

# **Neuropsychological functions in Unipolar Major Depression With and Without Co-morbid Anxiety**

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University of Oslo  
2011**

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*Series of dissertations submitted to the  
Faculty of Social Sciences, University of Oslo  
No. 275*

ISSN 1504-3991

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Cover: Inger Sandved Anfinssen.  
Printed in Norway: AIT Oslo AS.

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## ACKNOWLEDGEMENT

This thesis presents the results of a project carried out at the Center for the Study of Human Cognition (CSHC) at the Department of Psychology, with funding from the Department of Psychology and the Research Council of Norway.

Firstly, I am very grateful to and would like to thank my supervisor Professor Nils Inge Landrø for giving me the opportunity to develop this research project and for having made it all possible by his highly valuable advice, expertise, research experience and support throughout all the different stages in the process.

I would also thank my co-authors: Pål Ulleberg, Tore Stiles and Rune Jonassen for the collaboration. Pål Ulleberg deserves extra thank for all support and help regarding methodological issues, data analysis and interpretation of results when my mind was panicking.

A special thank and forever gratefulness goes to my friends and former colleagues Jan Egil Nordvik and Espen Walderhaug for all their help, support, encouragement, enthusiasm and generosity, both as friends and as highly skilled researchers.

I also would like to thank my colleagues at the Department of Psychology and especially my extreme competent and successful colleagues at the CSHC for giving me the perfect inspiring and stimulation environment.

The research-assistants that participated in different phases of the data acquisition: Martin Aker, Anne Marie Hoel, Monica Rutle, Aleksander Olsen and Rune Jonassen, thank you for your work.

This research could not have been performed without all the participants who volunteered for the studies, their contribution is gratefully acknowledged.

A special thank and gratitude goes to Kristin Nordseth for her generosity, support and expertise as the head of the administrative staff.

The IT-section at PSI with especially Øyvind and Victor, have always been supportive and helpful with all computer difficulties, technical mess and what not, thank you.

And of course I am deeply thankful for support and love from my family, Nasse and all my friends☺

Oslo, March, 2011

Pia E. Lyche

## LIST OF PAPERS

The thesis is based on the following papers which are referred to in the text by Roman numbers **I-III**.

### **Paper I**

Lyche, P., Jonassen, R., Stiles, T.C., Ulleberg, P., & Landrø, N.I. (2011). Attentional functions in MDD With and Without Co-morbid Anxiety disorder. *Archives of Clinical Neuropsychology*, 26, 38-47.

### **Paper II**

Lyche, P., Jonassen, R., Stiles, T.C., Ulleberg, P., & Landrø, N.I. (2011). Verbal Memory functions in Unipolar Major Depression With and Without Co-morbid Anxiety Disorder. *The Clinical Neuropsychologist*, 25, 359-375.

### **Paper III**

Lyche, P., Jonassen, R., Stiles, T.C., Ulleberg, P., & Landrø, N.I. (2010). Cognitive Control functions in Unipolar Major Depression (MDD) With and Without Co-morbid Anxiety disorder. *Frontiers in Psychiatry: Affective Disorders*, Vol. 1, article 149.

## ABBREVIATIONS

A	Anxiety Disorder
ANT	Attention Network Test
APA	American Psychiatric Association
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory (Second Edition)
CANTAB	Cambridge Neuropsychological Test Automated Battery
DIGS	Diagnostic interview for genetic studies
D-KEFS	Delis-Kaplan Executive Function System
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition
EF	Executive control functions
GAF	Global Assessment of Functioning Scale (DSM-IV)
HC	Healthy Controls
HVLT	Hopkins Verbal Learning Test
IED or ID/ED	Intra/Extra Dimensional Set –shift Task
ISCED	International Standard Classification of Education
LTM	Long Term Memory
MDD	Unipolar Major Depression
MDDA	MDD with comorbid Anxiety Disorder
PASAT	Paced Auditory Serial Addition Test
PC	Picture Completion (WAIS-III)
SAS	Supervisory Attention System
SCID	Structured Clinical Interview for DSM-IV, Axis I and II
SI	Similarities (WAIS-III)
SST	Stop Signal Task
STM	Short Term Memory
SWM	Spatial Working Memory
WAIS-III	Wechsler Adult Intelligent Scale- Third Edition
WHO	World Health Organization
WM	Working Memory

## **1.0. INTRODUCTION**

This thesis addresses two of the most common psychiatric illnesses, namely Unipolar Major Depression (MDD) and the frequent co-occurrence of anxiety disorder (A). The presence of co-morbid anxiety disorders in persons with MDD has largely gone unexamined, especially regarding the effects on neuropsychological functioning. The high rates of both MDD and anxiety disorders in the population, make the study of the co-occurrence of these two disorders highly relevant and important both for clinicians and the society. Both disorders are associated with cognitive/neuropsychological deficits, but separate studies of MDD and A has shown conflicting findings related to the functions affected and the extent of cognitive deficits. Also, not all patients with MDD display neuropsychological deficits, and these mixed results may partly be explained by unaddressed co-morbid anxiety. The studies we have conducted specifically address the effects of MDD and MDD with co-morbid anxiety (MDDA) on different neuropsychological measures. Due to the heterogeneity and multifactorial symptoms in both MDD and A, and hence MDDA, it is important to broaden the understanding of the associated specific neuropsychological dysfunctions. The clinical implications of cognitive deficits in MDD and A may lead to severe alteration in the ability to cope in daily life demands, and be a key factor in occupational functioning and the ability to functional recovery (Jaeger et al., 2006). Aspects of cognition highly relevant to daily life functioning are: attention, memory functions and executive control.

### **1.1. Prevalence**

Depression and anxiety disorders are among the most frequently occurring mental disorders in the general population world wide. However, prevalence estimates vary in different studies, and may be due to differences in assessment instruments, classification systems and/or sampling procedures.

Depressive disorders present a significant mental health concern to individuals and to our society and are among the most frequent occurring mental disorder in the general population. The lifetime risk for major depressive disorder (MDD) is between 10% and 25% for women and between 5% and 12% for men (APA, 1994). Numbers from The World Health Report (WHO; 2001) estimate that 5.8 % men and 9.5 % women will experience a depressive episode in any given year. According to the National Comorbidity Survey (NCS; Kessler et al., 2005) the lifetime prevalence of any anxiety disorders was 31.2% (female 36.4% and male 25.4%). The 12-month prevalence for any anxiety disorder is according to the same

survey was estimated to 19.1% (Female 23.4% and Male 14.3%). Both the lifetime and the one-year prevalence of the different anxiety disorders differed considerably, but in general, the public health impact of having any anxiety disorder should be evident.

MDD with co-morbid anxiety (MDDA) are characterized by diagnosable MDD and A according to DSM-IV (or ICD-10). There are extensive co-morbidity between MDD and other affective disorders, especially anxiety disorders (A). Both disorders are highly prevalent in the population and are associated with high levels of morbidity and mortality as well as great economic costs for the society. In individuals with depression or an anxiety disorder, co-morbidity with the other disorder occurs in one quarter to co-occurrence prevalence rates up to 60% in lifetime diagnoses, more specific, 58% of MDD patients were found to have an anxiety disorder. (NCS; Kessler et al., 2003; Kessler et al., 2005). But, varying degrees of co-morbidity between depression and anxiety have been reported in different studies, and vary according to the different anxiety disorder (Mineka et al., 1998). In the international WHO study (Sartorius et al., 1996) the rates were somewhat lower than in NCS, among cases of depression 39% had an anxiety disorder. Still, these numbers suggest that co-morbid anxiety and depression are “the rule rather than the exception”.

## **1.2. Impact on public health**

The Global Burden of Disease Study (GBD) ranked MDD as the fourth most important cause of global disability-adjusted life years (DALY; Murray & Lopez, 1997a) and MDD was also predicted to advance to the second most important cause by year 2020 (Murray & Lopez, 1997b). NCS estimated the annual costs of anxiety disorders to be 54% of the total costs due to treatment for somatic illness, and 31% of the costs due to treatment for mental illness (Greenberg et al., 1999)

The fact that co-morbidity between MDD and A is very high, and in clinical practice associated with barriers to treatment and worse psychiatric outcomes, such as treatment resistance, increased risk for suicide, greater chance for recurrence and greater utilization of medical resources, demands a greater attention to and understanding of the disorders through research on different levels. This to positively impact the economic burden of these costly disorders on society and the individuals' daily-life functioning and suffering.

However, much is still unknown about the underlying mechanisms both regarding aetiology, risk factors, medication, genetics, neurobiology, neuroanatomy, neuronal networks and the impact of cognition.



### **1.3. Diagnostic criteria**

Clinicians most often attempt to separate depression from anxiety, and sometimes these distinctions are challenging and often artificial (Aina & Susman, 2006). Factors that favour anxiety is the emotion of fear involving feelings of tension, worry, apprehension, and fear for something considered dangerous in the future, in addition to specific behaviour such as avoidance. Factors that favour depression include symptoms like the emotion of sadness, in addition to feelings of sorrow, hopelessness, gloom, lack of energy, anhedonia and often rumination about things from the past. These symptoms are according to the dimensional approach considered on a continuous scale from being absent to a maximum intensity. In contrast, the categorical approach views anxiety and depression as discrete psychopathological entities, or disorders. Such disorders are classified as being present or not according to a threshold for specific diagnostic criteria (Bjelland, 2004). In the present study, the diagnoses are based on categorical diagnoses based on DSM-IV, most commonly used in clinical research.

#### **1.3.1. Unipolar Major Depression (MDD)**

We've all felt "sad" or "blue" at one time or another. Rare bouts of depression that last only a few days are usually not a problem for most people. But, clinical depression, characterized as a mental disorder – the type that people seek help for - is a different story. Hence, the general term depression often refers to Unipolar Major Depression (MDD) that is a disabling condition which may seriously affect and deteriorate a persons daily functioning, family, friends, work or school, sleep, eating and health status in general (Austin et al., 2001; McCall & Dunn, 2003).

The DSM-IV uses the term "major depressive disorder" to classify and diagnose clinical depression. Major depressive episodes are the hallmark features of this type of depression. These episodes are often characterized by clinicians as extreme symptoms that interfere with daily functioning and may include low mood, which may interfere with all aspects of life, inability to experience pleasure or joy in activities that they formerly liked. Rumination is the preoccupation with thoughts and feelings of worthlessness, strong guilt and regret, helplessness, hopelessness and self-loathing and is thought of as one major factor that is believed to sustain and maintain the depressive episode. Other symptoms of MDD include poor concentration and memory, patients often complain about "falling out of conversations" and having dependence of checklists to be able to remember appointments, daily chores or

activities than they formerly did not need. These cognitive impairments cause a fall in daily functioning compared to premorbid level.

In order to fulfill the DSM-IV criteria for MDD, patients must exhibit at least five of the nine following symptoms during the same two week period, representing a change from previous functioning. At least one of the symptoms must be either (1) depressed mood most of the day, nearly every day, or (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. This mood must represent a change from the person's normal mood; social, occupational, educational or other important functioning must also be negatively impaired by the change in mood.

This disorder is further characterized by the presence of the majority of these symptoms:

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). (In children and adolescents, this may be characterized as an irritable mood.)
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- Diminished ability to think or concentrate, or indecisiveness, nearly every day
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Depressed mood caused by substances (drugs, alcohol, and medications) is not considered MDD, nor is one which is caused by a general medical condition. MDD cannot be diagnosed if a person has a history of manic, hypomanic, or mixed episodes (e.g., a bipolar disorder) or if the depressed mood is better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform, a delusional or psychotic disorder.

To qualify for recurrent MDD, the patients must have had a minimum of two depressive episodes with an interval of at least two consecutive months where the criteria for MDD are not fulfilled.

Cognitive functioning, which is also included in the diagnostic criteria of MDD, is the main focus of this study. The interaction between emotion and cognition is an important question from both a theoretical and a practical viewpoint. Mood congruent memory is a memory bias in which information with affective connotations is better remembered if it is congruent with the individual's mood during retrieval as compared with material that is incongruent with current mood (Bower, 1981). The mood congruency phenomenon is well established and has sparked a wealth of research into the effects of mood changes and emotional disorders on cognitive/neuropsychological functioning in general (Rogers et al., 2004). However, cognitive impairments are not present in all subjects with MDD. Why some individuals are impaired and some perform in the normal range, is not clear (Egeland et al., 2005).

MDD is polythetic, meaning that meeting criteria for the disorder is possible via more than one pattern of the diagnostic symptoms. As operationalized by DSM-IV for a diagnosis of MDD, 5 out of 9 symptoms with one of those being either depressed mood or irritability, or anhedonia, plus a diverse set of potential depressive symptoms, raises the question of the heterogeneity of depressive symptoms profiles and the possible different manifestations with comorbid anxiety disorders (Small et al., 2008), and specifically regarding associated cognitive impairments.

In addition, the variety of factors that may contribute to variability in symptom presentation may also influence the manifestation of cognitive impairments in depressive disorders, this can include: levels of severity, subtypes, number of episodes, co-morbidity and the range of negative affective traits and states have not been properly addressed or controlled for in the majority of studies in the field, and may explain the lack of consistently observed across studies. (e. g. Austin et al., 2001; Purcell et al., 1997; Porter et al., 2003; Mohanty et al., 2002, Rogers et al., 2004; Levin et al., 2007).

### **1.3.2. Anxiety (A)**

Anxiety is a natural human response and a necessary and beneficial response and warning adaptation in humans. For example, dangerous situations trigger anxiety in the form of a fight-or-flight stress response that is necessary for our survival. Or, sometimes anxiety gives us the necessary push we need to get things done

But anxiety may become a pathologic disorder when it's excessive, uncontrollable, requires no specific external stimulus and manifests in a range of affective and physical symptoms in addition to more behavioural and cognitive changes (Rowney et al., 2010).

The symptoms may lead to an anxiety disorder if they are: severe or last a long time, out of proportion to the situation at hand and/or causing extreme behaviours (i.e., avoidance) to reduce the anxiety. Phobias are derived from the Greek word *phobos* that means fear or fright. A phobia is physical reactions on fear, that comes automatic and that is not controlled by will. Phobias are characterized as an anxiety disorder. It should also be noted that anxiety can be a central aspect of depression, causing an anxious or agitated depression.

The primary anxiety disorders generally develop before the age of 30, are more common in women than men, and are associated with a family history of anxiety and depression (APA, 1994; Kessler et al., 1994).

DSM-IV categorize anxiety disorders into: generalized anxiety disorder (GAD), panic disorder (PD) with and without agoraphobia, agoraphobia without a history of panic disorder, phobic disorders (social anxiety and specific), obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), acute stress disorder, substance induced anxiety disorder or due to medical conditions and anxiety disorder not otherwise specified (NOS).

### **1.3.3. Co-morbid MDD and A (MDDA)**

The co-occurrence, or comorbidity, of two or more disorders is relatively common in psychiatry some critics claim that co-morbidity is simply an artefact of splitting nosological entities into separate classes. Hence, two disorders that have some common diagnostic criteria are more prone to co-occur, which is called diagnostic comorbidity (Kaplan & Feinstein, 1974).

Co-morbidity between two of the most common psychiatric disorders, namely depression and anxiety, has several consequences including increased symptom severity (Sherburne & Wells, 1997), impaired treatment response to antidepressive medication (Brown et al., 1996), impaired recovery rate from depression, increased time to recovery, decreased time to relapse (Hayden & Klein, 2001; Coryell et al., 1992), as well as increased risk for suicide (Angst, 1993). Anxiety can also potentially confound or contribute to neuropsychological impairments or anatomic changes in depressed individuals (Cameron et al., 2004; Leonardo et al., 2006).

Although it is well known that anxiety and depression are highly correlated (Mineka et al., 1998), and this is of high clinical significance, studies addressing the co-occurrence of MDD and A are very few, and the majority of studies of either MDD or A have up to date not accounted for the co-occurrence of the other. As a result of this, there is no broad consensus whether the findings are due to the depression or the anxiety component or both.

In addition, both MDD and A are syndromes and hence heterogeneous including different subtypes, and the research have often focused on one anxiety subtype or a merge of different depressive and anxiety disorders without differentiating between possible subtypes or combinations.

However, there is still controversy how one should characterize the constructs of MDD and A, and whether they should be considered as categorical diagnoses or phenomena on a continuum. Hence, studies addressing comorbidity have almost exclusively applied a categorical approach (Maser & Patterson, 2002), therefore due to the focus of this study and from a clinical point of view, it is necessary to diagnostically identify patients with MDD and/or A in order to obtain reliability of the samples, validity of results and to provide the optimal treatment in clinical settings and health care services.

#### **1.4. Symptom severity**

In this study we have included and controlled for measures of depressive and anxiety symptom severity in addition to the primary focus; the diagnoses (syndrome) according to DSM-IV criteria. Symptom severity measured with the self-report questionnaires: the Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1961) and the Beck Anxiety Inventory (BAI; Beck & Steer, 1988), may give additional information regarding the present level of symptoms the current day of testing and explore whether depressive and/or anxiety symptom severity may account for some of the variance.

MDD with more pronounced depressive symptoms have also shown associations with more prominent cognitive dysfunction (Grant et al. 2001; Albus et al., 1996; Weiland-Fiedler et al., 2004). In a study Channon and Green (1999) reported executive function deficits in dysphoric undergraduate students relative to those with normal mood as defined by Beck Depression Inventory (BDI). This might suggest that cognitive deficits may be associated with depressed mood or symptoms rather than clinical syndrome depression. Others have found no relation between self-reported depression and anxiety (BDI/STAI) and executive measures (see Smitherman et al., 2007).

A PET study by Osuch et al. (2000) found that depressive symptom severity correlated with increasing activation in the right dorsal lateral and bilateral medial frontal cortex as well as the right anterior cingulate gyrus. In contrast, increasing anxiety symptoms correlated with greater activation in the left anterior cingulate and right parahippocampal gyrus. This may imply that co-morbid depressive and anxiety symptoms may exert neurobehavioral effects that differ from those observed in one alone and may be attributable to co-morbid MDD and

A disorders. But the discussion about whether cognitive dysfunctions in depression and anxiety represent symptom or syndrome factors or an interaction of both with situational stress as a mediating factor is still ongoing (Eysenck & Calvo, 1992; Chong, 2003; Murray & Janelle, 2003).

### **1.5. Recurrent depressive episodes**

The majority of patients with MDD will experience recurrent episodes of depression, and it is therefore vital to achieve more information to the association between number of recurrent depressive episodes and neuropsychological function. Depression has a high recurrence rate: around 80% of depressed patients will experience more than one depressive episode over their lifetime (Kessler et al., 1997; Vanderhasselt et al., 2009), and research reveals that patients become more vulnerable after each depressive episode, with an increased chance for the onset and maintenance of a depressive episode (Monroe & Harkness, 2005; Vanderhasselt et al., 2009).

There are findings suggesting that cognitive impairments are prevalent in individuals with recurrent depression, and not in persons that experience their first episode (Basso & Bornstein, 1999b; Fossati et al., 2004). However, it is important to notice that findings differ across studies.

There are research findings where number of earlier depressive episodes show a cumulative effect on cognitive control dysfunctions in MDD (Vanderhasselt & De Raedt, 2009; Kessing, 1998), and hence support the theories of recurrent episodes leaving a “scar” that affects cognition and that patients become more vulnerable after each depressive episode with an increased chance for the onset and maintenance of a depressive episode (e.g. . Monroe & Harkness, 2005). Others have found no association between number of episodes and executive impairment in MDD (Grant et al., 2001; Reisches & Neu, 2000; Lampe et al., 2004). Post (1992) proposed that fundamental neurochemical changes occur as a function of successive depressive episodes. As a consequence of these changes cerebral dysfunction increases with each episode, this may in turn decrease the threshold for onset of subsequent depressive episodes. In a research report, Paelecke-Habermann et al. (2005) state that the database regarding the relationship between cognitive impairments and number of episodes is inconsistent and not well understood. Additional risk factors for recurrence that have been suggested other than previous depressive episodes are: female gender, length of first episode, loss events, genetic vulnerability, psychosocial factors, previous hospitalization, late-onset

depression, family history, to never have been married, and age of onset first depressive episode (Mueller et al, 1999; Angst, 1999; Burcusa & Iacono, 2007).

In sum, more research that take into account number of earlier depressive episodes when Studying cognitive functions in MDD are needed to expand the knowledge and understanding of the possible cumulative effects of recurring depressive episodes on cognition.

### **1.6. Age of onset**

One of several clinical features that may contribute as a risk factor for recurrence of depression is age of onset for first depressive episode (Burcusa & Iacono, 2007). Several studies have examined the role that age of onset for first episode relates to later recurrence of depression, but these studies have yielded conflicting results, from reports on relation between early onset greater and greater risk for recurrence (Gilman et al., 2003; Klein et al., 1999; O'Leary & Lee, 1996), to no findings of a relationship between age of onset and subsequent recurrent episodes (Birmaher et al., 2004; Kovacs et al., 2003). The studies that did not find a significant relationship are similar in that they did not control for number of prior depressive episodes, but looked at risk for recurrence in those with a history of any number of episodes. While age at onset and number of depressive episodes are moderately correlated, they are not completely synonymous, and should both be addressed (Burcusa & Iacono, 2007).

