Executive Functioning in recurrent - and first episode Major Depressive Disorder

Longitudinal studies

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To Kari and Anton Schmid

Scientific environment

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List of Abbreviations

CG	Control Group
CWIT	Color Word Interference Test
D-KEFS	Delis –Kaplan Executive Function System
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, 1994
MDD	Major Depressive Disorder
EF	Executive Function
HDRS	Hamilton Depression Rating Scale
MADRS	Montgomery Åsberg Depression Rating Scale
M.I.N.I	MINI International Neuropsychiatric Interview, Norwegian Version, 1999.
NCG	No Change Group
NRG	No Relapse Group
RLG	Relapse Group
SNRI	Serotonin Noradrenalin Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TeCA	Tetracyclic Antidepressant
TMT	Trail Making Test
TT	Tower Test
VFT	Verbal Fluency Test
WASI	Wechsler's Abbreviated Scales of Intelligence, 1999.

Abstract

Major Depressive Disorder (MDD) is in the acute phase of illness often associated with neuropsychological impairment in a range of cognitive domains such as attention, memory, psychomotor speed and Executive Functioning (EF). However, the literature is inconclusive regarding the pattern of cognitive impairment in MDD and if these functions are state or trait dependent. MDD is one of the most common psychiatric disorders and is characterized by a high relapse risk. However, the factors affecting the vulnerability for relapse are still not well understood.

This thesis is based on three papers that investigated EF in MDD, both in the acute phase of illness and in phases of symptom reduction and remission. The first paper investigated EF in a group of patients with recurrent unipolar MDD. The second and third paper investigated EF in a group of first- episode unipolar MDD patients. In all three papers, EF was investigated using neuropsychological tests from the Delis-Kaplan Executive Function System (D-KEFS).

Paper I investigated EF in a group of recurrent unipolar MDD patients in a follow- up study. More specifically, the paper addressed the question if the impairment in the specific EF functions of inhibition and semantic fluency seen in the acute phase of illness would persist or be normalized with symptom reduction in a 9 month follow - up study. The results showed that the patient group was still impaired in inhibition, inhibition/switching and semantic fluency compared to the control group, despite significant symptom reduction. Performance in mental flexibility in general and phonemic fluency was equal to the control subjects. There were no association between depressive symptoms and EF impairment. The results further showed that the same patients that were impaired in inhibition in the acute phase of illness were still impaired at the follow- up assessment. Thus, seen in a 9 month perspective, the results indicate that inhibition may represent a stable trait characterizing patients with recurrent MDD.

Paper II investigated EF in a group of first episode unipolar MDD patients in the acute phase of illness. More specifically, the paper addressed the question if the EF impairment that was found in the recurrent patient group also was evident in a group of first episode MDD patients. Inhibition, mental flexibility, phonemic- and semantic fluency, planning- and problem solving were investigated. The results showed that the patient group was impaired in the EF functions of inhibition, inhibition/switching and semantic fluency compared to the control group. The patient group did not show impairment in the other EF measures that were assessed, such as mental flexibility in general, phonemic fluency, planning and problem-solving. Furthermore, the patient group was impaired compared to the control group in three measures of processing speed. However, the results indicated that poor processing speed could not account for the poor EF performance. There was further no association between severity of depression and EF impairment. The results from paper II show that inhibition and semantic fluency are impaired in first episode MDD.

Paper III investigated EF in a group of first episode unipolar MDD patients in a follow-up study. More specifically, the paper addressed the question if the impairment in inhibition and semantic fluency seen in the acute phase persisted or normalized in a longitudinal perspective of one year. In addition the third paper investigated if there was a relationship between poor inhibition and semantic fluency and the experience of relapse during the follow-up period. The EF of inhibition, mental flexibility, phonemic and semantic fluency was reinvestigated. Mean scores showed that the patients were in remission at the follow-up assessment. The results showed that the patient group still performed poorer in inhibition, inhibition/switching, semantic fluency and some measures of processing speed compared to the control group. Poor processing speed could however not solely account for the impaired performance in EF. In addition, the results showed that the performance in inhibition were more impaired when an additional requirement of mental flexibility was demanded. The performance in inhibition/switching at inclusion was further found to be more impaired in patients that experienced a relapse during the follow- up period, and found to enhance the likelihood of experiencing relapse. However, due to small

sample size and other possible confounding variables that could affecting the association found between tendency to relapse and poor performance in inhibition/switching in paper III, these results should be viewed as preliminary and thus be interpreted with caution.

