible that persons severely affected by psychiatric disorders refused participation due to the nature of their disorder. An extensive non-participations analysis revealed that the individuals who answered the questionnaire and who were selected to the interview had a higher education, higher income, were more often female and born in the Nordic countries that those who did not participate. The associations between age, gender, country of origin, and in-patient hospital care due to psychiatric diagnosis were calculated for participants and non-participants separately. The OR’s for these associations were similar among participants and non-participants. In addition, linkage to diverse registers (i.e., The Hospital Discharge Register, The Register of Income and Wealth, and The Disability Pension Register) revealed that those who participated did not differ from those who did not (Lundberg et al., 2005). It is highly probable that the findings in this thesis have been affected by the high non-participation rate, such that the obtained effects of depression and anxiety on cognition were an underestimation of the true effects of these disorders in the population. Certainly, the high non-participation rate might also limit the external validity of these results such that generalizations of our findings to younger men born outside the Nordic countries should be made with caution.

Diagnostic procedure
Depression and anxiety diagnoses were made by using clinical judgments of experienced psychiatrists at the baseline examination. At follow-up, psychiatric nurses, therapists, or psychologists made diagnoses according to established diagnostic criteria. All interviewers were initially trained, in a one-week course, to use SCAN and received regular supervision by an assistant professor in psychiatry during the study. Videotaped interviews were used to increase the inter-rater reliability.

Limited Cognitive test battery
The cognitive test battery used in the PART study was rather limited by only including three different types of test. This was due to the fact that the cognitive testing constituted a minor part of the extensive examinations. Of course, a more
extensive test battery would have been desirable, but given the restricted time frame allowed for cognitive testing within the PART study, only a restricted number of cognitive tests were possible. However, as indicated in the background section, the selection of tests was based on previous research indicating that these cognitive domains were potentially the most sensitive for depression and anxiety disorders (Goodwin, 1997).

**Small sample sizes**

Even though we over-sampled persons who screened positive (i.e., reported many psychiatric symptoms) on the psychiatric interview in order to capture the largest possible group of depressed persons, some study samples were still small. Specifically, when we subdivided depression and anxiety into different diagnoses, we obtained small sample sizes in some of the groups (e.g., GAD, OCD) and had not enough power to detect potential differences. For example in the GAD group, as will be seen in the Table 3, the non significant mean values of free and cued recall of words are equal to size to the corresponding significant mean values in the PD group due to bigger sample size in this group.

**Study-specific considerations**

**Study III**

Due to the study design, one obvious limitation in Study III was the absence of a healthy control group at follow-up. Thus, it was not possible to determine to what extent potential retest effects confounded the findings. Also, the substantial dropout rate (43 out of the 400 persons) between baseline and follow-up should be noted. Nevertheless, the attrition analyses revealed no differences between non-participants and participants in any of the cognitive or social function variables at baseline. However, the dropouts were younger and of male sex as shown in several previous studies (e.g., Kringlen, Torgersen, & Cramer, 2001; McConnell, Bebbington, McClelland, Gillespie, & Houghton, 2002). This should be considered in the generalization of the results of this study.

A person was considered to be recovered if s/he did not fulfil the DSM-IV criteria for depression (i.e., MD, DD, and MAD) at the follow-up examination. It should be noted, however, that this kind of dichotomization in case/no case is a crude way to analyze the course of an illness. For example, a person might have had remaining symptoms but was still considered as recovered. Also, it is important to recognize that we did not have any information about the course of the disease during the three-year test interval and this may have affected the obtained results. Thus, it is theoretically possible that some of the depressed persons may have been depressed across all three years and recovered two weeks before the follow-up examination, whereas other persons may have recovered early.

**Study IV**

A major limitation in Study IV was the use of different diagnostic procedures for depression at inclusion and follow-up. The baseline diagnoses were based on SCAN interviews made by psychiatrists, whereas the follow-up diagnoses were based on self-reported data from the questionnaire. It is rather obvious that the SCAN
interviews constituted a more reliable instrument since they were based on interviews by clinically experienced psychiatrists. However, since we did not have psychiatric interviews for all persons at follow-up we did the MDI diagnoses based on self-reported data. We cannot rule out the possibility that this might have affected the results although the correspondence between these scales is known to be good (Bech et al., 2001; Forsell, 2005).

Directions for future research

Overall, more research is warranted regarding the relationships between cognitive functions in depression and anxiety in the population. As always, the findings from the present studies included in this thesis need to be confirmed also by other investigators. Population-based studies are important since they are the only ways to reach the majority of depressed persons who are untreated and who have not sought treatment. Two papers in this thesis focused on depressive illness from a longitudinal perspective. Thus, it would also be of interest to follow a cohort of persons affected by anxiety over time. Given that similar patterns of cognitive impairment were observed in the baseline measurement of depression and anxiety (Study I and II) one hypothesis is that similar long term effects of anxiety will be obtained as those observed in the longitudinal studies of depression.

Across studies we propose that atrophy of the hippocampus may serve as an important explanatory factor for our findings. However, as is evident in our work, the present observations do not include any neuroanatomical correlates to confirm this hypothesis. Therefore, an important future research avenue is to investigate baseline hippocampal volume in depression and anxiety-free persons in a prospective, longitudinal study design using neuroimaging techniques. Also, future neuropsychological studies in depression and anxiety should include a broader range of assessed cognitive domains to be evaluated as a function of different materials (e.g., visual, verbal, olfactory) and retrieval formats (explicit, implicit).
CONCLUSIONS

This doctoral thesis has extended the available knowledge on cognitive functioning in depression and anxiety disorders by including population-based samples. The findings from this thesis suggest that;

- Depression and anxiety disorders in the population are associated with cognitive dysfunction and in particular episodic memory functioning.
- Episodic memory impairment persists also after recovery from depression.
- Low episodic memory performance may be a premorbid marker of impending depression.

Taken together, the collected evidence from this thesis suggests that depression in particular, but also anxiety, are conditions that affects cognitive ability negatively also in those who have not attended the medical care system. These effects may have a large negative impact, not only for the working and social lives of the affected person, but also for society as a whole. Mental health is an individual resource that is of outermost importance for the society, it is for example a key input to human productivity. This stresses the importance of improving early recognition and adequate treatment of these disorders.
ACKNOWLEDGEMENTS

I hardly believe that the years as a doctoral student are at an end. I have been lucky to have many talented and generous persons around me during these years. Time has come to express my gratitude to all of you who have helped me in a way or another to complete this thesis. Without your guidance and support this thesis would not have been possible.

I would like to express my sincere thanks to:

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