Regarding age of onset of depression and relation to cognitive deficits, studies have found that younger onset of the disorder predict poorer performance on tasks demanding executive functions (Castaneda et al., 2008; Castaneda et al., 2010; Grant et al., 2001).

In sum, studies involving simultaneous assessment of onset age and number of recurrent episodes regarding effect on e.g. cognitive functioning in affective disorder patients are needed in order to gain information of different factors affecting clinical diagnoses and subtypes, formulation of prognosis, prediction of treatment requirements and to add information about phenotyping of mood disorders for the purpose of research (Tondo et al., 2010).

## **1.7. Neuropsychological impairments**

### **1.7.1. MDD**

A number of studies indicate cognitive impairments in mood disorders (Veiel, 1997; Austin et al., 2001; Landrø et al., 2001; Rogers et al., 2004, Levin et al., 2007), but a limited range of neuropsychological functions have typically been assessed in each individual study and the research field in general has, up to date, been characterized by contradictory, mixed patterns of findings and heterogeneous test performance.

However, there is a relative consensus in the research field regarding deficits in depression compared to healthy controls in broad domains of functioning regarding executive functions (Austin et al., 2001; Degl'Innocenti et al., 1998; Porter et al., 2003; Elliot et al., 1996; Fossati et al., 1999; Grant et al., 2001; Fossati et al., 2002; Kaiser et al., 2003; Gualtieri et al., 2006, Channon & Green, 1996; Harvey et al., 2004), psychomotor speed (Austin et al., 1992; Degl'Innocenti et al., 1998; Tsourtos et al., 2002; Gualtieri et al., 2006), attention (Landrø et al., 2001; Porter et al., 2003; Sweeney et al., 2000), and memory functions (Austin et al., 1992; Elliot et al., 1996; Landrø et al., 2001; Rose et al., 2003; Veiel et al., 1997).

The most frequent explanation that interactions between affect and cognition in mood disorders have yielded divergent results across studies, relates to between-subjects differences, namely: heterogeneity of patient samples, age differences, presence of psychosis, medication, psychomotor retardation, length and severity of illness, number of recurrent episodes and co-morbidities (Pardo et al., 2006). Another reason may be that the research field consists of the use of multidimensional definitions and operationalizations into tasks to assess cognitive functions or domains that often include several other subfunctions ("the task impurity problem") (Philips, 1997).

Although cognitive dysfunction is a feature in depression, the nature and specificity remains somewhat unclear. Therefore, to use models and tasks that separate the more underlying functions and related networks involved in the cognitive domains may enhance greater specificity, and better support for inferences from the task performance, in which cognitive functions that are affected and which are not.

In sum, the contradictory research field regarding neuropsychological functions in MDD may mainly be due to seldom accounted for between-subject factors, especially co-morbid anxiety in addition to the operationalizations of cognitive domains into tests that may measure multiple cognitive subfunctions.



### **1.7.2. Anxiety**

The impact of anxiety on cognitive functioning is much less explored than depression. Regarding anxiety disorders in general there are few studies and a mixed pattern of findings, from no deficits (Gladsjo et al., 1998; Purcell et al., 1998) to deficits on a range of different cognitive functions, such as memory and learning (Constant et al., 2005; Lucas et al., 1991; Asmundson et al, 1994; Boldrini et al., 2005), executive functions (Cohen et al., 1996; Olley et al., 2007; Purcell et al., 1998), and impaired attentional control to threat related stimuli (Broadbent et al., 1986; Bishop et al., 2004). Anxiety disorders have also been associated with heightened distractibility, poor concentration and increased responsivity to potential threat (Bishop et al., 2004).

The inconsistent and mixed findings in the research field may likely be the result of methodological differences between studies regarding selection of participants, that is, few studies differentiate between the different anxiety subtypes, and traditionally focus on one subtype or they mix different anxiety disorders into an overarching diagnostic disorder. More importantly, co-morbid depression is seldom accounted for, and the often contradictory findings may be related to whether cognitive dysfunctions in anxiety may be accounted for by co-morbid depression or by the anxiety disorder independent of depression.

### **1.7.3. MDDA**

There are extensive co-morbidity between MDD and other affective disorders, especially anxiety disorders (A), in regards to both phenomenological features and neuropsychological functioning. In individuals with depression or an anxiety disorder, co-morbidity with the other disorder is associated with pronounced cognitive dysfunction, and anxiety can potentially confound or contribute to neuropsychological impairments or anatomic changes in depressed individuals (Cameron et al., 2004; Leonardo et al., 2006; Castaneda et al., 2008).

Despite the high co-morbidity rate, and that co-morbid anxiety is an important factor that potentially can contribute to inconsistencies between studies and should be addressed accordingly, up to date research have paid little attention to and hence provided very little information regarding the effect of co-morbid anxiety on cognitive dysfunctions in MDD. Studies on cognitive impairments in depression have often inadequately controlled for or not taken into account co-morbid anxiety as a confounding variable, and may as a result, explain some of the contradictory results in the research field (Castaneda et al., 2008).

Lilienfeld (2007) points out challenges when dealing with co-morbid MDD and anxiety. The fact that co-morbidity is more often the rule than the exception gives rise to difficulties

regarding specificity. To be able to establish the specificity versus generalizability of abnormalities associated with MDD and MDDA in this study, the need to compare these clinical groups in addition to a healthy control groups is essential.

Rogers et al. (2004) highlight in a review the critical importance that very few studies measure and report co-morbid anxiety in their samples, even if the presence of co-morbid anxiety have been shown in some cases to account for a considerable portion of the cross-study variability in reported executive function impairments in individuals with depression. The very few studies on MDD with co-morbid anxiety disorder have also traditionally focused on one anxiety subgroup.

In a review of the existing literature on cognitive impairments in depression and anxiety among young adults, Castaneda et al. (2008) concluded that cognitive impairments are common in both anxiety and depression, whereas executive dysfunctions were associated with depression. The neuropsychological profile in anxiety; although their nature remains partly unclear, seem to be depend on anxiety subtype. Castaneda et al. (2008) explain the conflicting results in the literature by the heterogeneity found within study participants. This review, however, do not focus on MDD as primary diagnosis with co-morbid anxiety disorders, but take into account research on a wealth of depressive and anxiety disorders compared to healthy control groups.

Two studies that assessed co-morbidity, used anxiety as the primary diagnosis and addresses panic disorders (PD), MDD, and PD with co-morbid MDD. They did not, however, measure neuropsychological functions, but found the co-morbid PD with MDD having more severe psychopathology and symptoms of somatic preoccupation and social-evaluative fear than the two pure clinical groups (Andrade et al., 1994; Woody et al., 1998). These results suggest that co-morbid anxiety may hold additional maladaptive beliefs beyond specific cognitions typically associated with each disorder alone. Other studies that use anxiety as primary diagnosis, but include neuropsychological measures, focus on one anxiety subtype. Kaplan et al. (2006) compared patients with PD, PD with co-morbid MDD and matched healthy controls (HC) on subtests measuring attention, memory, psychomotor speed, executive functioning, decision-making and affective processing. The co-morbid group demonstrated deficits in visual discrimination and working memory compared to HC, in addition to an attentional bias towards negatively valenced stimuli. However, this study did not compare the clinical groups directly. Graver et al. (2006) studied the influence of stress on neuropsychological functioning and found no significant differences between groups with social phobia (SP), SP with co-morbid MDD and HC on baseline conditions without an

exogenous stressor. Basso et al. (2001) examined the relative impact of depression on executive function deficits and sensory-motor functions in OCD on a broad battery of neuropsychological tests. The results suggested that abnormalities involving executive function in OCD are linked to concurrent depressive severity, and less to OCD. However, the limitations of this study consists of patient data collected retrospectively and addressed co-morbid depressive symptoms and not diagnostic MDD (Basso et al., 2001).

Studies that address MDD as the primary diagnosis often use samples of mixed psychiatric axis I diagnoses and medical co-morbid disorders. One example is Castaneda et al. (2010) that conducted a study on a population-based sample of patients with a history of MDD compared to a healthy control group by examining the effects of co-morbidity Axis I disorders on a broad range of neuropsychological tests. They found that the groups with MDD and the MDD with co-morbid Axis I disorder group did not differ in any of the cognitive measures assessed, and conclude that psychiatric co-morbidity may not aggravate cognitive functioning among depressed young adults. That the co-morbid group consisted of a mix of anxiety disorders, substance abuse, eating disorders and other axis I disorders are limitations of this study, in addition only nine out of sixty-nine MDD patients had current MDD.

Contrary to these results, a study that aimed to investigate the association between cognitive performance and medical and psychiatric co-morbidity in MDD, Baune et al. (2009) concluded that the strongest predictor of poor cognitive performance in depression was psychiatric co-morbidity. The MDD with co-morbid psychiatric disorders showed decreased cognitive performance in visuospatial/constructional and language domain and total score on Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), but the study did not include a healthy control group. Mini Mental State was used as a mean for diagnosis, and the depressed sample consisted of both bipolar and unipolar patients in addition to the wide range of psychiatric co-morbid disorders, all of which are limitations to address.

DeLuca et al. (2005) studied geriatric patients with MDD, and MDD with comorbid GAD and/or PD using measures of symptoms, functional disability and cognitive disability (Mini Mental Status Exam (MMSE)). MDD and co-morbid GAD or PD were found to be associated with greater decline in memory in late life MDD, but the MMSE is a short questionnaire used for screening of daily life cognitive functions, and do not measure cognitive functioning with the same sensitivity as neuropsychological tests, in addition to the limited generalizability of the samples studied.

Other studies have used self-reported depression and anxiety symptoms in mixed psychiatric samples and not utilized diagnostic criteria according to DSM-IV. Smitherman et al. (2007)

evaluated the relation between mood and executive functioning in records from adult outpatients and found the correlations between the self-reported depression and anxiety and measures of executive functioning to be small and non-significant. Kizilbash et al. (2002) studied a large sample of veterans with self-reported depressive-, anxiety and co-morbid depressive and anxiety symptoms regarding memory functions, and found that depressive symptoms had an adverse effect on immediate recall, anxiety symptoms no effect, but the co-morbid group showed not only an adverse effect on immediate recall but also effect on retrieval of newly learned information. They conclude that the presence of co-morbid anxiety may, in part, account for the variability of previous research findings regarding the effects of depression in memory functioning, but this study did not have a defined diagnosis of depressive and anxiety disorders.

Airaksinen et al. (2004) studied population-based samples that fulfilled the DSM-IV criteria of MDD, dysthymia, mixed anxiety-depressive disorder and minor depression with a healthy comparison group on a variety of cognitive tasks. They found that both the MDD and mixed anxiety-depression group exhibited significant memory dysfunctions compared to HC. They did however not find differences between MDD and the mixed group, but found significant differences between the depressive subgroups dysthymia and minor depression compared to the two former. They conclude that cognitive impairments vary as a function of depressive subgroup.

One of the few studies that address and seek out to explore how co-morbid anxiety corresponds with neuropsychological dysfunction in unipolar depression is Basso et al. (2007) that compared depressed inpatients with and without co-morbid anxiety disorders to a group of healthy controls on a brief but broad battery of neuropsychological tests. The results showed that both clinical groups showed worse memory functions than controls, but that attention, executive dysfunction and psychomotor slowing were specific to the depressed group with co-morbid anxiety. The latter group also displayed more impaired scores than both “pure” MDD and HC. Basso et al. (2007) concluded that MDD corresponds with significant memory impairments regardless of co-morbid anxiety, but the presence of co-morbid anxiety displays deficits involving executive functions and psychomotor slowing. The limitations of this study are mainly the reliability of patient diagnoses; the data were collected retrospectively from available records and these recorded diagnoses lacked a structural diagnostic interview and were made by a psychiatrist at the hospital. The patient samples also consist entirely of inpatients, and the literature suggests that inpatients are more severely impaired than outpatients. The brief neuropsychological battery, do as many studies in the

field traditionally have been doing, namely choose tests that tap unitary, general purpose executive functions.

In a clinical trial, Herrera-Guzmán et al. (2009) found no differences between MDD patients with or without co-morbid anxiety at baseline on any of the neuropsychological variables studied. In line with these findings, Castaneda et al. (2010) also found no significant differences between the population-based clinical groups MDD, MDD with co-morbid mixed anxiety/substance abuse/eating disorders and other axis I disorders on a range of neuropsychological tests. However, the majority of the patients in the MDD group were in remission and only a few had current MDD.

In sum, research concerning MDD and A disorders separate, suggest that neuropsychological deficits are present in both disorders, but there are few studies that examine their simultaneous effect on neuropsychological functioning, and especially address primary MDD with co-morbid anxiety disorders. The co-morbid samples often consist of mixed axis I disorders and there are few that seek out to explore neuropsychological functions. The few studies that have systematically examined the impact of MDD with co-morbid A on neuropsychological functions, have yielded contradictory results (i.e. Basso et al., 2007; Castaneda, 2010; Herrera-Guzmán et al., 2009), and the conclusions must be regarded as tentative due to several inconsistencies between studies. Methodological factors that may account for some of the inconsistencies are; variability in clinical subtypes used in each study, small sample sizes, low reliability regarding diagnostic screening, difference of in- and outpatient samples, methodological heterogeneity regarding use of different and general tests to operationalize cognitive functions, and not taking into account the diversity of their subfunctions.

There were also performed more formal searches to identify research in the field. There were conducted electronically searches using PubMed, PcyInfo(Ovid), ISI Web of knowledge (all databases, all years) to identify research articles that focus on neuropsychological measures in MDD with co-morbid anxiety disorders. Different forms and combinations of the following search terms were used: depression, anxiety, panic disorder, phobia, generalized anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder, social phobia/anxiety, agoraphobia, co-morbid depression/ anxiety, neuropsychology, cognitive deficits/dysfunctions/impairment, executive functions, cognitive control functions, memory, working memory, attention. In addition, reference lists were screened in order to include further relevant studies. See overview in table below.

Study (alphabetical)	Sample (n) <sup>a</sup>	Age (mean+ sd)	Neuropsychological tests /cognitive functions	Main findings	Strengths	Limitations
<b>Airaksinen et al. (2004)</b>	MDD (68) Dysthymia (28) Mix. MDD+A (25) Minor depr. (66) HC (175)	Total group of patients aged 20-65 years	Variety of cognitive tasks i.e. TMT A and B, Episodic memory task (free and cued recall)	All showed impairments in episodic memory and mental flexibility. MDD and Mixed MDD+A displayed significant memory dysfunction compared to the other subgroups.	Population based samples.	High drop out rate, possible biased participation
<b>Basso et al. (2007)</b>	MDD (30) MDDA (22) HC (38)	33.57 (7.45) 40.32 (8.53) 36.29 (14.74)	Brief but broad battery of neuropsychological tests (CVLT, FAS, TMT A & B, Grooved Pegboard)	Both clinical groups showed worse memory functions than HC. Executive function and psychomotor slowing were specific to the MDDA group.	Addressing non-psychotic unipolar MDD and co-morbid anxiety disorders. Diagnoses according to DSM-IV criteria.	Inpatients. Data collected retrospectively from available records. Heterogeneity of A disorders.
<b>Castaneda et al. (2010)</b>	MDD (69) Comorbid MDD and other psychiatric disorders (57) HC (71)	Age range: 21-35 years (young adults)	CVLT, TMT A & B, WMS-R: Digit Span, Visual Span, WAIS-III: Letter Number Sequencing, Digit Span, Vocabulary subtest as estimate of general intelligence.	Both the clinical groups of lifetime depression did not differ in any of the measures assessed.	Population based sample.	The co-morbid disorders were a mix of anxiety disorders, substance abuse, eating disorders and other axis I disorders. Only 9 depressed were current, 60 in remission.
<b>Herrera-Guzmán et al. (2009)</b>	MDD (22) MDD+GAD (51)	34.22 (10.18) 32.56 (7.90)	CANTAB and traditional np. Tests regarding verbal learning and memory, WM, speed, attention, EF subfunctions: inhibition, set-shift, fluency, planning.	No significant differences between the groups regarding baseline cognitive functioning.	The A group consisted of only GAD. Tested prior to pharmacological treatment	Exclusion of OCD and PTSD, limits applicability to these anxiety disorders.

Notes. TMT= Trail Making Test (A and B), CVLT= California Verbal Learning Test, FAS= Verbal fluency task, WMS-R= Wechsler Memory Scale-Revised, CANTAB= The Cambridge Neuropsychological Test Automated Battery, WM= working memory, EF= executive functions,

## **1.8. Definitions and cognitive models**

The three papers have dealt with different cognitive domains such as executive control functions, attention and memory, the cognitive domains that are the most commonly observed deficits in MDD and A. There are unclear boundaries and relations between the concept executive functions and concepts such as attention and memory, both in regards to cognitive models and the use of overlapping or identical neuropsychological tests to measure the same functions, this mostly due to their complexity as cognitive domains comprising of different subfunctions. In our study, we separated the areas in the analyses to avoid the emergence of cognitive profiles that would cloud the main focus, that is, differences between MDD and MDDA in these specific cognitive areas. Operationalisations of the cognitive areas are based on theory and models, in addition to empirical traditions of the neuropsychological tests used to measure them.

### **1.8.1. Attention**

Attention have in the literature been described as both a more higher order or executive attentional system of sustained focus and control of cognitive resources on information while filtering or ignoring extraenous information, to be subdivided into basic subfunctions and seen as precursor to other cognitive functions (Lezak, 2004; Knudsen, 2007).

At a basic level, Fan et al. (2005) and Posner et al. (1990) fractionate three independent and separable aspects of attention, namely: Alerting (when), Orienting (where/spatial) and executive control (conflict or congruent/incongruent). These three aspects are subserved by three distinct and relatively independent neural networks (Fan et al., 2002).

In a review, Knudsen (2007) describes a general model which identifies four core processes of attention, with working memory at the centre, including selection processes that determines information access to WM, in addition to both top-down sensitivity control, higher cognitive processes that can regulate information processing to more bottom-up saliency filters of stimuli. Knudsen (2007) proposes a conceptual framework for attention that reflects the combined contributions of the different processes involved, from higher order to lower level processes and their potential overlapping. In our study, we wanted to address both the higher level and basic level attentional functions in order to specify, and perhaps identify key functional components in which attentional impairments manifest in MDD and MDDA.

### **1.8.2. Memory**

In our study we also wanted to address different memory functions in order to identify the components of memory in which MDD and MDDA show impairments.

Memory is often considered a higher-level cognitive function, and there is consensus that it is not a unitary concept, but involves several different processes. Cognitive models often make distinctions between short-term memory (STM), working memory (WM) and long-term memory (LTM) (Gazzaniga, 2008).

Theoretical frameworks on working memory (Baddeley, 1986; Norman & Shallice, 1986) have provided cognitive models that are still highly present in the field. Baddeley & Hitch (1974) state that the WM consists of the attentional system, the Central Executive (CE) and two slave systems/storage buffers assumed to be rather independent. They propose WM and the CE as an attention system related to Norman and Shallice's (1986) supervisory attention system (SAS), that describes the control of action and attention attributed to the central executive that regulates the active portion of memory. Similarly, Engle et al (2002) view WM capacity as fundamentally related to domain general executive attention or the central executive aspect of WM. Engle (2002) further states that WM capacity is about differences in ability to control attention to maintain information in an active, quickly retrievable state. Domain-specific skills or expertise, like reading comprehension and arithmetic, cannot account for why WM capacity tasks correlate with performance on higher-order tasks, and therefore WM capacity or CE is, according to Engle (2002) and Kane & Engle (2000); an ability to control attention and dealing with the effects of proactive interference rather than memory storage.

### **1.8.3. Executive functions**

Up to date there have been no broad consensus regarding the definition and operationalization of executive functions (EF). In addition, the differentiation between EF and concepts like attention and memory has also been unclear. This may be due to several reasons: EF is considered a higher-order top down processing involving many subfunctions, and therefore operate on and influence many lower level cognitive functions such as attention and memory functions (Lezak, 2004). Any deficits in executive function could then have a major impact on performance of normal daily routines, so their identification could be crucial for the development of therapies to support everyday function and to gain a better understanding of the nature of mood disorders (Taylor-Tavares et al., 2007).