Taken together, the present thesis demonstrates that inhibition and semantic fluency are impaired in patients with MDD across the course of the disorder, and thus may represent stable, enduring cognitive traits in MDD independent of symptom severity. Further, the present thesis indicates that impaired inhibition with the additional requirement of mental flexibility may represent a vulnerability factor for the experience of relapse.

List of publications

Paper I

Schmid, M., Strand, M., Årdal, G., Lund, A. & Hammar, Å. (2011). Prolonged Impairment in Inhibition and Semantic Fluency in a Follow-up Study of Recurrent Major Depression. *Archives of Clinical Neuropsychology*, 26, 677-686. Doi: 10.1093/arclin/acr048

Paper II

Schmid, M. & Hammar, Å. (2013a). Cognitive function in first episode major depressive disorder: Poor inhibition and semantic fluency performance. *Cognitive Neuropsychiatry, 18* (6), 515-530. DOI:10.1080/13546805.2012.754748

Paper III

Schmid, M. & Hammar, Å. (2013b). A follow-up study of First Episode Major Depressive Disorder. Impairment in inhibition and semantic fluency – potential predictors for relapse? *Frontiers in Psychology, 4*, 1-13. Doi: 10.3389/fpsyg.2013.00633

Contents

1.0 Major Depressive Disorder

Major Depressive Disorder (MDD) is one of the most common mental disorders, affecting more than 350 million people worldwide at any time (WHO, 2012). The World Health Organization (WHO) has ranked MDD as one of the leading causes of disability in the world (WHO, 2012). MDD is an affective disorder characterized by sustained lowered mood, distress and a generalized loss of interest (American Psychiatric Association (APA), 2000). Several patients suffering from depression report feelings of worthlessness and guilt, and patients are found to have uncontrollable reoccurring negative thoughts about the self and the future (APA, 2000; Nolen-Hoeksema, 1991; Nolen –Hoeksema, Wisco, Lyubomirsky, 2008). Difficulties in everyday functioning, often with reduced ability to sustain work or studies, and reduced quality of life are frequently reported from patients (Papakostas et al., 2004). In addition, many patients report that they have poor concentration and difficulties in remembering information. Challenges in such cognitive functions are further reported by many patients to persist despite relief of other symptoms of depression. Although only to a limited extent, research has found support for persistent reduced cognitive functioning despite symptom relief in this patient group, showing that these functions may not be state dependent (Hammar & Årdal, 2009; Hasselbalch, Knorr & Kessing, 2011). It is further important to highlight that despite advances in both medical and psychological treatment for MDD, a high proportion of patients experience a relapse of depressive symptoms and many suffer from several recurrent episodes of MDD (WHO, 2012; Vittengl, Clark, Dunn & Jarrett, 2007). The present thesis addressed the question of executive functioning across the course of MDD. Two subgroups of patients were included and followed longitudinally; one recurrent MDD patient group and one first episode MDD group.

1.1.0 Diagnostic criteria of Major Depressive Disorder

MDD is described and diagnosed based on evaluations of the presence of symptoms and the severity and duration of symptoms. Using the Diagnostic and Statistical

Manual of Mental Disorders- Fourth Edition (DSM-IV), (APA, 2000), a diagnosis of MDD requires that at least one of the core symptoms of depressed mood, and substantially diminished interest or pleasure in all, or most, activities, must have been present most of the day, nearly every day for two weeks. In addition to one or two of these core symptoms, a minimum of four of the following symptoms must be present nearly every day during the two week period; significant weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, diminished ability to think or concentrate or indecisiveness and/ or recurrent thoughts of death with or without a specific plan or suicide attempt (APA, 2000).

MDD is divided into mild, moderate and severe based on the presence of symptoms and how it affects general everyday functioning. A mild MDD is diagnosed if there are few symptoms that exceed one of the core symptoms and when the subject experience minor impairment in general everyday functioning. A moderate depression is diagnosed if symptoms and function falls between the mild and severe MDD. Severe MDD requires several of the symptoms besides the core symptoms, and that symptoms substantially interfere with everyday functioning. To measure severity in the present thesis, the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) and/or the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) were used.

MDD may also be characterized by the presence of psychotic symptoms. In the diagnosis of MDD a distinction between single- or first episode and recurrent MDD is made (APA, 2000). If a person suffers more than one episode of MDD the illness is characterized as recurrent MDD.

1.1.1 Differential diagnoses and comorbidity in MDD

A diagnosis of MDD must be distinguished from uncomplicated grief, and it must be established that an organic - or neurologic factor did not initiate and are not causing the symptoms. Because of somewhat similar symptoms of difficulties in concentration

and memory loss, apathy and disorientation, MDD can be difficult to distinguish from dementia in the elderly (APA, 2000). Further, when diagnosing MDD, there should be no history of hypomanic- and manic episodes. Depression is often comorbid with other psychiatric disorders such as anxiety disorders, posttraumatic stress disorder, substance abuse and developmental disorders (APA, 2000). Furthermore, depression is frequently associated with chronic somatic disorders such as asthma, angina, arthritis and diabetes (APA, 2000; Moussavi, et al., 2007).

1.1.2 Prevalence of MDD

Lifetime prevalence of MDD has been estimated to be 16, 6 % in the United States (Kessler et al., 2005). In a Norwegian epidemiological study lifetime prevalence of MDD was 17,8% (Kringlen, Torgersen & Kramer, 2001). A prospective study has reported lifetime prevalence for MDD as high as 41.4 % (Moffitt et al., 2010). The highest prevalence risk for MDD has been found to be between 18- 43 years of age (Kessler et al., 2005). A higher prevalence rate has also been found for females (Lewinsohn, Rohde & Seeley, 1998; Kessler et al., 2005; Eaton, et al., 2008), with lifetime prevalence rates estimated to be 24% for females and 9,9% for males in a Norwegian sample (Kringlen et al., 2001). The gender differences in prevalence are visible from late adolescence and into adulthood (Lewinsohn et al., 1998) and found to persist throughout life (Piccinelli & Wilkinson, 2000). The reason for these gender differences may be caused by several factors, such as adverse life experiences, sociocultural roles and effects of psychological coping skills. Less effect on this relationship is found for social support, genetic and biological factors (Piccinelli & Wilkinson, 2000).

1.1.3 The etiology of MDD

The causes of MDD are complex, with no clear casual factors. However, several individual and environmental vulnerability factors have been recognized to be involved in the development of an episode (Gotlib & Hammen, 2009).