Executive control functions refer to mental functions that have the overarching control and modulation of cognitive processes, and therefore they have traditionally been considered a unitary, general purpose ability that can be measured with a single complex task (i.e. WCST, Stroop, TMT-B) (Lezak, 2004). Executive tasks have therefore tended to suffer from relatively low internal and/or test-retest reliability (Denckla, 1996; Rabbitt, 1997; Miyake et al., 2000), and the widely used and accepted tests to measure EF have based their construct validity on loose criterion as “sensitive to frontal lobe damage”. This limits their usefulness in identifying specificity in impairment, and to seize out the more basic underlying executive control functions hypothesized to be subserved by the prefrontal cortex (PFC), and especially the anterior cingulate cortex (ACC) and its networks (Colette et al., 2002; Bar-Haim et al., 2007; Fan et al. 2002; Bush et al., 2000; Thomas & Elliot, 2009; Pizzagali et al., 2001). The tests traditionally used to measure EF have therefore been too broad, and “executive tests” often used in neuropsychological studies involve many functions, making it difficult to seize out the primary functional deficit associated with any one complex task, that is, which cognitive functions that are measured, hence “the task impurity problem (Burgess, 1997; Philips, 1997; Friedman et al., 2009). Different “executive tests” have also shown to typically correlate low with each other. It is therefore reasonable to assume that these tests partly measure different functions/processes from higher-level to more basic functions, making it difficult to cease out the primary functional deficit. Evidence from neuropsychological research indicates, however, that executive control more accurately can be characterized as a collection of related but separable abilities (Baddeley, 1986; Friedman et al., 2006; Friedman et al., 2009).

Since the consensus about EF is difficult, the focus may be on the way EF have been operationalized and measured. To increase the ecological validity, the need for better tests and models to capture and operationalize all aspects of EF will be crucial in future research. Even if there have been no clear consensus on how to best define or conceptualize executive functions, recent neuropsychological research suggests that executive functions are multifaceted and that different types of executive functions are correlated but separable (Friedman et al., 2006). These three executive functions (inhibiting dominant responses, updating working memory representations, and shifting between task sets) have dominated recent executive control function research, and have been confirmed in studies by Miyake et al. (2000) and Friedman et al. (2009).

Based on a firm theoretically driven model, Miyake et al. (2000) used latent variable analysis in a study to determine to what extent different executive processes can be considered to be

unitary (in the sense that they are reflections of the same underlying mechanism or ability) or non-unitary. They focused on the following three basic executive functions: (1) shifting between tasks or mental sets, (2) inhibition of dominant or prepotent responses, and (3) updating and monitoring of the contents of working memory. Confirmatory factor analysis indicated that these three executive processes, although moderately correlated with one another, are clearly separable. Moreover, structural equation modeling suggested that the three functions contribute differentially to performance on complex executive tasks. These results suggest that it is important to recognize both the unity and the diversity of executive functions (Miyake et al., 2000).

Neuropsychological studies of mood disorders based on an empirically based model of basic executive control functions are lacking, and therefore we wanted to address this in our study.

### **1.9. Explanatory frameworks**

Two frameworks that have been trying to explain the impact of affect on cognitive deficits are the Effort-hypothesis/Cognitive load theory and the Cognitive Speed hypothesis.

Cognitive load theory or the Effortful-processing theory is a theoretical position trying to explain impairments in depression where patients show more difficulties on tasks that demand cognitive effort as opposed to automatic and over learned material, that is, higher level effortful tasks versus more basic lower level tasks. Effortful information processing requires considerable cognitive resources and may interfere with other cognitive activities that also require cognitive capacity. One example is the well-known “Stroop-effect” that consists of four trials where the first two are automatic and the second two require mental effort.

Cognitive load have also broadly been referred to cognitive load related to the executive control of WM or, at a more basic level, the load on working memory in a task.

Negative mood and rumination require generally more attention than neutral and positive stimuli (Dolcos & McCarthy, 2006; Van Dillen & Koole, 2007). And as in major depression, strong negative stimuli may trigger more mood-congruent processing and thus employ more WM capacity. Eysenck & Calvo (1992) have suggested that the impact anxiety have on cognitive load, is associated with depletion of central executive resources (restrictions in WM capacity) in accordance with the original model of Baddeley & Hitch (1974). Due to the task-irrelevant worrisome thoughts, anxiety is thought to depley resources otherwise available to support WM, or more specific; central executive resources. However, this does not explain all the findings in the field. Others explain anxiety as a heightened attention to threat and therefore more load in visuospatial attention (Shackman et al., 2006).

The Cognitive Speed-hypothesis proposes that cognitive dysfunction in depression are caused by cognitive slowness (i.e. reduction in mental speed or cognitive speed processing) that are general, task-independent non-specific slowing of processing speed, and therefore may negatively affect higher cognitive functioning (Den Hartog et al., 2003; Egeland et al., 2003). Several studies have provided support for this speed hypothesis of cognitive deficits in both depressed patients and patients with co-morbid anxiety (e.g. Zakzanis et al., 1998; Nebes et al., 2000, Castaneda et al., 2008). But when problems of higher cognitive processing are not accompanied by speed problems, this hypothesis appears to be invalid (Den Hartog et al., 2003). Other studies have shown contradictory findings, and argue that cognitive deficits are not associated with non-specific changes in cognitive performance but to specific processes, such as attentional processes (Erickson et al., 2005). To our knowledge, a few studies (Dutke and Stöber, 2001) have found that anxiety affect psychomotor acceleration, whereas numerous theories states that the presence of anxiety (specifically OCD) yields slower processing due to an obsessive or ruminative approach to testing (Basso et al., 2007). In light of these frameworks, it may be hypothesized that both MDD and A, and thus MDDA, may affect cognitive load and /or psychomotor speed.

## **2.0. AIMS OF THE STUDY**

The overall aim of the study was to investigate neuropsychological functions in persons with MDD compared to MDDA and HC, by assessing neuropsychological performance in executive control functions, attentional functions and memory functions.

Other facets examined in the papers were the effects of potentially confounding factors such as a) number of depressive episodes, b) anxiety and depressive symptom severity, and b) age of onset for the first depressive episode on neuropsychological functioning.

### **2.1. Paper I**

The aim of the first paper was to investigate different levels of attentional networks for neutral stimuli processing in patients with MDD and MDDA compared to HC.

### **2.2. Paper II**

The aim of the second paper was to examine the central executive control aspects of verbal working memory (WM) functions, as well as verbal learning and long-term storage functions in MDD and MDDA compared to HC.

### **2.3. Paper III**

The aim the third paper was to systematically investigate basic components of executive cognitive control functions according to Miyake's model, in patients with MDD and MDDA compared to a HC group.

## **3.0. METHODS**

### **3.1. Design**

The papers included in this thesis are based on between-subjects designs.

### **3.2. Sample**

The study was approved by the Regional Committee for Medical Research Ethics, Norwegian Social Science Data Services (NSD) and adhered to the Helsinki Convention. Written informed consent was obtained from all participants.

#### **3.2.1. Participants**

The three studies included in this thesis are based on the same samples. The neuropsychological data collected were divided into three studies according to the different neuropsychological functional areas, from basic attention, via memory to executive control functions. Paper III includes all participants, but due to technical and/or administrative problems data are lacking for participants in Paper II: 1 HC. Paper I lacks 4 MDD and 3 HC on the ANT, and 1 HC on Stroop.

The distribution of the anxiety subtypes in the MDDA group was: General Anxiety Disorder (GAD) = 3, Social phobia= 13, Obsessive-Compulsive Disorder (OCD) =4, Posttraumatic Stress Disorder (PTSD) = 2, Panic with agoraphobia= 6, Panic without agoraphobia= 4, Specific phobia= 3, Anxiety Not Otherwise Specified (NOS) = 2. Fourteen participants had one anxiety diagnosis, and ten participants had two or three anxiety disorders.

#### **3.2.2. Inclusion criteria**

General inclusion criteria were age between 18-65 years, to speak fluent Norwegian and no medication taken other than Selective Serotonin Reuptake Inhibitors or Serotonin-Norepinephrine Reuptake Inhibitors (SSRI/SNRI). Prior to testing the patients were required to be medication-fasting the day of testing.

#### **3.2.3. Exclusion criteria**

General exclusion criteria were a history of neurological disorders (i.e. Adhd, Tourettes, unconsciousness for more than 30 minutes), bipolar disorder, psychosis, present drug and/or

alcohol-abuse. Two participants were excluded due to scaled score  $\leq 4$  on the WAIS-III subtest Similarities.

### **3.3. Clinical evaluation**

#### **3.3.1. Diagnostics SCID-I/II**

Clinical and diagnostic assessment was made in accordance with Structured Clinical Interviews for DSM-IV criteria (APA, 1994). Both SCID-I and SCID-II were utilized by trained professional clinical psychologists. All assessment was audio-taped with consent and with instruction to the participant of not using names or other recognizable issues.

In addition, the rating was later blindly repeated by means of the original audio-taped interviews by an external experienced clinical psychologist who was unaware as to whether the participants were MDD or MDDA (validated by one of the co-authors; TCS).

#### **3.3.2. Symptom severity**

The Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1961) and The Beck Anxiety Inventory (BAI; Beck & Steer, 1988) were filled out by the participants at the time of testing, to measure severity of depression and anxiety symptoms.

#### **3.3.3. General functioning**

General level of functioning were screened using Global Assessment of Functions Scale for symptom and function, split version (GAF-S and GAF-F; DSM-IV; APA, 2000). The scale is presented and described in the DSM-IV. The split version of GAF is divided in one version for functioning and one for symptomatology.

#### **3.3.4. Demographics**

Education level was classified by means of The International Standard Classification of Education (ISCED; UNESCO, 1997) in addition to years of education.

General medical and psychiatric background, demographic information, number of past episodes of recurrent major depression, age of onset and family medical and psychiatric history were screened using a semi-structured interview developed by P. Lyche (2006) based on the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994) and a semi-structured screening-instrument for recurrent depressive episodes and length of episodes developed by Biringier (2005) (See Appendix 1).

### **3.4. General cognitive measures**

General cognitive functioning was estimated from the mean of two subtests from the Wechsler Adult Intelligence Scale Third edition (WAIS-III); Picture Completion (PC) and Similarities (SI) (Wechsler, 1999). The two subtests were thought to represent the verbal and performance aspect of general cognitive functioning and are highly correlated with their respective indexes that is Perceptual organization index (POI) and Verbal comprehension index (VCI), whereas POI and VCI together are, according to Egeland et al. (2009) considered an adequate alternative measure of general cognitive functioning. We are aware that most studies rely on other subtests like Verbal Comprehension as a resistant measure when it comes to measuring premorbid intellectual functioning in i.e. brain injured patients. But our rationale was that the dyad VIQ (Verbal Comprehension) and PIQ (Perceptual organization), that represent the most and second most reliable index, were adequate when we in our study needed a time effective measurement of general cognitive functioning in the clinical groups MDD and MDDA, that we assume do not affect intellectual functioning directly like other clinical groups. We also choose SI and PC as representative subtests to estimate general cognitive functioning/intelligence due to the adequate correlations with VIQ (.76) and PIQ (.56), and the time aspect, respectively.

**Table 1. Demographic and clinical characteristics**

Table 1 displays descriptives of mean values (M) and standard deviations (SD) on demographic and clinical characteristics.

	<b>MDD (n=37)</b>		<b>MDDA (n=24)</b>		<b>HC (n=92)</b>	
	<b>M</b>	<b>SD</b>	<b>M</b>	<b>SD</b>	<b>M</b>	<b>SD</b>
<b>Age (years)</b>	44.2	12.3	35.5	14.2	35.7	12.0
<b>Age range (min - max)</b>	18.0	60.0	18.5	60.0	19.0	61.0
<b>Education (years)</b>	15.8	3.2	13.5	2.3	16.4	2.5
<b>BDI-II</b>	21.3	11.1	25.4	7.4	2.1	2.7
<b>BAI</b>	11.7	8.3	18.7	6.7	2.1	2.5
<b>Symptom-GAF</b>	60.2	12.1	53.8	8.5	95.6	7.3
<b>Function -GAF</b>	63.6	13.8	55.2	10.1	96.7	5.6
<b>General Cognitive Functioning</b>	11.1	2.1	9.3	2.6	12.2	2.5
<b>Age of Onset first MDD episode</b>	33.5	14.4	30.1	16.1		
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
<b>Gender</b>						
<b>Male</b>	14	37.8	11	45.8	29	31.5
<b>Female</b>	23	62.2	13	54.2	63	68.5
<b>Handedness</b>						
<b>Right</b>	35	94.6	24	100	81	88
<b>Left</b>	1	2.7	0	0	11	12
<b>Ambidextrous</b>	1	2.7	0	0	0	0

*Note. MDD = Unipolar Major depressive disorder, MDDA = MDD with co-morbid anxiety Disorder, HC = Healthy controls, BDI-II = Beck Depression Inventory-II, BAI = Beck Anxiety Inventory, GAF = Global Assessment Scale (Symptom and Function; DSM-IV), General cognitive functioning estimated from WAIS-III subtests; Picture Completion and Similarities.*

### 3.5. Neuropsychological assessment

All participants underwent a battery of neuropsychological tests and paradigms administered by a trained test technician or a clinical psychologist trained in standardized assessment. Most tests are traditional neuropsychological tests that possess acceptable psychometric properties and have both extensive empirical and are theoretically based. Subjects were tested individually in well suited locations. Approximate total time required for clinical evaluation and neuropsychological testing varied from 3 hours up to 7 hours depending on different factors. Neuropsychological tests were applied, which according to research, have been found to measure cognitive functions that often are impaired in MDD and MDDA. The tests load on the main cognitive domains: attention, memory and executive functions and the subfunctions involved.



### 3.5.1. ANT

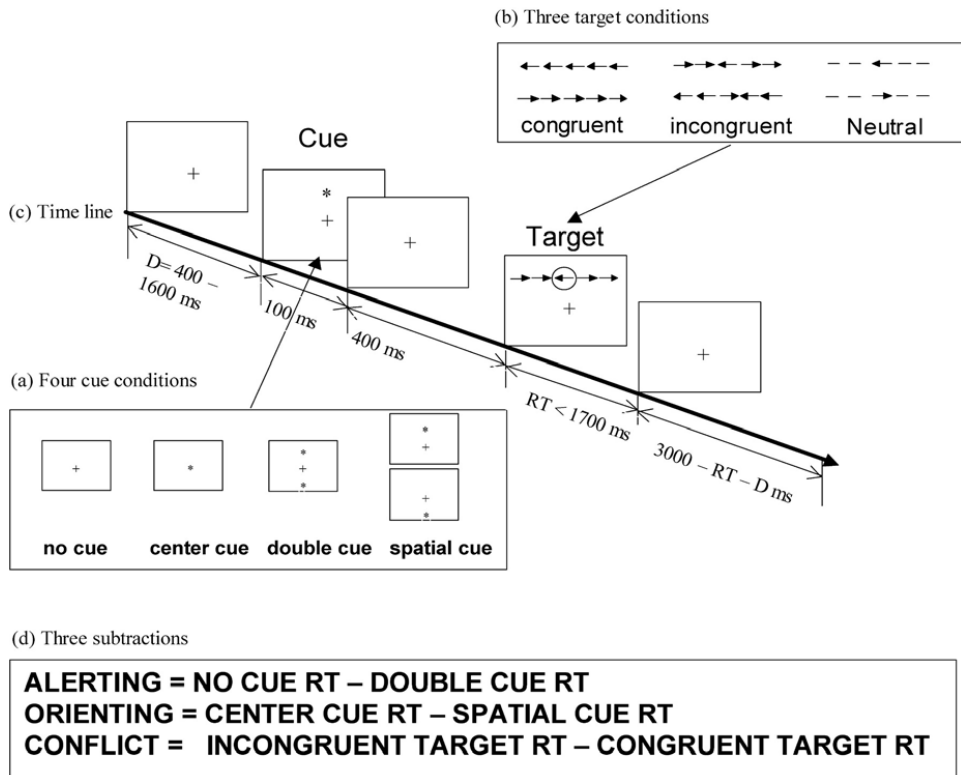
By including Stroop and ANT we intended to tap both higher-level cognitive effortful functions as well as more basic level attentional functions derived from Posner's cognitive model. The Attention Network Task (ANT; Fan et al., 2002) was developed as a way to operationalize and measure the efficiency of each of the proposed networks; alerting, orienting and executive attention, within a single non-verbal task.

In the experimental ANT paradigm, one of four possible cues precedes a target arrow surrounded by congruent and incongruent arrows. Orthogonal subtraction scores provide a measure of each network (See Fig 1d). Participants are shown the successive presented stimuli on a computer screen and there are 4 cue conditions and 3 target conditions, as shown in Fig 1a and 1b. Stimuli consisted of a row of 5 visually presented horizontal black lines, with arrowheads pointing leftward or rightward. The target was a leftward or rightward arrowhead at the centre. Subjects respond on buttons on keyboard, depending on the direction of the target arrows in the centre. The target arrows are flanked by neutral, congruent or incongruent distracters (conflict). Before presentation of the target, subjects are either given a spatial cue (orienting), a centre temporal cue (alerting) or no cue (control condition). In the congruent condition, all 5 arrows point in the same direction. In the incongruent condition, the arrows that flank the target point in the opposite direction to the target arrow. Thus, there is response conflict in the incongruent condition, but not in the congruent condition. In the neutral condition, no flanker arrows appear. When the target display appears, the task is to indicate as fast and accurately as possible which way the target arrow is pointing. RT is recorded to the nearest millisecond.

Efficiency of the alerting network is examined by changes in RT resulting from a warning signal. Efficiency of orienting is examined by changes in RT that accompany cues indicating where the target will occur. The efficiency of the executive network is examined by requiring the subject to respond by pressing two keys indicating the direction (left or right) of a central arrow surrounded by congruent, incongruent or neutral flankers.

ANT consisted of a 24 trial practice block and three experimental blocks of trials. Each block consisted of 96 trials. The presentation of trials was in random order (See fig 1a-d)

**Fig 1 a-d.**



(<http://www.sacklerinstitute.org/users/jin.fan/>; 2010).

### 3.5.2. D-KEFS Color-Word Interference Paradigm (Stroop)

A paradigm often used to study attention is the Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test (Stroop) (Delis et al., 2001; Stroop 1935).

Stroop is designed to measure higher level attentional control/executive control of attention by involvement of conflict. The D-KEFS paradigm is proposed to measure executive control of attention by involvement of conflict. The task requires response to one aspect of a stimulus, while ignoring a more dominant aspect. The Stroop effect refers to the difference in color-naming performance between congruent (e.g. the word green printed in green color) and incongruent (e.g. the word green printed in red color) stimuli. The D-KEFS Stroop test consists of four trials, the first two consisting of reading words and naming the colors of words, respectively. The latter two are the incongruent task (conflict/inhibition) where the word and color are different, and the participant is to name the color of the word, and the last trial uses the same principle as the former but with some words enclosed within boxes which

then requires the participant to read the word instead of the printed color (switching/inhibition). There are four primary outcome variables based on reaction time (RT). There are also three primary contrast scores that may be computed, namely: inhibition versus color naming, switching/inhibition versus combined color and word naming, and switching/inhibition versus inhibition. Two additional contrast scores are also included: switching/inhibition versus color, and switching/inhibition versus word. Age effects are associated with trial 3 and 4, therefore all 4 outcome variables are standardized age-corrected scaled scores based on response time.

### **3.5.3. The Paced Auditory Serial Addition Test (PASAT)**

The Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977) was chosen to measure the executive control of WM. PASAT is a test measuring working memory or working attention. The processing requires processing speed, attention and working memory capacity in accordance with CE function (Baddeley, 1986). In the present version, translated into Norwegian language and audiotaped by Landrø (Landrø et al., 2004), the subjects listen to an audiotape where 60 digits are read successive in a 2 second rate/2 second stimulus-interval. Instructions to the subjects are to add each one-digit number presented every 2 second to the immediately presented digit preceding it and orally present the sum to the administrator. Dependent variables are Total correct answers, Total Errors and Total number of No answers.

### **3.5.4. Hopkins Verbal Learning Test (HVLT-R)**

To operationalize short term (STM) and long term memory functions (LTM) we choose Hopkins Verbal Learning Test (HVLT-R; Benedict et al., 1998) in this study, due to the high reliability and validity of the task supported by many studies.

HVLT (Brandt, 1991) is considered a conventional neuropsychological method that taps verbal memory, and is divided into immediate recall, delayed recall and recognition. The HVLT revised version in this study consists of immediate recall/learning, delayed recall and recognition. HVLT-R is considered a conventional neuropsychological method. The test is administered in paper-and-pencil format. The test begins with three learning trials; 12 words are read aloud by the examiner at a rate of seconds, and the subject is asked to freely recall them immediately after reading, and not consider the proper succession in which they were read. The 12 words are grouped in taxonomic categories with 4 words from each of three semantic categories. The words recalled for each trial were recorded and total recall score recorded for the 3 trials. The 3 free recall trials were 20-25 minutes later followed by a

delayed recall trial (Trial 4), were the participants were asked to recall as many of the words from trial 1-3. Immediately following trial 4, a forced-choice recognition test is administered (Trial 5). In trial 5, a list of 24 words is read aloud (including 12 target words and 12 distracters) and the participant is then asked to answer yes/no if the words were one of the 12 from the previously target list words. The dependent variables (in addition to recognition) were a) verbal learning (sum of trials 1-3), b) retention/delayed recall and c) recognition ability. The former two variables (Immediate Recall and Delayed recall) were transformed into standard scores (T-scores) that are corrected for potential age differences.

### **3.5.5. CANTAB**

The Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition, 2006) is comprised of computerized neuropsychological tests that examine various areas of cognitive function. The CANTAB tests are simple, computerized, non-linguistic and culturally blind, and allow us to break down executive control functions into cognitive components in order to define more readily which functions are impaired or spared. Three subtests from the CANTAB battery were selected and administered in Paper III; ID/ED, SWM and SST, which correspond to the three functional areas according to Miyake et al.'s (2000) non-unitary model of executive functions, namely shifting (ID/ED), updating (SWM) and inhibition (SST), respectively.

In addition; a motor screening test (MOT) was administered in the beginning of the test session and serves as a simple introduction to the touch screen for the subject. If a subject is unable to comply with the simple requirements of this test it is unlikely that they will be able to complete other tests successfully. This test therefore screens for visual, movement and comprehension difficulties. Administration time is around 3 minutes. This test has two outcome measures which measure the subject's speed of response and the accuracy of the subject's pointing

#### **3.5.5.1. ID/ED**

The Intra-Extra Dimensional set-shift task (ID/ED) is a test of rule acquisition and reversal. The task assesses the ability to maintain attention to different examples within a stimulus dimension (ID stages), and the ability to shift attention to a previously irrelevant stimulus dimension (ED shifts) across nine stages. Subjects proceed to the next stage when a criterion of six consecutive correct responses has been reached.

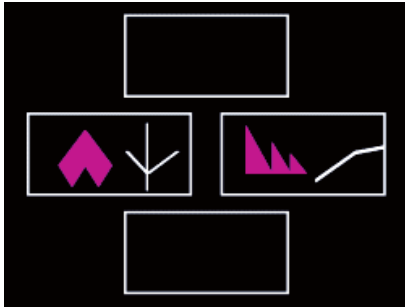
Stimuli consist of four rectangular boxes—to the top and bottom and to the right and left of centre, appear on the screen. Two of these contain the test stimuli, but the boxes used changes from trial to trial. Two artificial dimensions are used in the test: colour-filled shapes (purple) and white lines (see fig.2) Simple stimuli are made up of just one of these dimensions, whereas compound stimuli are made up of both, namely white lines overlying colour-filled shapes.

The subject starts by seeing two simple colour-filled shapes, and must learn which one is correct by touching it (simple discrimination which varies just along one of the two dimensions). Feedback for responses are in the form of the words correct and wrong, presented respectively in green and red lettering above the middle two boxes and teaches the subject which stimulus is correct, and after six correct responses, the stimuli and/or rules are changed. Subjects progress through the test by satisfying a set criterion of learning at each stage (6 consecutive correct responses). If at any stage the subject fails to reach this criterion after 50 trials, the test terminates.) The test proceeds through a number of stages, each with a different contingency, up to a maximum of nine. For each, continuation to the next stage is dependent on a criterion of six successive correct discriminations being reached (Robbins et al., 1998; Downes et al., 1989).

Following the initial simple discrimination (SD), in the remaining subsequent eight stages the contingencies are reversed (i.e. the previously correct response becomes incorrect and vice versa) and in the third stage the second dimension the compound stimulus (each dimension paired together) is introduced in two of the response boxes.

For this and all subsequent stages, exemplars of the different dimensions were paired in a pseudo-random fashion so that all four possible compound stimuli were used, with the constraint that runs of no more than three trials with the same pairings were allowed, but with reversals and new exemplars of both dimensions introduced; the intradimensional shift (IDS), but the relevant dimension (i.e. shapes or lines) was unchanged from stage 1. (Every new stimulus can be regarded as IDS). For the penultimate stage, the extradimensional shift (EDS), new exemplars were again introduced, but success at this point depended on the participant shifting response set to the exemplars of the previously irrelevant dimension. The two performance variables of interest are the number of stages completed, and the total error score adjusted for whether the entire task is completed (Kaplan et al., 2006).

**Figure 2:**

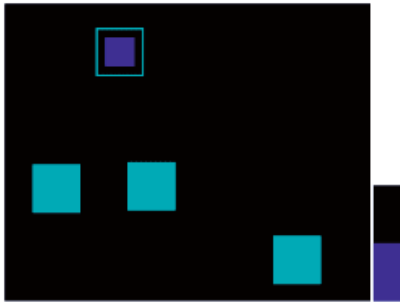


### 3.5.5.2. SWM

Spatial Working Memory (SWM) is a test of the subject's ability to retain spatial information and to manipulate remembered items in working memory. It is a self-ordered task which requires subjects to search for hidden “tokens” within a spatial array of coloured boxes. By touching the boxes and using a process of elimination, the subject should find one blue ‘token’ in each of a number of boxes, and then use them to fill up an empty column on the right hand side of the screen (see fig.3). The number of boxes is gradually increased until it is necessary to search a total of eight boxes. The colour and position of the boxes used are changed from trial to trial in order to discourage the use of stereotyped search strategies. The participants were instructed that at any one time there would be a single token hidden inside one of the boxes. Their task was to search until they found it, at which point the next token would be hidden. The key instruction was that, once a blue token had been found within a particular box, that box would not be used again to hide a token for that particular trial. Since every box was used once, the total number of blue tokens to be found on each trial corresponded to the number of boxes on the screen.

Outcome measures of interest are a “between” errors score, which is calculated when a subject returns to a square where a token was already found in a previous trial. This assesses the accuracy of working memory, as a strategy measure is derived; i.e. a subject’s ability to adopt a systematic search strategy: a lower strategy score reflects more efficient task performance on SWM (Owen et al., 1990; Weiland-Fiedler et al., 2004).

**Figure 3:**



### 3.5.5.3. SST

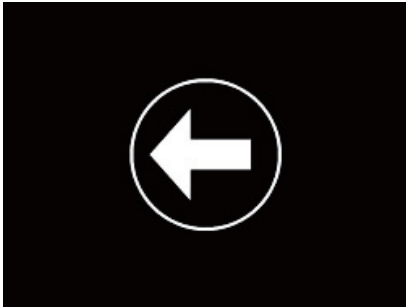
The Stop Signal Task (SST) is a classic stop signal response inhibition test (Logan et al., 1984; Logan et al., 1997; Osman et al., 1986). It uses staircase functions to generate an estimate of stop signal reaction time. The test gives a measure of an individual's ability to inhibit a prepotent response. The term "response inhibition" refers to cognitive processes enabling executive control over prepotent responses in accordance with changing situational demands.

The test was administered on a laptop computer connected to two external speakers and a two-button press pad. SST consists of two parts. In the first part, the subject is introduced to the press pad, and told to press the left hand button when they see a left-pointing arrow and the right hand button when they see a right-pointing arrow. There is one block of 16 trials for the subject to practice this. This practice is used to build up a prepotent response.

In the second part, the subject is told to continue pressing the buttons on the press pad when they see the arrows, as before, but, if they hear an auditory signal (a beep) emitted randomly from the computer, they are instructed not to respond/ withhold their response and not press the button (i.e. inhibit the prepotent response). They are further instructed that they will not always be able to stop, but sometimes they will, and encouraged to try their best (see fig.4)

The main outcome variable of interest for our purpose is the stop signal reaction time (SSRT), which is an estimate of the subject's response time to the stop signal, i.e. the time it takes to react to the *stop* signal by inhibiting the prepotent response to the *go* signal (i.e. the time required to inhibit a response after it has been initiated). SSRT is estimated by subtracting Stop signal delay (SSD) from mean Go signal reaction time (RTonGT).

**Figure 4:**



#### **3.5.5.4. Psychomotor speed**

In addition to the main variable of inhibition on the SST task, an outcome measure of reaction time on Go trials (GoRT), an indicator of psychomotor speed, was included.



### **3.6. Statistical analyses**

Data analysis was completed by means of SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) for Papers I-III.

#### **3.6.1. Demographic variables**

A series of one-way analyses of variance (ANOVAs) and Chi-square tests was conducted to compare the three groups across the demographic variables: age, education level, general cognitive functioning, gender, handedness and age of onset first depressive episode, followed by post hoc tests with Bonferroni corrections to determine which groups differed.

#### **3.6.2. Paper I.**

There were conducted two multivariate analysis of covariance (MANCOVA), followed by separate ANCOVAS and post hoc tests with Bonferroni corrections to compare the two clinical groups (MDD, MDDA) and HC with ANT and Stroop as dependent variables. The dependent variables were measured at an individual level, while simultaneously controlling for age, gender and education level and adjusted for multiple comparisons with Bonferroni corrections. Median RTs for each cue type and flanker type were calculated for each participant, and Alerting, Orienting and Executive attention were calculated. Analysis of variance (ANOVA) was performed to compare the MDD and MDDA groups on the effect of number of earlier depressive episodes. In addition, Pearson correlations between scores on BDI and BAI and the dependent variables for the clinical groups were performed.

#### **3.6.3. Paper II**

There were conducted two multivariate analysis of covariance (MANCOVA), followed by separate ANCOVAS and post hoc tests with Bonferroni corrections to compare the two clinical groups (MDD, MDDA) and the HC group with HVLT and PASAT as the dependent variables. The dependent variables were measured at an individual level, while simultaneously controlling for age, gender and education level and adjusted for multiple comparisons with Bonferroni corrections. We also performed pairwise comparisons between the two clinical groups without adjusting for the family-wise error rate. Analysis of variance (ANOVA) was performed in the following to compare the MDD and MDDA subjects with respect the effect of number of earlier depressive episodes, in addition to a Pearson's correlations between scores on BDI and BAI and the dependent variables, and between PASAT and HVLT-R T-scores for the clinical groups.

### **3.6.4. Paper III**

Multivariate analysis of covariance (MANCOVA) was first used to compare the two clinical groups (MDD and MDDA) and the healthy controls (HC) on the combined score of the six dependent variables measured at the individual level: ID/ED stages completed, ID/ED Total errors adjusted, SWM strategy, SWM between errors, SST RT on Go trials, and SST SSRT, while simultaneously controlling for age, gender and education level adjusted for multiple comparisons with Bonferroni corrections. Follow-up univariate analysis of covariance (ANCOVA) was then performed to detect which of the six dependent variables the three groups differed significantly from each other in mean scores. Finally, ANCOVAs was also used to compare the MDD group and the MDDA group on the six dependent variables controlling for the number of earlier depressive episodes and age of onset of first depressive episode. In addition, Pearson correlations between scores on BDI and BAI and the dependent variables for the clinical groups were performed.

### **3.7. Ethical considerations**

The study was approved by the Regional Committee for Medical Research Ethics, Norwegian Social Science Data Services (NSD) and adhered to the Helsinki Convention. Written informed consent was obtained from all participants after provision of a complete written and oral description of the study. They were informed that at any time, without any explanation they could withdraw from the study. There were no participants that withdrew during the study.

None of the participants were in a patient relationship with the researcher and test administrators. As a service for participation the participants and their therapists were given the opportunity to receive an individual report of their results, both written and oral. This was done directly to the participant, but also often together with their therapist, depending on the participants wishes.

A dilemma that concerns the use of diagnostic interviews and self report questionnaires regarding the healthy comparison subjects may be that they uncover symptoms and experiences they were not prepared to uncover or discuss. However, they were all informed about the instruments beforehand, about the anonymity and the right to withdraw at any moment without any explanation. In addition, the test administrators were prepared to handle these situations as professional clinical psychologists, and when needed guide and help the participants for further treatment.

## 4.0. RESULTS

### 4.1. Demographic results for Papers I-III

Differences between the groups were found regarding age [ $F(2, 152)=6.637$ ;  $p<.01$ ], education level (ISCED) [ $F(2, 152)= 9.67$  ;  $p< .001$ ] and general cognitive functioning (WAIS-MEAN) [ $F(2, 152)= 14.055$ ;  $p< .001$ ]. There were no significant between-group differences in terms of gender distribution [ $\chi^2(2) = 1.85, p= 0.397$ ] and handedness [ $\chi^2(4) = 8.60, p= 0.072$ ].

The patients with MDD differed significantly from the HC group regarding age, the mean age being older for MDD. The MDDA group differed significantly from the MDD group, the mean age being younger for the former. There were no statistical differences in age between MDDA and HC. According to general cognitive functioning, the MDDA group had significantly lower mean than HC and MDD. The MDDA differed significantly from the HC group regarding education level, the former having lower mean educational level. Since educational level and estimated general cognitive functioning was correlated we did not enter the latter in the MANCOVA. Although there was a significant difference between the co-morbid group and healthy controls on the general cognitive measure, the patients nevertheless performed well within the normal range. As compared to the formal norms the performance level equals less than one-third of a standard deviation from the mean.

As for the facets: number of depressive episodes, age of onset first depressive episode and depressive and anxiety symptom severity; there were no significant group differences between the two clinical groups MDD and MDDA regarding age of onset first depressive episode. (There are nine missing values in the MDD group and four missing values in the MDDA group, due to difficulties in gaining accurate information about age of onset from these subjects), neither did the groups differ significantly regarding number of depressive episodes. The MDD and MDDA groups did not differ significantly on depressive symptoms measured with BDI-II, but MDDA had a higher score on BAI than MDD [ $F(2, 151) = 115.259, p< 0.001$ ].

Furthermore, we performed ANCOVA's to test whether there was a difference between MDD and MDDA on the dependent variables (ANT, Stroop, PASAT, HVLT, CANTAB-variables) respectively, when controlling for number of earlier depressive episodes and age of onset first depressive episode. Our results show that neither number of episodes nor age of onset of first depressive episode significantly related to performance on either of the

dependent performances. The exception was on the variable Word in Stroop, but since this variable did not show significant differences between the diagnostic groups, this may indicate that the number of episodes may be independent of diagnosis. Hence, including number of depressive episodes and age of onset as covariates in the analyses, did not alter the results, i.e., there were no significant differences in mean scores on the dependent variables between the two groups.

Regarding symptom severity, we performed correlations between scores on BDI-II and BAI and the dependent variables for both the MDD and MDDA groups. The correlations between scores on BDI-II and BAI and the dependent variables showed no significant correlations between BDI-II on any of the variables on ANT and Stroop, but BAI correlated with Alerting ( $r = -.281, p < .05$ ) and Orienting ( $r = -.277, p < .05$ ) on ANT, and with Inhibition ( $r = -.268, p < .05$ ) on Stroop. Both BDI-II and BAI correlated significantly with the variables Total correct (BDI:  $r = -.286, p < .05$ ; BAI:  $r = -.360, p < .01$ ) and No answer (BDI:  $r = .259, p < .05$ ; BAI:  $r = .354, p < .01$ ) on PASAT. BDI correlated significantly with Immediate Recall ( $r = -.284, p = .05$ ), and both BDI and BAI correlated significantly with Delayed recall (BDI:  $r = -.384, p < .01$ ; BAI:  $r = -.339, p < .01$ ) on HVLT. There were no other significant correlations between BDI-II and BAI on any of the other variables for the two groups.

#### **4.2. Neuropsychological results Paper I**

The MANCOVA showed a significant overall group difference in performance on the Stroop task regarding the four primary outcome variables,  $F(8, 290) = 3.44, p = .001$ . Follow-up ANCOVAs and post hoc tests demonstrated significant differences for the variables Color, Inhibition, and Switching. The MDDA group had significantly longer RT than HC on Color, Inhibition, and Switching, and significantly longer RT on Switching than the MDD group. There were no other statistically significant differences between any of the groups on the variables. When using the three primary and two additional contrast scores, the MANCOVA showed a significant overall group difference in performance,  $F(12, 286) = 2.916, p = .001$ . Follow-up ANCOVAs and post hoc tests demonstrated significant differences between MDDA and HC on the primary contrast scores: Switching versus a combined Color-Word score, Switching versus Inhibition, and the additional contrast scores: Switching versus Color and Switching versus Word. There were no other statistically significant differences between any of the groups.

Regarding performance on the ANT, the MANCOVA showed a significant overall group difference,  $F(8, 276) = 3.300, p < .002$ . Follow-up ANCOVAs and post hoc tests demonstrated

significant differences regarding the variable Alerting: MDD showed significantly higher RT compared with HC. There were no statistically significant differences between any of the groups on the variables Orienting, Executive, and Overall Accuracy. The standard deviation on all of the four ANT measures was substantially larger in the two clinical groups when compared with HC. This meant that the assumption of homogeneity of variance did not hold. Logarithmic transformation of all five dependent variables and the exclusion of two outliers in the clinical groups produced acceptable values for the test of homogeneity of variance on all dependent variables. Repeating the above mentioned analyses using the transformed dependent variables gave the same conclusion in terms of the statistical significance of the group differences and the post hoc test, that is, a significant group difference on Alerting ( $F = 8.66, p < .001$ ), and the MDD showing significantly higher RT compared with HC. In addition, a Kruskal–Wallis nonparametric test for differences between the groups was also performed. This gave the same conclusion.

#### **4.3. Neuropsychological results Paper II**

MANCOVA demonstrated significant overall group differences in performance on PASAT [ $F(6, 288)=4.452, p < .001$ ]. Follow-up ANCOVAs and post-hoc tests demonstrated significant differences regarding the variables Total correct and No answer, where the clinical groups MDD and MDDA performed with fewer Total correct answers and more cases of No answers compared to the HC group. There were no other statistically significant differences between any of the groups on the variable errors. The standard deviation on all three dependent variables on PASAT was substantially larger in the two clinical groups compared to the HC group. This meant that the assumption of homogeneity of variance did not hold. Logarithmic transformation of all three dependent variables produced non-significant values for the test of homogeneity of variance on all dependent variables. Repeating the above-mentioned analyses using the transformed dependent variables resulted in the same conclusion in terms of the statistical significance of the group differences. No outliers were found within any of the three groups.

Since we had a priori hypothesis concerning the differences between the two clinical groups, Bonferroni corrections may be too conservative. Therefore, we also performed pairwise comparisons between the two clinical groups without adjusting for the family-wise error rate. The results of these comparisons revealed that the MDDA group had a significantly lower score on Total correct answers ( $p = .040$ , two-tailed) and a nearly significant lower score on errors ( $p = .053$ , two-tailed) compared to the MDD group.

The MANCOVA did not demonstrate a significant overall group difference in performance on HVLТ [F(6, 292)= 1.574,  $p = .171$ ]. However, due to the expected direction of the results, we performed follow-up ANCOVAs and post-hoc tests. The results demonstrated that there were near-significant overall group differences for variables Delayed Recall ( $p = .051$ ) and Recognition ( $p = .058$ ). Post-hoc tests demonstrated that the MDDA group showed trends toward lower scores compared to the HC group on variables Delayed Recall ( $p = .050$ ) and Recognition ( $p = .052$ ). There were no statistically significant differences between any of the groups for the variable Immediate Recall. As previously mentioned, Bonferroni corrections may be too conservative in situations where a priori hypotheses concerning group differences are present. Therefore, we also performed pairwise comparisons without adjusting for the family-wise error rate. The results revealed no significant differences between the two MDD and MDDA clinical groups on any of the HVLТ variables, but they confirmed significant differences between the MDDA and HC group for Delayed Recall ( $p = .017$ , two-tailed) and Recognition ( $p = .017$ , two-tailed).

#### **4.4. Neuropsychological results Paper III**

The MANCOVA demonstrated a significant overall group difference in performance on the CANTAB tests [ $F(12, 284) = 2370, p < 0.01$ ] Follow-up ANCOVAs and post hoc tests demonstrated significant differences between the MDDA group and HC on two of the dependent variables: ID/ED total errors adjusted and SWM between errors. The MDDA group performed the tasks with more errors than the HC. There were significant differences between the MDD group and the HC group on SST RT on Go Trials. MDD performed the task with slower psychomotor speed compared to the HC group. There were no statistical significant differences between the clinical groups on any of the other variables.

A significant Pearson correlation was found for the MDDA group between BAI and ID/ED; total errors adjusted ( $r = 0.48, p < 0.05$ ). There were other no significant correlations for the SWM; between errors, and no significant correlations were found between BDI and the two CANTAB measures regarding the MDDA group.

## 5.0 SUMMARY OF PAPERS

### 5.1. Paper I

**Background:** The aim of this study was to explore if the divergent results regarding attentional functions in patients with mood disorders are due to selective impairments in higher level or more basic and distinctive attentional subcomponents. **Method:** We compared out-patients with current MDD (n=37) and MDD with co-morbid anxiety (MDDA) (n=24), to healthy controls (n=92) on Stroop and Attentional Network Test. **Results:** The current data indicate that significant impairment in attentional functions correspond with the presence of MDD and MDDA. MDDA displayed significantly impaired performance on Stroop variables, and MDD were significantly impaired in the Alerting function in ANT. Number of episodes, age of onset first depressive episode was not significantly related to performance on neither Stroop nor ANT variables. Symptom severity measured with BDI-II did not correlate significantly with any of the dependent variables, but BAI correlated significantly with Alerting and Orienting on ANT, and with Inhibition on Stroop.

**Conclusion:** These results show impairments on different levels of attention in mood disorders. MDDA show impairments on higher level executive attention functions and MDD display deficit at a more basic attentional level. The findings suggest that including co-morbid anxiety in MDD is imperative for future research.

### 5.2. Paper II

**Background:** The aim of this study was to examine both executive control of verbal working memory and verbal learning as well as long-term storage function. **Method:** We compared outpatients with current MDD (n=37) and MDD with co-morbid anxiety (MDDA; n=24) to healthy controls (n=92) on PASAT and HVL T. **Results:** Both patient groups showed impaired working memory test performance compared to healthy controls. Patients with MDDA performed significantly below the MDD group. Only patients with MDDA displayed deficient long-term memory function compared to healthy controls. Number of episodes and age of onset first depressive episode were not significantly related to performance on neither PASAT nor HVL T variables. Both BDI-II and BAI correlated significantly with the variables Total correct and No answer on PASAT. BDI correlated significantly with Immediate Recall, and both BDI and BAI correlated significantly with Delayed recall on HVL T.

**Conclusion:** The present results show impairments in various memory functions in patients presenting depression and depression with co-morbid anxiety disorder.

### 5.3. Paper III

**Background:** Impaired cognitive control functions have been demonstrated in both major depression (MDD) and anxiety disorder (A), but few studies have systematically examined the impact of MDD with co-morbid A (MDDA), which is the main aim of this study.

**Method:** We compared patients with MDD ( $n=37$ ) and MDD with co-morbid anxiety (MDDA;  $n = 24$ ) to a group of healthy controls (HC;  $n = 92$ ) on three subtests from the Cambridge Neuropsychological Test Automated Battery; intra–extra dimensional set –shift task, stop signal task, and spatial working memory. These tasks correspond to a theoretical model consisting of three separable but interrelated executive control functions: Shifting, Inhibition, and Updating. A simple psychomotor speed measure was also included. **Results:** After controlling for age, gender, and education level, the results showed that the MDDA group displayed significantly impaired performance on the functions Shifting and Updating compared to HC. There emerged no significant differences between any of the patient groups and HC regarding Inhibition. The pure MDD group did not display dysfunctions relative to the HC group on the main executive control variables, but displayed slowed psychomotor speed. Contrary to expectation there were no significant differences between the MDDA and the MDD groups. Number of episodes, age of onset first depressive episode were not significantly related to performance on any of the dependent variables. Symptom severity measured with BDI-II and BAI did not correlate significantly with any of the variables for the clinical groups combined. **Conclusion:** Co-morbid anxiety should be taken into account when studying cognitive control functions in major depression.



## 6.0. DISCUSSION

The present work is based on a study of neuropsychological functioning in patients with unipolar major depression with and without co-morbid anxiety disorders compared to healthy controls. The neuropsychological test battery consisted of tests chosen to explore selective functions that have shown divergent results in the research field regarding MDD, and that have been little investigated as regards to MDDA. The focus has been basic and distinctive attentional subcomponents to different levels of memory functions and to subcomponents of higher level executive functions. Although the presents study presents some potential limitations, it contributes knowledge to the existing contradictory and sparse literature of understanding neuropsychological performance in patients with MDD and co-morbid anxiety disorders. In addition we also wanted to determine whether cognitive deficits vary as a function of characteristics such as number of depressive episodes, symptom severity and age of onset first depressive episode.

### 6.1. Discussion of the main findings

The aim of paper I was to investigate if the divergent results in studies of attention in MDD and MDDA are due to impairments in distinctive attentional subcomponents and/or that the patient groups display impairments on different levels of attention. Our results showed that MDD and MDDA exhibit impairments at different levels of attention and on specific subcomponents. MDD displayed impairment on the basic level subfunction: alerting, whereas MDDA showed specific impairments in the higher level attentional functions of Switching and switching/inhibition compared to HC. Differences between MDD and MDDA were only found regarding switching/inhibition. These results show the specific effects of co-morbid anxiety on attentional functioning in MDD. Furthermore, the results support the “cognitive effort”-hypothesis and contradicts the “cognitive speed”-hypothesis in that it is specifically the higher level switching/Inhibition component that is affected in MDDA compared to MDD, not any of the other more basic variables.

In paper II, the aim was to examine different verbal memory functions, from the central executive aspects of WM to learning and LTM. The results showed that both patient groups show impairments in different memory functions in that they displayed WM deficits compared to HC, with MDDA performing significantly worse than MDD. Only the MDDA group displayed deficits in LTM compared to HC. These results reflect the effect that co-

morbid anxiety has on different verbal memory functions in MDD. It seems that it is the anxiety component in the MDDA group that contribute to deficits in LTM and to the worse performance than MDD regarding WM. These results are also in line with the cognitive effort-hypothesis, in that MDDA showed a specific deficit in a more higher-order function and worse deficit than MDD in WM. As regards to working memory, WM dysfunctions in MDD patients have been reported in other studies (Landrø et al., 2001; Pealecke-Habermann et al., 2005; Porter et al., 2003) and a recent review has highlighted deficits in WM as central in MDD (DeBattista, 2005). Our results show that when the anxiety component is added, the effect on WM capacity is worse than in MDD alone.

In Paper III we investigated three separable higher-order executive control functions according to Miyake et al.'s (2000) theoretical and empirical based model. We found that only MDDA showed impaired performance on two of the subfunctions; Shifting and Updating, whereas MDD only displayed slowed psychomotor speed compared to HC. This adds information to the existing contradictory literature, regarding MDD where both presence of inhibition deficits (Lampe et al., 2004; Paelecke-Habermann et al., 2005) and no deficits have been found (Degl'Innocenti et al., 1998). The mixed findings may, according to our results, be due to unaccounted for co-morbid anxiety in MDD.

To sum up papers I-III: MDD showed basic attention deficits, working memory deficits and slowed psychomotor speed compared to healthy controls. MDDA showed deficits in working memory, long term memory, higher order attentional control functions (switching/inhibition) and the executive subfunctions inhibition and updating compared to healthy controls. MDDA compared to MDD, showed deficits in switching/inhibition, and worse performance in working memory than MDD.

The present study support the notion that the co-morbidity of MDD and A may contribute to enhanced neuropsychological impairment. Where some studies find that the pure MDD and anxiety disorders do not exhibit significant impairments, it seems that it may be the presence of co-occurrence of these two disorders that increases the likelihood of cognitive dysfunctions in patients with MDDA.

The results also confirm earlier findings that patients with current MDD show impairments regarding basic level attention (Alerting), working memory and psychomotor retardation compared to healthy controls. This is in line with Reppermund et al. (2009), that found no selective or specific deficits, but merely a generalized, unspecific impairment profile in depression, whereas a high number of the patients were impaired in basic attentional tasks (e.g. 56% in alertness). They propose that due to the interrelations between cognitive

processes, these attentional deficits might be responsible for impairments in other cognitive domains. They propose the notion that if a sufficient attentional level cannot be reached or maintained, a global unspecific reduction of performance in all cognitive domains may result and are in line with the final common pathway disorder hypothesis proposed by Mialet et al. (1996) and Zihl et al. (1998).

Regarding MDDA, these results adds knowledge to the existing literature, by contradicting the findings of no group differences by Castaneda et al. (2010) and Herrera-Gusmàn et al. (2009), but supporting both Basso et al's. (2007) and Airaksinen et al's. (2004) findings that both MDD and MDDA showed worse memory functions than HC, but MDDA significant worse than the other groups. Basso et al. (2007) found that executive function was specific to the MDDA group, in accordance with our results. However, we did only find the MDD group to show psychomotor slowing and not MDDA as in Basso et al's study. That MDDA performed worse than MDD on higher order functions and did not show psychomotor slowing as MDD did, may be due to the impact that the co-morbid anxiety disorder in MDD has on the central executive attention in WM, and minor impact from differences in information-speed processing. Another argument is that anxiety patients often exhibit a fear of new or unfamiliar situations, and that the test-situation itself is sufficiently threatening to arouse a significantly greater amount of manifest anxiety in the MDDA group than in the MDD group. Hence, the anxiety component may then contribute to increased information processing speed/acceleration and the depression component to decreased speed, so that in the MDDA group these inverse tendencies may have been counterbalanced.

WM may be sensitive to information-processing speed, but the comparisons between MDDA and MDD still show that MDDA have significant lower scores than MDD, hence that we consider this to be due mainly to dysfunction in the CE aspect of WM in MDDA and less impaired information-processing speed. Miyake et al's. (2000) approach focusing on the sub functions of executive control functions, are related to the goal-directed attentional system and to the central executive earlier proposed by i.e. Baddeley et al. (1986) and Norman and Shallice, (1986; SAS). Eysenck et al. (2007) suggest that both inhibition and shifting involves using attentional control, except updating which they consider not to be directly concerned with attentional control. However, the three separable but highly inter-related functions proposed by Miyake et al. (2000) are also partially interdependent in their functioning, suggesting they all rely to some extent on the resources of the central executive or top-down attentional system (Eysenck et al., 2007). Relating this to our results, there seem to be only the impairments in the MDDA group that are directly related to higher level executive

control. Still, the differences in results across studies regarding which EF components that are spared or affected in MDD and MDDA may be due to methodological problems related to differences in e.g. operationalizations of EF subcomponents.

Effortful processing or cognitive load may broadly be related to the executive control of WM, or at a more basic level, the load on working memory in a task. So, the effort-hypothesis may explain our results regarding MDD as well as the MDDA. Lower level basic automatic functions, as opposed to higher-level effortful functions that require more cognitive load and effort, may be viewed as processing stages where the higher level functions are dependent on the lower level subfunctions.

Up to date, a consistent and clear-cut profile of cognitive impairments has not been established, and Mialet et al. (1996) have in a meta-analysis therefore interpreted the rather unspecific and contradictory cognitive deficit pattern in depression as a “final common pathway”-disorder, and highlight the role of attention and its executive components. The assumption is that there are supramodal functional networks that are affected and which represents the highest and final level of integration of regional cognitive networks subserving e.g. information processing, attention and memory. Support for this theory comes from imaging studies (Kane & Engle, 2002) and from studies on depressed subjects where it has been shown that PFC plays the dominant role as a final common pathway (Austin et al., 2001; Rogers et al., 2004). Cognitive processing is seen in a diagram as a hierarchy, where EF exhibits the highest level and includes tertiary integrations areas in the brain. Memory (WM, learning, recall) exhibits medium level and secondary integrations areas in the brain, whereas both dependent on primary functions such as alertness, attention and activation. Working memory is often regarded as a factor in EF. WM is an active system that manipulates information necessary for other more complex and higher order functions, and good WM function often correlates with good function in other cognitive domains.

Knudsen (2007) also provides a conceptual framework that proposes four fundamental processes to attention that each makes a distinct and essential contribution. Three voluntary control attentional processes: working memory, top-down sensitivity control and competitive selection operating in a recurrent loop, in addition to an automatic bottom-up filtering for salient stimuli. WM and attention are according to this model inextricably inter-related. WM represents the objects of attention and comprises of competitive processes where multiple types of information compete for full control of the circuitry underlying WM, that are widely distributed in the brain with the PFC acting as an executive controller. According to Knudsen (2007), a benefit of this framework is in interpreting the symptoms of which many disorders

may affect attention in different ways. Relating this to the results in our study, it seems that what differentiate MDDA and MDD is the way MDDA affects WM and top-down competitive selection, whereas MDD affects more bottom-up processes.

In our study we included patients with different co-morbid anxiety subtypes, and this may contribute to the discussion if the interaction of different anxiety subtypes and MDD may give influence on the mixed results in the field. However, we thought it reasonable to aggregate patients with different anxiety disorders in the MDDA group for the purpose of this research. Despite the heterogeneity and the different diagnostic subclassifications among anxiety disorders, much is shared between them. Anxiety disorders, according to LeDoux (1996) all share an experience of anxious distress, avoidance of situations that provoke such distress and anxiety symptomatology is commonly shared between these disorders (Kruger & Finger, 2001; Basso et al., 2007). High rates of shared symptom variance exist among these even with administration of structured diagnostic interviews and psychometrical pure self-report measures (Mineka et al, 1996; Basso et al 2007). Neural substrates of the fear response are also presumed to be uniform across anxiety disorders (LeDoux, 1996). Up to date, there are only a few studies that address the neuropsychological functioning in a variety of anxiety subtypes, and evidence from this research presents a mixed pattern of results (Airaksinen et al., 2005). The inconsistent and mixed results regarding anxiety subtypes may be due to the heterogeneity of the syndromes itself, and/or the high rate of co-morbidity that makes it difficult to obtain a “pure” sample.

Neither number of depressive episodes nor age of onset did affect the significant variables in our study, and this contradicts studies which show that both number of episodes and early age of onset for first depressive episode have shown to affect cognition in mood disorders (Basso & Bornstein, 1999b; Fossati et al., 2004; Paelecke-Habermann et al., 2005; Grant et al., 2001; Kessing, 1998; Castaneda et al., 2008; Castaneda et al., 2010). However, the literature is comprised of rather mixed results, and our findings are in line with Grant et al. (2000) Reisches & Neu (2000) and Lampe et al. (2004). There are number of reasons why the database regarding cognitive functions and number of episodes is inconsistent, and additional risk factors may have had an impact in our study and also regarding the inconsistencies in the research field; length of first episode, loss events, genetic vulnerability, family history and previous hospitalization, information that we did not control for. Previous studies have typically not controlled age of onset and risk for recurrent depressive episode simultaneously, and since they are moderately correlated and therefore not synonymous, this may be the reason for the mixed and often conflicting results.

Depression and anxiety symptom severity, measured with BDI-II and BAI, both correlated with variables related to WM functions and long term memory functions. BDI correlated with Immediate recall and BAI with Alerting and Orienting and with Inhibition. Thus, even though our main focus was syndrome/diagnosis, it seems that symptom severity of depressive and anxiety may account for some of the variance. As mentioned earlier, the discussion whether cognitive dysfunction represent symptom or syndrome factors or an interaction is still under discussion.

## **6.2. Possible implications of the findings for models of depression and anxiety**

There are several discussions about the relationship between depression and anxiety in regards to differences and/or similarities; whether MDDA may represent a quantitatively and/or qualitatively distinct clinical group from pure depression and anxiety. Or as the notion says: “a whole is different from the sum in parts”.

Regarding the relation between depression and anxiety, Hirschfeld (2001) states that both disorders are manifestations of a single disorder. Is one disorder an epiphenomenon of the other? Numerous studies have documented the negative consequences of co-morbidity of MDD and anxiety on aspects at the symptomatic level and psychopathology; higher severity of illness, course, chronicity, recovery and relapse rates, suicide rates, psychosocial impairment and greater impairment of work functioning and higher hospitalization rate, while other studies report no effects of the co-occurrence of the two disorders. Tarsia et al. (2003) even suggest that mixed anxiety-depression may represent a distinct entity in which cognitive functions differ from that in both MDD and anxiety disorders.

The controversy between unitary versus dual models have been replaced by a more nuanced view where both disorders are posited to have both shared, common components and specific, unique components. Mineka et al. (1998) proposed an integrative hierarchical model in response to evidence of the substantial co-morbidity between mood and anxiety disorders. In the model each syndrome contains both a common and unique component. The shared component represents broad individual differences in general distress and negative emotionality. In addition, each disorder also includes a unique component that differentiates it from all the others. For instance, low positive emotionality is positioned to be specific to depression whereas autonomic arousal is characteristic to panic disorder (Gamez et al., 2007). Other comparable findings of similarities of both types of disorders in addition to several common symptoms have been proposed. Depression and anxiety share a genetic vulnerability linked to the serotonin- and norepinephrine-system, a shared association between a

polymorphism in the serotonin transporter gene (5-HTT-LPR) and the personality trait of neuroticism has also been reported (Munafò et al., 2006). This also gives susceptibility to the same pharmacological treatment suggesting a similar underlying dysfunction (den Boer et al., 2001). In addition to these similar risk factors and gender distribution (Pèlissolo & Lèpine, 2001), other neuronal substrates have also been proposed as common for affective disorders. Anderson (2010) suggests four key brain regions involved in affective disorders: a) Orbital prefrontal cortex (OPFC) and the Ventromedial prefrontal cortex (VMPFC), b) Dorsolateral prefrontal cortex (DLPFC), c) Hippocampus and Amygdala and d) Anterior Cingulate Cortex (ACC). Phenotypically the affective disorders are considered to have both common and distinct features. Common are their shared mood/emotion component and shared negative affect. Distinctions have been made regarding symptomatic heterogeneity, and that MDD show mood congruent memory biases, whereas anxiety display attention biases for threatening information. MDD have been linked to feelings of loss and hopelessness, while anxiety to threat and helplessness, consistent with findings of anticipated threat /danger in anxiety and major loss event in the past for depressive (Beck & Emery, 1985; Brown & Harris, 1993; Mineka et al., 1998). Also, abnormalities in the regulatory mechanisms of the gamma-aminobutyric acid (GABA) have been implicated due to response to treatment with benzodiazepines in anxiety (Kirkwood & Hayes, 2005). As mentioned, Osuch et al. (2000) used PET and found difference in patterns of cerebral metabolism between depression and anxiety symptom severity; this may imply that co-morbid depression and anxiety may exert neurobehavioral effects that differ from those observed in depression and anxiety alone. In line with Mineka et al.'s (1998) quantitative approach and demonstrating that the size of general distress/negative affectivity component differs markedly across symptoms and disorders, Watson & Clark (2006) address the atheoretical DSM system and suggests a reorganization of the diagnostic classes and implementation of fully dimensional scheme that move away from the purely descriptive schemes to a system that reflects the more underlying causes of psychopathology e.g. genetics. As an example they suggest that generalized anxiety disorder (GAD) would be placed within the same diagnostic class as MDD, based on evidence of similarity; phenotypically (e.g. Krueger, 2001) and genotypically (Kendler et al., 2003). In line with this, a study by Gamez, Watson, & Doebbeling (2007) suggests that both GAD and PTSD have more in common with MDD than with their anxiety counterparts. The model (see fig. 5) illustrates how the mood and anxiety disorders might be reorganized. They further argue that the new scheme will model co-morbidity directly: strongly correlated syndromes are placed together, making it easier for clinicians and researchers to incorporate

co-morbidity. Also, the problem of within-disorders heterogeneity can be bypassed by adopting a fully dimensional taxonomy, according to Watson & Clark (2006).

**Figure 5:**

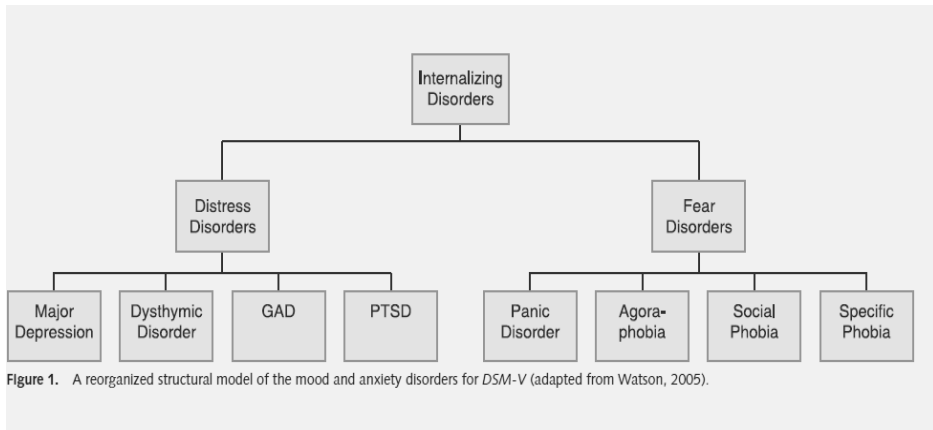


Figure 1. A reorganized structural model of the mood and anxiety disorders for DSM-V (adapted from Watson, 2005).

According to this model an alternative empirically based taxonomy of the mood and anxiety disorders will be replaced by distress and fear disorders under the umbrella term Internalizing disorders, which better captures co-morbidity as opposed to separation of mood and anxiety disorders. Moreover, they argue that both mood and anxiety disorders are strongly related, and should not be artificially separated into different diagnostic classes like in DSM diagnoses that they consider to be a pseudo-hierarchical, rational folk system that do not reflect highly co-morbid disorders.

In a more recent article, Watson (2009) reviews past and more contemporary models of the relation between depression and anxiety, and ends up with synthesizing the evidence into a quadripartite model that is supposed to represent the best aspects of these. In short, the model demonstrates that two quantitative elements need to be considered when analyzing the properties of symptoms – the level of specificity and the magnitude of the general distress variance. These elements can then be used to organise relevant symptoms into four groups that reflect varying combinations of distress and specificity (Watson, 2009). The use of theory-driven analyses and the quadripartite model may be a tool to properly address and understand the marked heterogeneity both between and within disorders like depression and anxiety that may be the cause of different cognitive impairments and lack of consensus across studies.

Can the constellation of findings shed light on these issues?

Our findings indicate that there may be the combination of syndrome MDD and A that result in many of the cognitive impairments seen in the literature regarding MDD. Some of the



results are in accordance with a continuum model, where the MDD group can be placed between the HC and the MDDA groups with respect to neuropsychological functioning. On the other hand, there are also some indications of more basic, qualitative differences between MDD and MDDA along the bottom-up versus top-down dimension. However, the relation between aspects of neuropsychological functioning and overarching models of psychopathology is complex and should be more focused on in future research.

### **6.3. General methodological considerations**

The inconsistent findings across studies in the research field may to a degree be explained by differences in study populations and measurement. The main findings in this thesis are not an exception. A number of potential methodological issues are related to sample characteristics, assessment measures and possible confounding variables that may threaten the interpretations and generalizability of the current findings.

#### **6.3.1. External validity**

We aimed for a clinical sample representative for subjects in an outpatient setting both regarding MDD and MDDA. Given the high prevalence rate in the population, the majority that seek professional help end up in a setting as polyclinical outpatients, not inpatients.

Outpatients are also considered less severely ill than inpatients and thus more representative for a larger part of the population. Inpatients are also more likely than outpatients to display impaired cognitive function (Basso et al., 2007). Still, clinical samples versus population-based samples may represent more selected and hence more severe. The sample of healthy controls, without any history of psychiatry and consisting of subjects interested in participating in a study focusing on cognitive functioning, is probably not representative for the general population in that they may represent an above average level of functioning and education level. The general high level of education in all the samples may be a problem concerning generalizability to other populations, especially internationally. Norwegians are, due to international standards, highly educated in general.

The male-female ratio regarding MDD was as expected, as there are twice as much women seeking treatment for depression symptoms, whereas the ratio in MDDA was almost equal. The healthy control group had a similar proportion of female-male-ratio as the MDD group. Regarding representative considerations and selection biases, the patients participating in this study are patients that are in therapy and/or medicated. Patients that most often seek treatment and also see the advantage in participating in this kind of research project are often patients

with complaints and cognitive problems that affect their daily lives and occupation. The participants were given the opportunity for feedback regarding the test results by the test administrator, either alone or together with their therapist.

The patients were recruited through outpatient clinics in Oslo and close areas, mostly through written information from their therapist, or from posters hanging in the waiting area in the clinics they were attending. Hence, there was a majority of recruitment through information from the therapist, but they contacted us in a mix between getting an appointment through the therapist or through direct phonecalls to the administrators. So, it is difficult to know exactly the distribution of the “pure” self-referrals. Regarding the healthy controls, the majority were self-referrals.

One of the strengths in our study is the reliability of the patients’ diagnoses. Clinical and diagnostic assessment was made in accordance with the structured clinical interviews for DSM-IV criteria (SCID). Both SCID-I and SCID-II were used by trained professional clinical psychologists. In addition, to increase the inter-rater reliability, the rating was blindly repeated using the original audio taped interviews, by an external experienced and certified clinical psychologist who was unaware as to whether the participants were HC, MDD, or MDDA. All diagnoses were current.

Another strength is the exclusion of psychosis, bipolar, neurological disorders, drug/OTC/alcohol-abuse and melancholic participants, characteristics that are associated with increased morbidity and hence impaired cognitive functions (Basso et al., 2007; Austin et al., 2001; Basso & Bornstein, 1999a; McCall & Dunn, 2003; Stordal et al., 2004).

Potential limitations regarding number of recurrent depressive episodes and age on onset for first depressive episode because they may be subject to information bias. This information was collected via self-report, and the specific age and number of episodes were at times difficult for the patients to pinpoint exactly. This may lead to misclassification in that the patients could be prone to both under- and over-estimating, thus resulting in inaccuracy regarding number and age. The heterogeneity of the anxiety disorders in our study may be both a strength in that it mirrors a clinical population that often exhibit a range of different anxiety disorders, but limits the results in that, even though the research on anxiety disorders have concentrated on few subtypes and therefore little is known about all subtypes, different anxiety disorders have shown to have different impact on cognitive functions. Therefore, different combinations of diagnosis interactions between MDD and different anxiety subtypes may give different and specific neuropsychological deficits. Due to low numbers, no subdivisions were made of the anxiety disorders in our study.

### 6.3.2. Possible confounding factors

The possible confounding factors age, gender, education level, general cognitive functioning (IQ estimate), depressive and anxiety symptom, level age of onset first depressive episode and number of recurrent depressive episodes were controlled for in the analyses. Some baseline demographic variables differed between the groups: age, education level and general cognitive functioning (IQ). Nonetheless, education, age, number of depressive episodes, age of onset and gender failed to account for significant variance in the multivariate analyses of neuropsychological test performance. The MDDA and HC groups did not differ in age, but the MDD group differed significantly, the age being older than the HC group. Importantly, the MDDA group did not differ in age from HC and the age being younger than the MDD group.

Estimating the general cognitive functioning (IQ) is an important confounding factor in the association between psychiatric disorders and neuropsychological functions (Lezak, 2004). Since, education level and general cognitive functioning correlated, we did not enter the latter in our analyses, but controlled for education level. Even if the MDDA group had significant lower mean regarding IQ than both HC and MDD, and lower education level than the HC group, the MDDA group still performed within the normal range.

Differences in estimated IQ between clinical and healthy control samples represents a theoretically and statistically challenge in general. To what extent these group differences is a result of sampling error or a difference accounted for by the diagnoses itself, is an important issue to address. That MDDA represents a more severe symptomatology, more psychosocial strain and in general reduction in many domains, may lead one to conclude that with this follow the reduction of general cognitive functioning. One possibility could have been to match the groups on IQ, but then important information about the MDDA group would have been lacking.

Possible effects of medication are also one confounding factor that must be addressed. The proportion of the patients in each of the two the clinical groups that were using SSRI/SNRI may be considered fairly representative for the clinical population at large, with a larger proportion in the MDDA group, as expected. The proportion in the groups regarding use of SSRI/SNRI was MDD=13 out of 37 and MDDA=11 out of 24. There are however opposing views to whether medication have effects on cognitive test performance or not, and if un-medicated patients show more impaired cognition than medicated patients (Den Hartog et al., 2003). Some studies suggest that medication may enhance cognition in MDD (Fergusson et al., 2003), but that the effects on MDDA may be different than for MDD (Herrera-Guzmán et

al., 2009). Other studies suggest that modern antidepressants do not have deleterious effects on cognitive test performance (Den Hartog et al., 2003). However, the proportion of subjects in each clinical group in our study currently on medication may be considered fairly representative of the clinical population of MDD and MDDA. Thus the significant results in our study should not be an artefact of medication.

Still, there may be many other factors that could potentially confound to the association between MDD, MDDA and neuropsychological functioning. To mention a few characteristics we did not control for: work status, sleep disturbances, motivation for the test situation, level of physical activity, personality traits and coping abilities. In addition, effects of severity and length of depressive disorders, combinations of different anxiety diagnoses in the MDDA group, patient subgroups regarding subtypes and duration of depression in both MDD and MDDA were also not controlled for. All these potentially confounding factors may exist independently of depression and anxiety or MDDA, or as parts of vulnerability present which could also lead to poorer test performance.

### **6.3.3. Measurement and operationalizations of neuropsychological functions**

In the current study, the neuropsychological tests were grouped in domains a priori; this was due to the hypothesis based on earlier findings. Still, the selection of which test used in the study is not unproblematic because many of the functions are closely related and traditionally the same tests have been used do measure the same functions. Furthermore, the considerable diversity of tests used in different studies also complicate the comparability of results. Also, intercorrelations (overlap) between constructs (dimensions) of neuropsychological function are substantial. In our study, we tried to minimize this by using tests that assess the subfunctions of the construct at hand, that is, to divide the constructs into the basic components that the theoretically and empirically based models are suggesting.

The construction of the test battery used in the papers are based on theory and research traditions, and that seek out to assess basic level attentional subfunctions based on Posner's model (1990), to working memory functions according to Baddeley & Hitch's (1986) model, and last; executive control subfunctions with tests corresponding with Miyake et al's. (2000) model.

The cognitive functions were operationalized into tests based on theoretical foundations in addition to traditional empirical based neuropsychological tests. The tests were both computer based and pen/paper-tests, culture free and representative for the functions we wanted to study. To use single tests to measure neuropsychological performance and create profiles, are

traditionally used in clinical practice to create cognitive profiles. The overlap of many of the dimensions/functions that these often broad tests measure may lower the reliability. Theoretically, the operationalizations of the constructs in our study that are based on single tests that tap different variables, may lower the reliability, and cautions should be made when interpreting the results based on these single variables because confidence intervals often overlap. Another concern about this approach in this study is the risk of committing Type I error when multiple comparisons are performed. Results from the research literature are often based on analyses from many single tasks, and statistical significant results on one or few associations may then be subject to over-interpretation. To correct this, we performed Bonferroni corrections in all our analyses.

#### **6.3.4. Statistics**

In our study we corrected for multiple comparisons by post hoc adjustment with Bonferroni corrections to avoid Type I errors. The use of Bonferroni corrections in our study may be too conservative since we had a priori hypothesis concerning the difference between the two clinical groups, and between the clinical versus the healthy control group. We therefore performed a pairwise comparison without adjusting for the family-wise error rate between the two clinical groups regarding the dependent variables.

Most studies that investigate the difference between patients with psychiatric disorders and healthy controls with regards to neuropsychological functioning base their findings on significance testing. However, in significant testing the p-value do not provide the magnitude of difference between groups, in addition to that the differences in means between the groups do not distinguish whether they apply to all participants in the groups or to subgroups within the groups. Even though there were no outliers that could explain the variance between the groups in our study, there could still be factors that testing of significance do not detect. Due to relatively small sample sizes in our study, there is a risk for Type II errors, that is, lower possibility of positive findings. That our study generated statistical significant differences between the groups on several variables, may be seen as strength for the results. Importantly, statistical significance does not automatically imply clinical significance, and the results should be addressed accordingly.

#### **6.4. Clinical implications**

Many patients with diagnosable mood disorders have co-morbid anxiety, characterized by a severe and persistent clinical course that makes diagnosis and treatment challenging (Kuzel,

2005; Brown et al., 2005). Higher rates of healthcare use and costs are also associated with co-morbidity because these patients have more psychological, physical, and social impairment than those with either disorder alone (Kuzel, 2005; Brown et al., 2005). It is crucial for clinicians to recognize both anxiety and depression early in the clinical course and institute appropriate therapy aimed at making the patient well (i.e. achieving full remission) rather than merely improving symptoms. Patients with co-morbid anxiety and depression tend to discontinue treatment earlier than those with depression alone, and MDD accompanied by high levels of anxiety symptoms have been shown to be significantly less likely to benefit from anti-depressant medication of any kind (Fava et al., 2008) in addition to that they may not respond as robustly to conventional treatments (Kuzel, 2005; Brown et al., 2005). The introduction of newer classes of antidepressants that exhibit both robust antidepressant and anxiolytic effects has provided the ability to treat both disorders with a single medication, and therefore it is vital to be aware of the high rate of patients that exhibit both disorders, and the effect this co-morbidity have on cognitive difficulties in their everyday lives (Howland & Thase, 2005). In addition, MDDA are more likely be unemployed, have less education, more severe depression, suicidal thoughts and in general more co-existing illnesses. Fava et al. (2008) states that “Clinicians should be aware of a patient’s sociodemographic situation and take note of co-occurring anxiety along with depression. The combination likely warrants a more personalized treatment approach”.

Neuropsychological functions, and hence neuropsychological testing of these functions has clinical implications for the therapist and patient. It provides important additional information about daily functioning to adjust and fit the therapeutic process and goals according to the additional information about the individual patient’s neuropsychological functional profile and deficits. In addition, neuropsychological characteristics may be predictors of SSRI treatment response, where lowered level of functioning have been found in e.g. working memory and executive functions in non-responders to SSRI (Gorlyn et al., 2008).

### **6.5. Future perspectives**

Future research should focus on examining the effects of co-morbidity between different subtypes of the depression spectrum and anxiety subtypes to examine whether there are specific combinations or subtypes that are more prone to neuropsychological deficits than others. Whether effects of number of recurrent episodes, age of onset, family history, euthymic phases or current diagnosis (state/trait), medication versus non-medicated patients, and/or in/outpatients/population-based samples, are important issues to address to shed light

on the specific associations between these psychiatric disorders and neuropsychological functioning.

In addition, future studies should also undertake to specify the cognitive functions and corresponding tests, to help pinpoint the more basic underlying functions that may be the contributors to the higher level functions that are often seen impaired in both MDD and MDDA.

## **7.0. CONCLUSIONS**

### **7.1. Paper I**

Patients with MDD displayed impairment in basic level attention subfunction Alerting, whereas MDDA showed specific impairments in top-down/higher level attentional functions.

### **7.2. Paper II**

Both MDD and MDDA showed impaired WM, but MDDA performed significantly below MDD. Only MDDA displayed deficient verbal LTM.

### **7.3. Paper III**

Patients with MDDA demonstrated selective deficits in the executive control functions; Shifting and Updating, whereas MDD displayed psychomotor slowing.

### **In sum:**

These findings imply that the presence of co-morbid anxiety disorders in MDD may be a risk for more severe neuropsychological dysfunction. This may in turn indicate higher morbidity, poorer response to medication and psychotherapy, poorer ability to manage daily living and activities such as work and hence impaired occupational status.



## 8.0. ERRATA

### 1.

Paper I and II: Method section, Participants:  $n= 165$  shall be changed to  $n=153$ .

This error was due to not changing the number of healthy control participants we started with before we did a double-check and found that due to our exclusion criteria's we had to exclude 12 participants. Unfortunately we did not change this in the articles.

### 2.

Paper I: In the Abstract, it states HC ( $n=92$ ). This should be changed to  $n= 91$ , which is the correct number of HC participants.

### 3.

In paper I, Results section, first line, there shall be written three groups, not four groups as stated.

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## PAPERS I-III

















# Cognitive control functions in unipolar major depression with and without co-morbid anxiety disorder

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**Background:** Impaired cognitive control functions have been demonstrated in both major depression (MDD) and anxiety disorder (A), but few studies have systematically examined the impact of MDD with co-morbid A (MDDA), which is the main aim of this study. **Method:** We compared patients with MDD with (MDDA;  $n = 24$ ) and without co-morbid A ( $n = 37$ ) to a group of healthy controls (HC;  $n = 92$ ) on three subtests from the Cambridge Neuropsychological Test Automated Battery; intra-extra dimensional, stop signal task, and spatial working memory. These tasks correspond to a theoretical model consisting of three separable but interrelated executive control functions: Shifting, Inhibition, and Updating. A simple psychomotor speed measure was also included. **Results:** After controlling for age, gender, and education level, the results showed that the MDDA group displayed significantly impaired performance on the functions Shifting and Updating compared to HC. There emerged no significant differences between any of the patient groups and HC regarding Inhibition. The pure MDD group did not display dysfunctions relative to the HC group on the main executive control variables, but displayed slowed psychomotor speed. Contrary to expectation there were no significant differences between the MDDA and the MDD groups. **Conclusion:** Co-morbid anxiety should be taken into account when studying cognitive control functions in major depression.

**Keywords:** unipolar major depression, co-morbid anxiety disorder, cognitive control functions, CANTAB

## INTRODUCTION

Depressive disorders present a significant mental health concern to individuals and to our society. It is estimated that mood disorders will be the most frequent cause of serious health problems worldwide in 2020 (WHO). The lifetime risk for major depressive disorder (MDD) is between 10 and 25% for women and between 5 and 12% for men (American Psychiatric Association, 1994).

Affective neuroscience research has been increasingly focusing on cognitive or executive control processes (for a review, see Ochsner and Gross, 2005). Investigations of executive control functions are in general relevant across a range of psychiatric disorders, like schizophrenia (Wilmsmeier et al., 2010), obsessive compulsive disorder (Olley et al., 2007), and bipolar disorder (Daban et al., 2006). Although these disorders share a common deficit in executive functions, a main issue is to what degree there are differences and similarities along various dimensions of executive functions across such disorders.

Retarded psychomotor speed, as measured by simple reaction time tests, was traditionally considered a basic clinical characteristic of unipolar MDD. Although slowed reactions obviously are a relevant aspect of the neuropsychological profile in depression (Egeland et al., 2005), associated cognitive dysfunctions cover a broad range (Burt et al., 1995; Christensen et al., 1997; Kindermann and Brown, 1997; Veiel, 1997; Austin et al., 2001; Landrø et al., 2001; Porter et al., 2007). Impaired executive cognitive control functions seems to be particularly salient (Austin et al., 2001; Rogers et al.,

2004; Levin et al., 2007; Porter et al., 2007 for reviews). The few studies distinguishing between unipolar and bipolar depressed patients have not displayed a consistent picture (Gruber et al., 2007) but impaired inhibitory control seem to be more pronounced in bipolar versus MDD patients.

Findings link cognitive control deficits in MDD to increase in negative affect (McNeely et al., 2005; Dennis and Chen, 2007), a tendency to ruminate (Nolen-Hoeksema, 1991), increasing number of depressive episodes (Vanderhasselt and De Raedt, 2009), and a family history of depression in children (Perez-Edgar et al., 2006; Vanderhasselt and De Raedt, 2009).

Cognitive control embodies the ability to organize incoming stimuli and inhibit a dominant response in order to perform a subdominant response (MacLeod et al., 2002). However, executive functions are complex, and because they manifest themselves by operating on other cognitive processes, this implicates other cognitive processes not directly relevant to the target executive function, hence “the task impurity problem” (Philips, 1997). Executive tasks have also tended to suffer from relatively low internal and/or test-retest reliability (Denckla, 1996; Rabbit, 1997; Miyake et al., 2000), and widely used and accepted tests like, i.e., WCST and TOH have based their construct validity on loose criteria such as “sensitive to frontal lobe damage.” The complexity of the construct is also reflected in the myriad of terms and definitions used to characterize executive control functions in addition to the tests used to measure them.

In an attempt to minimize the task impurity problem, Miyake et al. (2000) used latent variable analysis to determine to what extent different executive processes can be considered to be unitary (in the sense that they are reflections of the same underlying mechanism or ability) or non-unitary. They focused on the following three basic executive functions: (1) shifting between tasks or mental sets, (2) inhibition of dominant or prepotent responses, and (3) updating and monitoring the contents of working memory. Confirmatory factor analysis indicated that these three executive processes, although moderately correlated with one another, are clearly separable. The model proposes relatively circumscribed lower (basic) level functions compared to many of the wider and higher level definitions and general measures of executive functioning, thus allowing precision as to which cognitive control functions are affected and which are not. However, neuropsychological studies of mood disorders based on an empirically based model of basic executive control functions are relatively sparse.

There is extensive co-morbidity between MDD and other affective disorders, especially anxiety disorders (A), regarding phenomenological features as well as neuropsychological functioning. Individuals with depression and co-morbid anxiety disorders occur in from 25 to 60% of cases, and are associated with increased severity, greater chronicity, slower recovery, increased rates of recurrence, greater risk for suicide, and greater psychosocial disability (Cameron et al., 2004; Leonardo and Hen, 2006).

Anxiety can potentially confound or contribute to neuropsychological impairments or anatomic changes in depressed individuals (Cameron et al., 2004; Leonardo and Hen, 2006), and is in general associated with heightened distractibility, poor concentration, and increased responsivity to potential threat (Bishop et al., 2004b). Several studies have demonstrated neuropsychological deficits involving, i.e., executive function, attention, working memory, and attentional control to threat-related stimuli in anxiety disorders (Broadbent et al., 1986; Asmundson et al., 1994; Cohen et al., 1996; Vasterling et al., 2000; Lautenbacher et al., 2002; Danckwerts and Leatham, 2003; Ludewig et al., 2003; Bishop et al., 2004b; Basso et al., 2007). The latter have been demonstrated with emotional Stroop (Mathews et al., 1997) and associated with deficits that are particular to the execution of attentional inhibition (Fox, 1994). This impaired cognitive control over threat-related distractors has also been supported by fMRI studies (Bishop et al., 2004a).

The effects of co-morbid anxiety in MDD have been systematically investigated in only a few studies. It has been suggested that executive dysfunction and psychomotor slowing are specific to the depressed group with co-morbid anxiety (Basso et al., 2007). The latter group also displayed more impaired scores than both "pure" MDD and HC. The limitations of this study are mainly the reliability of patient diagnoses; the data were collected retrospectively from available records, and the diagnoses lacked a structural diagnostic interview. The patient sample also consisted entirely of inpatients, and the literature suggests that inpatients are more severely impaired than outpatients (Burt et al., 1995; Christensen et al., 1997; Veiel, 1997). Corroborating these results, a recent study concluded that the strongest predictor of poor cognitive performance in depression was psychiatric co-morbidity (Baune et al., 2009). The co-morbid group showed decreased cognitive performance in visuospatial and language domains and in total score on the repeatable battery for

the assessment of neuropsychological status (RBANS) in relation to the pure depression group. They found no relevant differences in mean scores for the depressed group in the study and the depressed group in the RBANS validation study. However, the inclusion of a healthy control group would give an indication of how the clinical groups differ compared to a healthy population.

On the other hand, in a review Levin et al. (2007) states that when the noise introduced by unassessed co-morbid anxiety is successfully addressed, executive function impairments specific to depression can account for many of the cognitive deficits identified. Similarly, within the context of a population based sample it was found that the subgroups of MDD and MDD with co-morbid Axis I disorder did not differ on any of the cognitive measures assessed, and conclude that psychiatric co-morbidity may not aggravate cognitive functioning among depressed young adults (Castaneda et al., 2009).

While a substantial number of patients with MDD have co-morbid anxiety that possibly contributes to cognitive impairments, most patients with MDD also experience recurrent episodes. Research on the possible effects of number of episodes on cognition has yielded inconsistent results regarding whether number of recurrent depressive episodes confounds with increased cognitive impairment or not (Veiel, 1997; Basso and Bornstein, 1999; Stordal et al., 2004). In light of the previous limited research, inconsistent results and clinical importance, there is a vital need for further research to address these issues.

Although a considerable body of research documents that children of depressed parents exhibit higher rates of mood disorders than comparison groups (see Klimes-Dougan et al., 2006), there are only a few studies that have been directed toward examining neurocognitive functioning in this risk group. One of few studies that examined family history and executive functions is Klimes-Dougan et al. (2006) who studied neuropsychological functioning in offspring of parents with a history of mood disorders and found deficits in, e.g., executive functioning in BPD offspring compared to offspring of well mothers. Deficits were not found for children of MDD mothers. Still, heritability is estimated as high as 70%. Characteristics that have generally been shown to predict a larger increase in risk to their relatives are, e.g., recurrent episodes (Sullivan et al., 2000) and earlier age at onset (see review by Levinson et al., 2003).

The main aim of this study was to investigate basic components of cognitive control functions in patients with MDD with or without co-morbid anxiety disorders, and compare to a healthy control group. Consistent with prior research regarding neurocognition in affective disorders, we expected both patient groups to perform worse than the HC, but that the MDDA group would perform worse than the MDD without anxiety. Possible effect of number of depressive episodes and age of onset first depressive episode was also investigated.

## MATERIALS AND METHODS

The study was approved by the Regional Committee for Medical Research Ethics, Norwegian Social Science Data Services (NSD) and adhered to the Helsinki Convention.

Written informed consent was obtained after the participants had been provided with a complete description of the study.

## PARTICIPANTS

A total of 165 subjects were included in the study. From this sample, 61 fulfilled the criteria for current primary non-psychotic unipolar major depression (MDD), according to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders for Axis I (DSM-IV; APA, 1994). Of these 24 subjects fulfilled the MDD criteria with co-morbid anxiety disorder, whereas 37 had no co-morbid anxiety disorder.

The distribution of the anxiety subtypes for the MDDA group was: GAD = 3, SP = 13, OCD = 4, PTSD = 2, panic with agoraphobia = 6, panic without agoraphobia = 4, specific phobia = 3, anxiety NOS = 2. Fourteen patients had one anxiety diagnosis, and 10 patients had two or three anxiety disorders.

The proportion of patients medicated in each group was: MDD (SSRI = 12, SNRI = 1) and MDDA (SSRI = 9, SNRI = 2). In the MDD group, 24 were unmedicated and there were 13 unmedicated in the MDDA group. The HC group was unmedicated.

The number of depressive episodes was distributed as follows for the MDD group: 1 episode (the current one) = 20, 2 = 5, 3 = 3, 4 = 2, 5 = 2, 6 = 1, 10 = 2, 40 = 2. For the MDDA group: 1 episode (the current one) = 12, 2 = 3, 3 = 2, 4 = 1, 6 = 1, 10 = 1, 15 = 1, above 50 episodes = 3. The MDD group had one with dysthymia (i.e., "double-depression"), and the MDDA group had 2 with dysthymia (i.e., "double-depression"). All the subjects in the MDD and MDDA group had a non-melancholic subtype. The distribution of family history of depression versus no history, were as follows: HC (77/15), MDD (4/33), and MDDA (6/18).

The patients were recruited from psychiatric clinics for outpatients in the Oslo and Trondheim area. Inclusion criteria were: to be fluent in Norwegian, and to be taking no medication other than SSRI/SNRI. The subjects were required to be medication-fasting the day of testing. General exclusion criteria were: a history of neurological disorders, bipolar, psychosis, drug/alcohol-abuse including non-prescription OTC drugs. Two participants were excluded due to scaled score  $\leq 4$  on the Wechsler Adult Intelligence Scale Third edition (WAIS-III) subtest Similarities. For comparison, 91 healthy controls (HC) were selected from an original sample of 125 subjects. They were recruited via newspaper ads, posters and through various private companies in the Oslo region. They were screened for psychopathology using SCID-I and SCID-II. Thirty-three subjects were excluded from the original sample of 125 due to the following criteria: brain injury exceeding 30 min. loss of consciousness ( $n = 2$ ), BDI  $\geq 10$  ( $n = 9$ ), weekly alcohol intake  $>15$  IU ( $n = 1$ ), daily use of drugs ( $n = 1$ ), and personality disorder (according to DSM-IV; SCID-II;  $n = 2$ ). Furthermore, 18 participants were excluded who had had one or more depressive episodes in the past.

## CLINICAL EVALUATION

Clinical and diagnostic assessment was made in accordance with the structured clinical interviews for DSM-IV criteria (SCID). Both SCID-I and SCID-II were used by trained professional clinical psychologists. In addition, the rating was blindly repeated using the original audio taped interviews, by an external experienced clinical psychologist who was unaware as to whether the participants were HC, MDD, or MDDA (validated by one of the co-authors: TCS).

The Beck Depression Inventory (BDI-II; Beck et al., 1961) and The Beck Anxiety Inventory (BAI; Beck and Steer, 1988) were filled out by the participants to measure severity of depression and anxiety symptoms. General level of functioning were screened using Global Assessment of Functions Scale for symptom and function (GAF-S and GAF-F; DSM-IV).

General medical and psychiatric background, demographic information, past episodes of recurrent major depression and family medical and psychiatric history were obtained using a semi-structured interview developed by the first author (Lyche, 2006) based on the diagnostic interview for genetic studies (DIGS; Nurnberger et al., 1994) and a semi-structured screening instrument developed by Biringier (2005), University of Bergen. Education level was classified by means of The International Standard Classification of Education (ISCED; UNESCO, 1997).

## GENERAL COGNITIVE MEASURES

General cognitive functioning was estimated from the mean of two subtests from the WAIS-III: picture completion (PC) and similarities (SI) (Wechsler, 1999).

## NEUROPSYCHOLOGICAL ASSESSMENT

Three subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) which measure executive control functions according to Miyake et al. (2000) model were administered. In addition; a motor screening test (MOT) was administered in the beginning of the test session.

The neuropsychological tests were administered by a clinical psychologist trained in standardized assessment, or by an experienced test technician.

### Cambridge Neuropsychological Test Automated Battery

The Cambridge Neuropsychological Test Automated Battery (CANTAB, 2006) is comprised of computerized neuropsychological tests that examine various areas of cognitive function. The CANTAB tests are simple, computerized, non-linguistic and culturally blind, and allow us to break down executive control functions into cognitive components in order to define more readily which functions are impaired or spared. Three subtests were used in this study; intra-extra dimensional (ID/ED), spatial working memory (SWM), and stop signal task (SST), which correspond to the three functional areas according to Miyake et al. (2000) non-unitary model of executive functions.

**Shifting.** The ID/ED set-shift task is a test of rule acquisition and reversal. The task assesses the ability to maintain attention to different examples within a stimulus dimension (ID stages), and the ability to shift attention to a previously irrelevant stimulus dimension (ED shifts) across nine stages. Subjects proceed to the next stage when a criterion of six consecutive correct responses has been reached.

The two performance variables of interest are the number of stages completed, and the total error score adjusted for whether the entire task is completed (Kaplan et al., 2006).

**Inhibition.** The SST is a classic stop signal response inhibition test (Logan et al., 1984, 1997; Osman et al., 1986). It uses staircase functions to generate an estimate of stop signal reaction time. The test gives

a measure of an individual's ability to inhibit a prepotent response. The term "response inhibition" refers to cognitive processes enabling executive control over prepotent responses in accordance with changing situational demands. The main outcome variable of interest for our purpose is the stop signal reaction time (SSRT), which is an estimate of the subject's response time to the stop signal, i.e., the time it takes to react to the *stop* signal by inhibiting the prepotent response to the *go* signal (i.e., the time required to inhibit a response after it has been initiated). SSRT is estimated by subtracting stop signal delay (SSD) from mean Go signal reaction time (RTonGT).

**Updating.** Spatial working memory is a test of the subject's ability to retain spatial information and to manipulate remembered items in working memory. It is a self-ordered task which requires subjects to search for hidden "tokens" within a spatial array of colored boxes. By touching the boxes and using a process of elimination, the subject should find one blue "token" in each of a number of boxes, and then use them to fill up an empty column on the right hand side of the screen. The number of boxes is gradually increased until it is necessary to search a total of eight boxes. The color and position of the boxes used are changed from trial to trial in order to discourage the use of stereotyped search strategies. The rationale for this task and its implementation has been described previously in some detail (Owen et al., 1990). Outcome measures of interest are a "between" errors score, which is calculated when a subject returns to a square where a token was already found in a previous trial. This assesses the accuracy of working memory, as a strategy measure is derived; i.e., a subject's ability to adopt a systematic search strategy: a lower strategy score reflects more efficient task performance on SWM (Owen et al., 1990; Weiland-Fiedler et al., 2004).

### PSYCHOMOTOR SPEED

In addition to the main variable of inhibition on the SST task, an outcome measure of reaction time on Go trials (GoRT), an indicator of psychomotor speed, was included.

### DATA ANALYSIS

Data analysis was completed by means of SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Multivariate analysis of covariance (MANCOVA) was first used to compare the patient groups (MDD and MDDA) and the HC on the combined score of the six dependent variables measured at the individual level: ID/ED stages completed, ID/ED total errors adjusted, SWM strategy, SWM between errors, SST RT on Go trials, and SST SSRT, while simultaneously controlling for age, sex, and education level. Follow-up univariate analysis of covariance (ANCOVA) was then performed to detect which of the six dependent variables the three groups differed significantly from each other in mean scores. Finally, ANCOVA was also used to compare the MDD group and the MDDA group on the six dependent variables controlling for the number of earlier depressive episodes and age of onset of first depressive episode.

### RESULTS

A series of one-way analyses of variance (ANOVAs) and Chi-square tests was conducted to compare the four groups across the demographic variables, followed by *post hoc* tests with Bonferroni corrections to determine which groups differed (Table 1).

**Table 1 | Descriptive statistics for demographic variables, clinical characteristics, and general cognitive functioning (estimated from the WAIS-III subtests Similarities and Picture Completion) for patients with MDD, MDDA, and healthy comparison subjects.**

	MDD (n = 37)		MDDA (n = 24)		Healthy controls (n = 91)	
	M	SD	M	SD	M	SD
Age (years)	44.2	12.3	35.5	14.2	35.8	12.0
Education (years)	15.8	3.2	13.5	2.3	16.4	2.5
BDI	21.4	11.1	25.4	7.4	2.1	2.7
BAI	11.6	8.2	18.7	6.7	2.1	2.5
Symptom-GAF	60.2	12.1	53.8	8.5	95.6	7.3
Function-GAF	63.6	13.8	55.2	10.1	96.7	5.6
General cognitive functioning	11.1	2.1	9.3	2.6	12.1	2.4
Age of onset first MDD episode	33.5	14.4	30.1	16.1		
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
<b>GENDER</b>						
Male	14	37.8	11	45.8	28	30.7
Female	23	62.2	13	54.2	63	69.3
<b>HANDEDNESS</b>						
Right	35	94.6	24	100	8	42.1
Left	1	2.7	0	0	11	57.9
Amibidextrous	1	2.7	0	0	0	0

MDD, current major depressive disorder; BDI, Beck depression inventory; BAI, Beck anxiety inventory; GAF, global assessment of functioning axis-V in Diagnostic and statistical manual of mental disorders – Fourth Edition (DSM-IV).

Differences between the groups were found regarding age [ $F(2, 152) = 6.637, p < 0.01$ ], education level (ISCED) [ $F(2, 152) = 9.67, p < 0.001$ ], and general cognitive functioning (WAIS-MEAN) [ $F(2, 152) = 14.055, p < 0.001$ ]. There were no significant differences between MDD and MDDA on BDI, but MDDA had a higher score on BAI than MDD [ $F(2, 151) = 115.259, p < 0.001$ ].

There were no significant between-group differences in terms of gender [ $\chi^2(2) = 1.85, p = 0.397$ ] distribution and handedness [ $\chi^2(4) = 8.60, p = 0.072$ ].

The patients with MDD differed significantly from the HC group regarding age, the mean age being older for MDD. The MDDA group differed significantly from the MDD group, the mean age being younger for the former. There were no statistical differences in age between MDDA and HC.

According to estimated general cognitive functioning, the MDDA group had significantly lower mean than HC and MDD. The MDDA differed significantly from the HC group regarding education level, the former having lower mean ISCED-level.

Since educational level and estimated general cognitive functioning was correlated we did not enter the latter in the MANCOVA.

Although there was a significant difference between the MDDA group and HC on the general cognitive measure, the patients nevertheless performed well within the normal range. As compared to the formal norms the performance level equals less than one-third SD from the mean.

The MANCOVA demonstrated a significant overall group difference in performance on the CANTAB tests [ $F(12, 284) = 2370, p < 0.01$ ] Follow-up ANCOVAs and *post hoc* tests demonstrated that after controlling for gender, age, and education level and adjusted for multiple comparisons (Bonferroni), there were significant differences between the MDDA group and HC on two of

the dependent variables: ID/ED total errors adjusted and SWM between errors. The MDDA group performed the tasks with more errors than the HC.

There were significant differences between the MDD group and the HC group on SST RT on Go Trials. MDD performed the task with slower psychomotor speed compared to the HC group. There were no statistical significant differences between the clinical groups on any of the other variables.

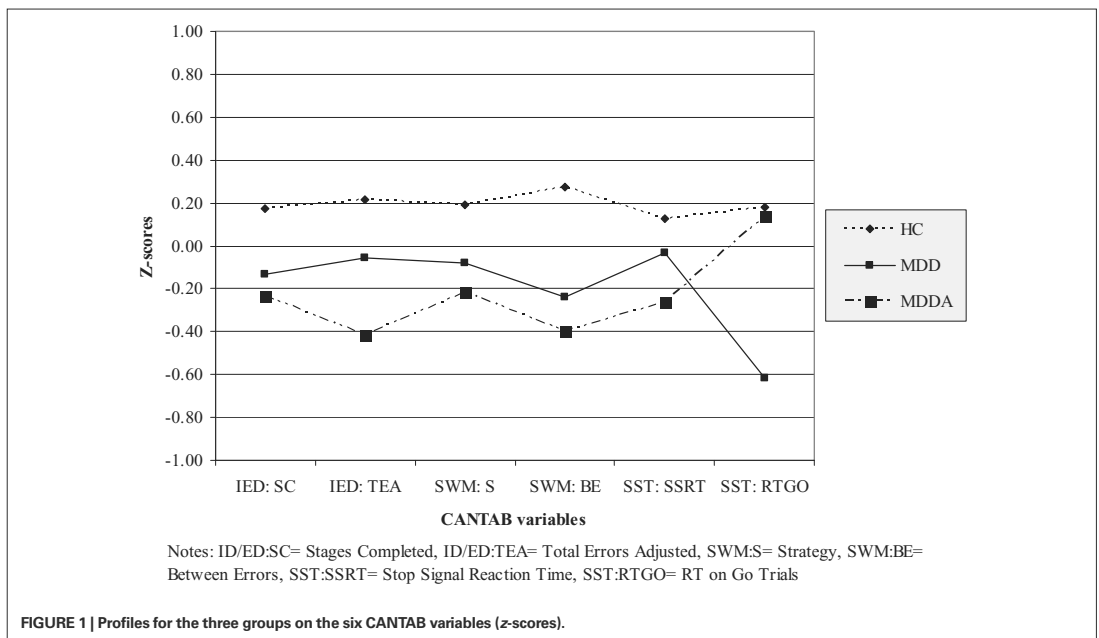
The results and mean scores for each group are presented in **Table 2**. Profiles of the three groups on the CANTAB variables are presented in **Figure 1**.

**Table 2 | Neuropsychological test performance on the CANTAB variables for patients with MDD, MDDA, and healthy comparison subjects (HC).**

Difference in mean scores is controlled for age, gender, and education level.

	MDD (n = 37)		MDDA (n = 24)		Healthy controls (n = 91)		Statistical analyses ANCOVA		
	M	SD	M	SD	M	SD	F	df	p
<b>SET-SHIFT</b>									
ID/ED; stages completed	8.4	1.6	8.3	0.9	8.7	0.7	1.399	2	0.250
ID/ED; total errors adj.	25.8	19.4	33.0	22.0	20.4	18.0	4.255	2	0.016*
<b>WORKING MEMORY/UPDATING</b>									
SWM; between errors	25.1	17.9	27.8	18.1	16.3	15.1	4.658	2	0.011*
SWM; strategy	32.3	6.0	33.1	5.4	30.8	6.0	1.764	2	0.175
<b>INHIBITION</b>									
SST; SSRT last half	189.1	64.9	202.5	74.5	180.1	50.4	1.785	2	0.171
<b>RT/PSYCHOMOTOR SPEED</b>									
SST; RT on GO trials	506.1	140.8	412.3	82.7	407.7	123.7	3.701	2	0.027*

\* $p < 0.05$ .



**FIGURE 1 | Profiles for the three groups on the six CANTAB variables (z-scores).**

Furthermore, we performed two ANCOVAs to test whether there was a difference between the two mood disorder patient groups (MDD and MDDA) on the CANTAB variables when we controlled for the number of depressive episodes and age of onset first depressive episode. (There are nine missing in the MDD group and four missing in the MDDA group due to difficulties in gaining accurate information about age of onset from these subjects).

The results showed that the number of episodes and age of onset was not significantly related to the dependent variables. Hence, including number of depressive episodes and age of onset as covariates in the analyses, did not alter the results, i.e., there were no significant differences in mean scores on the dependent variables between the two groups.

A significant Pearson correlation was found for the MDDA group between BAI and ID/ED; total errors adjusted ( $r = 0.48$ ,  $p < 0.05$ ). There were no significant correlations for the SWM; between errors. No significant correlations were found between BDI and the two CANTAB measures.

## DISCUSSION

The current data indicate that significant neuropsychological impairment in cognitive control functions corresponds with the presence of MDD and co-morbid anxiety. The MDDA group displayed significantly impaired performance with respect to working memory and set shifting compared to the HC. The MDD group did not show cognitive control dysfunctions relative to the HC, except for displaying slowed psychomotor speed. Contrary to expectation the MDDA group did not perform worse than the MDD group. There emerged no significant differences between any of the clinical groups and HC on the ability to inhibit a prepotent response. Number of depressive episodes and age of onset for first depressive episode was not significantly related to either working memory or set shifting test performance.

The MDDA group displayed impairment in relation to the HC group on the variable assessing updating in working memory. This is an error score, and not the variable assessing the ability to adopt a systematic strategy. This indicates that it is the “pure” working memory that is affected. This is in concert with general theories of affect–cognition interactions, stating that anxiety impacts cognitive load by the depletion of central executive resources, i.e., restrictions in WM capacity (Eysenck and Calvo, 1992; Shackman et al., 2006).

Negative mood and rumination require generally more attention than neutral and positive stimuli (Dolcos and McCarthy, 2006; Van Dillen and Koole, 2007). Strong negative stimuli (as in major depression) may trigger more mood-congruent processing and thus employ more WM capacity. This interactive relationship between WM load and emotional intensity of negative stimuli were examined by Van Dillen and Koole (2007). Participants reported attenuated negative moods in WM trials with high demands, suggesting that negative mood and WM capacity interact. Since we found no significant correlation between symptom severity (BAI or BDI) for the MDDA group on the working memory variable, this may indicate that it is the diagnostic validity of the clinical ratings of syndrome MDD and co-morbid anxiety disorder that is reflected in the WM impairment. This adds data to the ongoing discussion and research about whether cognitive dysfunctions in

WM in depression and anxiety represent symptom or syndrome factors, or an interaction of both with situational stress as a mediating factor (Eysenck and Calvo, 1992; Chong, 2003; Murray and Janelle, 2003).

The ID/ED results indicate that the MDDA group showed more total errors and thus were less able than HC to learn to shift or switch attention to new previously irrelevant exemplars of stimuli or mental sets. Symptom severity on BAI, but not BDI, showed a significant correlation with set shifting. This indicates that self-reported anxiety symptom severity and the set-shift function are linked in the MDDA group; this relates to the specific roles of symptom and syndrome anxiety in executive control functions.

In contrast to Basso et al. (2007), we found no significant psychomotor slowing in the MDDA group. However, in the MDD group showed reduced psychomotor speed compared to HC. The research field has published frequent findings of psychomotor slowing in both MDD and in MDDA, but to our knowledge only a few studies (Dutke and Stöber, 2001) have found more rapid psychomotor speed in anxiety. There are numerous theories stating that the presence of anxiety yields slower processing due to an obsessive or ruminative approach to testing (Basso et al., 2007). Moreover, the profile and nature of cognitive dysfunction is hypothesized to depend upon anxiety subtype, and the majority of studies have focused mainly on OCD.

Anxiety patients often exhibit a fear of new or unfamiliar situations. Therefore the experimental situation itself is often sufficiently threatening to arouse a significantly greater amount of manifest anxiety in the anxiety group than in the other two groups with depression. One may wonder if this creates a drive or motivation that can be measured as increased psychomotor speed. It may be hypothesized that in this study, it is the depression component that contributes to the deficits in speed, and that the lack of psychomotor deficit in the MDDA group was due to counterbalance by two inverse tendencies, or to a competition between psychomotor retardation and “acceleration.”

Number of earlier depressive episodes in the MDD and MDDA group was not significantly associated with the dependent variables. This result contradicts research findings where number of depressive episodes seems to have a cumulative effect on cognitive control impairment in MDD (Vanderhasselt and De Raedt, 2009). One of the main hypotheses is that each repeated depressive episode “leaves a mark” in the brain (Sheline, 2000). Stordal et al. (2005) found no impairment in executive functions in about half the patients with recurrent MDD, although the depressed patients with executive function impairments were the ones with more episodes than the patients without such impairments. In line with our present results, other studies have found no association between number of episodes and performance on tests that tap executive functions (Reischies and Neu, 2000; Grant et al., 2001).

Regarding the notion that the MDDA group represents an additive effect in severity, studies by Purcell et al. (1997), Elliott et al. (1996), and Beats et al. (1996) show that both inpatients with a more severe history of depression and hospitalization, and elderly patients may exhibit more evident set-shift deficits than do younger/middle-aged outpatients (Purcell et al., 1997). One reason why the research field has yielded different results may be that to our knowledge, the previous research concerning MDD with

co-morbid anxiety was based mostly on inpatient samples (i.e., Basso et al., 2007); the literature concerning neuropsychological function in depression suggests that inpatients are more severely impaired than outpatients (Burt et al., 1995; Veiel, 1997).

It seems that the “error component” is mutual for both the WM and the ID/ED tasks, and this is where MDDA patients are dysfunctional. Theories state that ACC is involved in, i.e., error detection (Bush et al., 2000). It has frequently been hypothesized to make critical contributions to the function of neural systems involved in the executive control of cognition (Carter et al., 1999). It may be hypothesized that ACC may be one area in common for the co-morbid group’s error component in performance on both SWM and ID/ED.

There are some potential limitations in this study. In light of the present findings additional research is needed to further address and possibly replicate current or previous findings on the effects of co-morbid anxiety disorders on executive control functions in patients with MDD. It would be advantageous to use larger samples, differentiated patient diagnoses and multiple tests to assess cognitive control functions. Possible effects of medication may also be a factor. Even though most of the patients in the two clinical groups were medication-fasting the day of testing, these subjects cannot be considered medication-free in regard to SSRI/SNRI. However, the proportion of subjects in each group with versus without medication may be considered fairly representative of the clinical

population with a larger proportion of medicated subjects in the MDDA group. Research suggests both that modern antidepressants do not have deleterious effects on cognitive test performance, and that that unmedicated patients may show more impaired attention functions compared to patients on medication (Den Hartog et al., 2003). Some studies also suggest that antidepressants may improve cognitive functions, including attention, in MDD patients (Fergusson et al., 2003), and that the effects of medication may be different on MDD from those with MDDA (Herrera-Guzmán et al., 2009). Furthermore, functional imaging should be included to provide a greater understanding of the associated neurobiological correlates of cognitive control functions.

In sum, the data suggest that the presence of co-morbid anxiety in MDD results in impairment of the basic cognitive control functions Updating and Shifting, whereas patients with MDD displayed no cognitive control impairment, but reduced psychomotor speed.

## ACKNOWLEDGMENTS

The study was supported by a grant from the Department of Psychology, University of Oslo to Pia Lyche, and a grant from the Research Council of Norway to Nils Inge Landrø. We wish to thank research assistants Martin Aker, Anne Marie Hoel, and Monika Rutle for assisting us with the data collection. We also thank Jan Egil Nordvik and Marcus Sneve Handal.

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- Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
- Received: 03 May 2010; paper pending published: 28 September 2010; accepted: 24 November 2010; published online: 21 December 2010.*
- Citation: Lyche P, Jonassen R, Stiles TC, Ulleberg P and Landro NI (2010) Cognitive control functions in unipolar major depression with and without co-morbid anxiety disorder. Front. Psychiatry 1:149. doi: 10.3389/fpsy.2010.00149*
- This article was submitted to Frontiers in Affective Disorders, a specialty of Frontiers in Psychiatry.*
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## **APPENDIX 1**

## BAKGRUNNSINFORMASJON

Instruksjon: Sett kryss ved rett svaralternativ eller fyll ut ledig plass

<b>Dato for intervjuet:</b>	
<b>Forsøksperson nr:</b>	
<b>Intervjuer:</b>	
<b>Henvist fra:</b>	

### Demografi

**Kjønn**

1. Mann

2. Kvinne

**Alder** \_\_\_\_\_

**Dominant hånd**

1. Høyrehendt

2. Venstrehendt

**Sivil status**

1. Gift/samboer

2. Skilt/separert

3. Singel/ugift

4. Enke/enkemann

**Barn** Ja  Nei  Hvis, ja: antall \_\_\_\_\_

**Fullført utdanning (ISCED; 1997):**

**Hvor mange år har du gått på skole?:** \_\_\_\_\_

**Utdanningsnivå. Kryss av:**

1. 6-årig grunnskole eller mindre
2. Grunnskole 7-9-år
3. Videregående skole 10-12 år: (teknisk/VK1/VK2 og 3/voksenopplæring)  
antall år: \_\_\_\_\_

(Ikke akademisk utdanning dvs. som ikke krever artium eller lignende kodes under pkt 3.)

4. Påbegynt postgymnasial utdanning/ voksenopplæring  
antall år: \_\_\_\_\_
5. a) Fullført inntil Bachelor/Cand.Mag:  
antall år: \_\_\_\_\_  
b) eller distriksthøyskolegrad/lærerutdanning:  
antall år: \_\_\_\_\_
6. Fullført Embedseksamen/Master/Hovedfag: \_\_\_\_\_
7. Fullført doktorgrad

**Utdanningsfelt:** \_\_\_\_\_

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**Hvis ufullstendig studium, hvorfor gjorde du deg ikke ferdig?** \_\_\_\_\_

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- |               |                              |                          |                          |
|---------------|------------------------------|--------------------------|--------------------------|
| <b>Arbeid</b> | 1. Fast arbeid               | <input type="checkbox"/> | Angi prosentandel: _____ |
|               | 2. Student                   | <input type="checkbox"/> |                          |
|               | 3. Arbeidssøker              | <input type="checkbox"/> |                          |
|               | 4. Trygd/sykemeldt/attføring | <input type="checkbox"/> |                          |
|               | 5. Ingen inntekt             | <input type="checkbox"/> |                          |

## Smerter

(Dette arket bør fylles ut av forsøksperson)

**1. Har du kroppslige smerter som har vart mer enn 6 måneder?** (Sett ring rundt svaret)

Ja                      Nei

**2. Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 ukene?** (Sett ring rundt svaret)

Ingen                      Meget svake                      Svake                      Moderate                      Sterke                      Meget sterke

**3. Hvor mye smerter har du nå?** (Sett ring rundt svaret)

Ingen                      Meget svake                      Svake                      Moderate                      Sterke                      Meget sterke

## Trettbarhet : PRE-testing

**Hvordan vil du beskrive ditt nåværende nivå av generell trettbarhet?**

(eks. nedsatt energi fysisk og psykisk, utmattelse)

Ingen                      Meget svakt                      Svakt                      Moderat                      Sterkt                      Meget sterkt

## Somatisk sykdom

**Har du hatt noen somatiske sykdommer?** (Oppgi starttidspunkt og varighet)

(Eks. Stoffskiftesykdommer, Organisk hjernesykdom (epilepsi, migrene, nevrologisk etc.), Sykemeldinger, Familiære sykdommer/opphopning)

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## Skader

**Har du hatt hjernerystelse/hodeskader?** (Oppgi antall ganger og hvilke skader)

Hvis ja: antall ganger \_\_\_\_\_

**Var du bevisstløs i sammenheng med dette?**

Bevisstløshet (min, timer, mnd, år): \_\_\_\_\_

**Har du hatt andre skader som benbrudd etc?** (Hvilke, antall ganger)

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**Psykisk sykdom** Oppgi debuttidspunkt og varighet

- Tidligere lidelser og nåværende
- Komorbiditet
- Innleggelse psykiatrisk institusjoner
- Familiære lidelser (1. gradsslektninger)

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**Sosiale endringer det siste året:**

(Eks. Skilsmisse, Død i familie eller nær vennekrets, Mistet arbeid, Ulykker)

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**Stressende livshendelser/påkjenninger i løpet av livet:**

(Eks. Skilsmisse, Død i familie eller nær vennekrets, Mistet arbeid, Ulykker)

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**Tidligere medikamentell behandling:**

Medisiner (Tidsrom, type preparat og varighet)

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**Nåværende medikamentell behandling** (tidsrom, type preparat og antatt varighet  
behandling, seponering)

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**Behandling:**

- Samtaleterapi (individuell/gruppe)
  - ECT |
- (Eksklusjon: mindre enn 3 mnd siden ECT)
- Annet

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### Utredning:

- EEG/PET/CAT/MRI
  - Nevropsykologisk utredning
  - Nevrologisk utredning
  - Annet: \_\_\_\_\_
- 

- Sigaretter  
Røyker  Røyker ikke

### Depresjonsutvikling/historikk:

Hvor gammel var du ved første gangs kontakt med psykiatrisk poliklinikk, privatpraktiserende psykolog/psykiater eller primærhelsetjeneste i forbindelse med psykiske plager/vansker?

**Debutalder** (ca): \_\_\_\_\_

Hvor mange ganger har du vært deprimert mesteparten av dagen i over to uker av gangen?

**Antall ganger** (ca): \_\_\_\_\_

Har du hatt regelmessig psykoterapi/gruppepsykoterapi tidligere?

(regelmessig er her minst 1 gang per uke i mer enn 3 mnd)

Ja

Nei

Hvis ja: hvor mange behandlingsperioder? \_\_\_\_\_

Har du tidligere vært innlagt ved psykiatrisk døgnavdeling?

Ja

Nei

Hvis ja: antall ganger? \_\_\_\_\_

## Depresjonsutvikling i løpet av livet:

DEPRESJON	VARIGHET (mnd)	Innleggelser under episoden	Medikamentell behandling	Sykemeldinger
1. episode		Ja / Nei	Ja / Nei	Ja / Nei
2. episode		Ja / Nei	Ja / Nei	Ja / Nei
3. episode		Ja / Nei	Ja / Nei	Ja / Nei
4. episode		Ja / Nei	Ja / Nei	Ja / Nei
5. episode		Ja / Nei	Ja / Nei	Ja / Nei
6. episode		Ja / Nei	Ja / Nei	Ja / Nei
Sum:	Sum:	Sum:	Sum:	Sum:

Ble du frisk av depresjonen mellom episodene?

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Hvis ja, var du frisk i mer enn to måneder?

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**Dersom JA ved ett eller flere punkt i tabellen, oppgi:**

**Varighet av innleggelsen (oppgi antall dager):**

ved episode 1: \_\_\_\_\_ dager

ved episode 2: \_\_\_\_\_ dager

ved episode 3: \_\_\_\_\_ dager

ved episode 4: \_\_\_\_\_ dager

evt. ved episode 5, 6, 7 osv.

**Varighet av medikamentell behandling relatert til depresjonsepisodene (oppgi antall mnd):**

ved episode 1: \_\_\_\_\_ dager

ved episode 2: \_\_\_\_\_ dager

ved episode 3: \_\_\_\_\_ dager

ved episode 4: \_\_\_\_\_ dager

evt. ved episode 5, 6, 7 osv.

**Varighet av sykemelding eller manglende evne til å studere/arbeide på grunn av  
depresjonsrelaterte plager (oppgi antall uker):**

ved episode 1: \_\_\_\_\_ uker

ved episode 2: \_\_\_\_\_ uker

ved episode 3: \_\_\_\_\_ uker

ved episode 4: \_\_\_\_\_ uker

evt. ved episode 5, 6, 7 osv.

## SCID SILINGSMODUL

Nå vil jeg stille deg noen mer konkrete spørsmål om problemer du kan ha opplevd. Vi skal se på disse mer detaljert siden.

BESVAR BEKEFTENDE SVAR MED: Vi skal snakke mer om det siden.

3 P1 Har du noen gang i løpet av ditt liv drukket fem eller flere drinker (øl, vin eller sprit) ved en og samme anledning?

1 2

RING RUNDT "NEI" PÅ E. 10	RING RUNDT "JA" PÅ E. 10
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3 P2 Har du noensinne brukt ulovlige narkotiske stoffer?

1 2

RING RUNDT "NEI" PÅ E. 10	RING RUNDT "JA" PÅ E. 10
------------------------------	-----------------------------

3 P3 Har du noensinne blitt "hekta" på en reseptmedisin eller tatt mer av det enn du skulle?

1 2

RING RUNDT "NEI" PÅ E. 10	RING RUNDT "JA" PÅ E. 10
------------------------------	-----------------------------

3 P4 Har du noensinne hatt et panikkanfall hvor du plutselig følte deg skremt eller engstelig eller plutselig utviklet en rekke fysiske symptomer?

1 2

RING RUNDT "NEI" PÅ F. 1	RING RUNDT "JA" PÅ F. 1
-----------------------------	----------------------------

3 P5 Har du noensinne vært redd for å forlate huset alene, være i folkemengder, stå i kø eller for å reise med buss eller tog?

1 2

RING RUNDT "NEI" PÅ F. 7	RING RUNDT "JA" PÅ F. 7
-----------------------------	----------------------------

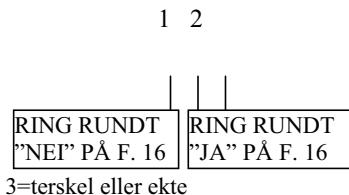
3 P6 Er det enkelte ting du var redd for å gjøre eller følte deg ubekvem når du gjorde foran andre folk, som f.eks å snakke spise eller skrive?

1 2

RING RUNDT "NEI" PÅ F. 11	RING RUNDT "JA" PÅ F. 11
------------------------------	-----------------------------

3 P7 Er det andre ting du var spesielt redd for, slik som å fly, se blod  
ta sprøyte, lukkede rom, eller enkelte typer dyr eller insekter?

1=ikke tilstedeværende eller falsk 2=subterskel



SCID-1 Versjon 2.0 (for DSM-IV) (Jan 1995 endelig) Silingsspørsmål Siling - Side2

3 P8 Har du noensinne vært plaget av tanker som virket meningsløse og som  
kom tilbake til deg selv om du prøvde å stenge dem ute?

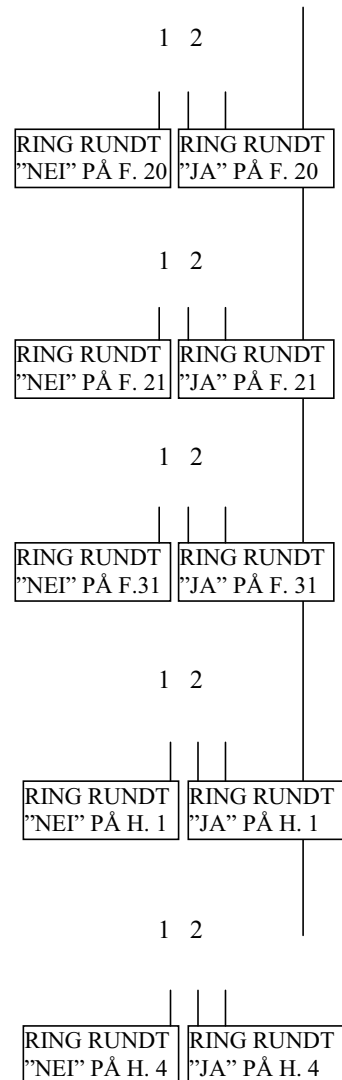
3 P2 Var det enkelte ting du måtte gjøre om og om igjen og som du ikke  
kunne stå i mot, slik som å vaske hendene dine igjen og igjen, telle  
opp til ett bestemt tall, eller sjekke noe mange ganger for å være  
sikker på at du hadde gjort det riktig?

3 P3 Har du vært spesielt nervøs eller engstelig i løpet av de siste  
seks månedene?

3 P4 Har du noensinne opplevd en periode hvor du veide mye mindre  
enn hva andre folk syntes du burde veie?

3 P5 Har du ofte opplevd perioder hvor spisingen din var ukontrollert?

1=ikke tilstedeværende eller falsk 2=subterskel 3=terskel eller ekte



## Tillegg screening SCID-I silingsmodul:

### 1. Stimulantia/Rusmidler

Har du noen gang i løpet av ditt liv drukket fem eller flere drinker (øl, vin eller sprit) ved en og samme anledning? **Ja**  **Nei**

Hvor ofte har det skjedd? \_\_\_\_\_  
\_\_\_\_\_

- Alkohol

Enheter (AE) pr uke: 0-5  5-10  10-15  mer enn 15



Har drikkingen skapt problemer for deg eller andre? \_\_\_\_\_  
\_\_\_\_\_

### 2. Har du noensinne brukt ulovlige narkotiske stoffer?

**Ja**  **Nei**

Over tid? \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Hvor mye? \_\_\_\_\_

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Hva slags stoffer?

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Andre rusmidler/blanding:

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Er det historie med alkohol og /eller rusmisbruk i familie/nær slekt?

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### **13. Somatisering/somatoform (G.1)**

Har du før du ble 30 år hatt en del plagsomme symptomer der legen din ikke kunne finne at noe var galt/fant ut hva det skyldtes?

1 2 3  
(3= gå til G.1)

### **14. PTSD (F.25)**

Har du opplevd traumatiske hendelser, sånn som å være i en livstruende situasjon, stor katastrofe, veldig alvorlig ulykke eller brann, blitt overfalt eller voldtatt, se en annen person bli drept eller som er død og hardt skadet, eller høre om noe grusomt som har skjedd dine nærmeste. Har noe slikt hendt deg i løpet av ditt liv?

1 2 3  
(3= gå til F.25)

## 15. Psykotiske og assosierte symptomer (B.1)

### Vrangforestillinger:

Har du hatt uvanlige opplevelser som folk av og til har?

- å motta spesielle beskjeder gjennom tv, radio eller aviser, eller ut fra måten ting var plassert rundt deg? (selvhenførende vf)
- at noen aktivt har gått inn for at du skulle komme opp i vanskeligheter eller forsøkt å såre deg?(forfølgelses vf)
- at du var veldig betydningsfull på en eller annen måte, eller at du hadde makt til å gjøre ting andre ikke kunne? (grandiose vf)
- at det var noen veldig galt med kroppen din selv om legen sa at det ikke var noe i veien med deg, som for eksempel at du hadde kreft eller en annen alvorlig sykdom? (somatisk vf)
- hatt noen uvanlige religiøse opplevelser eller følt at du har begått en forbrytelse eller gjort noe forferdelig som du burde straffes for? (religiøst, sjalusi, skyld)
- at noen eller noe utenfor deg selv kontrollerte tankene eller handlingene mot din vilje? (tanker påført av andre, tanketyveri)

### Hallusinasjoner

dvs. se, høre eller kjenne på kroppen eller huden noe andre ikke kunne se/høre/kjenne?

**Hvis treff på noen av disse, gå til B.1**

## Trettbarhet : POST-testing

**Hvordan vil du beskrive ditt nåværende nivå av generell trettbarhet?**

(eks. nedsatt energi fysisk og psykisk, utmattelse)

Ingen

Meget svakt

Svakt

Moderat

Sterkt

Meget sterkt