Reviews of the genetic epidemiology in MDD states that heritability is reported to be between 40- and 50%, and there is higher risk of developing the illness if first-generation relatives suffering from depression (Levinson, 2006; Sullivan, Neale & Kendler, 2000). Despite no clear relationships, there has been found some evidence of genetic susceptibility in MDD, including the influence of candidate genes (Levinson, 2006; Eaton et al., 2008). Further, early life maltreatment and adverse - and stressful life events have been identified as being risk factors; however the extent of these risk factors in influencing first onset of depression have been found to depend on the gene- environment interplay (Heim & Binder, 2012; Keers & Uher, 2012; Bukh et al., 2009; Caspi et al., 2003). Other individual vulnerability factors such as personality traits and cognitive characteristics such as temperament, rumination, dysfunctional attitudes and beliefs (schemata) have also been found to represent vulnerability factors for first onset – and recurrence of depression (Christensen & Kessing, 2006; Nolen- Hoeksema, 2000; Beck, 2008; Alloy et al., 2006; Halvorsen, Wang, Eisemann & Waterloo, 2010; Wang, Halvorsen, Eisemann & Waterloo, 2010). Thus, the first onset of an episode of MDD may be a result of several interacting factors, which again may be specific for one particular individual. Vulnerability for first onset of MDD may also be recognized from the majority of studies within the field of neuropsychology that have found this patient group to be impaired in cognitive functioning (Austin, Mitchell & Goodwin, 2001; Hammar & Årdal, 2009; Porter, Bourke & Gallagher, 2007). These cognitive impairments have been associated with dysfunctional neuronal activity and neuronal abnormalities in structural and neuroendocrine processes (Drevets, 2000; Rogers et al., 2004). One study found results showing that poor cognitive functioning is present before the onset of MDD (Christensen, Kyvik & Kessing, 2006). However, knowledge is still limited concerning the course of these cognitive impairments and the relationship with neuronal dysfunctions, if they are present before- or initial in the disorder.

1.1.4 Course of MDD

Assessing duration of both first- and recurrent episodes of depression, a large epidemiological study reported that 50% of patients recovered within 3 months, within 6 moths 13% more were found to be recovered, adding up to 63%, and within 12 months a total of 76% were found to be recovered. For approximately 20% of the patients their symptoms persisted and exceeded 24 months, thus developing a more chronic course (Spijker et al., 2002). Based on the same epidemiological data the authors found that severity of the index episode, long duration of pervious episodes, chronic physical illness and lack of social support represented factors contributing to persistence of symptoms (Spijker et al., 2004). Another study found that patients with a chronic course of depression had more severe depressive- and somatic symptoms, and greater mental dysfunction in the acute phase compared to those that remitted from their episode (Stegenga, Kamphuis, King, Nazareth, Geerlings, 2012).

A large percentage of individuals diagnosed with MDD will experience a relapse or recurrence of their depression (Mueller et al., 1999; Hardeveld, Spijker, De Graaf, Nolen, Beekman, 2010). It has been estimated that approximately 50% of patients will experience a relapse of their depression within two years and that approximately 80% will experience more than one episode during their lifetime (Mueller et al., 1999; Solomon et al., 2000; Stegenga et al., 2012). A meta- analytic study reported that 54 % of patients had a relapse or recurrence within two years (Vittengl et al., 2007). One study, following MDD patients in primary care for 18 months, showed that 25% achieved and remained in remission, 25% had persisting symptoms and the remaining 49% suffered relapse or recurrence (Vuorilehto, Melartin & Isometsä, 2009). Following the same patient group for 5 years, the study reported that 90% of patients reached a symptom severity state below the criteria for an episode of MDD, but that 51% experienced a relapse after two consecutive months of partial or full remission (Riihimäki, Vuorilehto, Melartin, Isometsä, 2011). A prospective study, following patients 23 years after their first onset episode, found that about 50 % recovered, with

no further episodes, while the remaining subjects experienced a recurrent or chronic course (Eaton et al., 2008).

1.1.5 Factors contributing to relapse and recurrence in MDD

Rate of recurrence has been found to correlate with previous number of depressive episodes (Hardeveld et al., 2010; Kessing, Hansen, Andersen & Angst, 2004; Solomon et al., 2000; Mueller et al., 1999). Severity of the preceding episode (Vuorilehto et al, 2009; Riihimäki et al., 201; Stegenga et al., 2012) and presence of residual symptoms (Hardeveld et al., 2010), has also been found to predict relapse and recurrence. In contrast, a follow- up study of 8- 10 years found that individuals with residual symptoms showed greater impairment in social adjustment but not more frequent recurrences of depression compared to individuals without residual symptoms (Kennedy & Paykel, 2004). One study did not find any relationship between severity of residual symptoms, rate of recurrence and number of previous episodes (Bertschy et al., 2010). Greater risk of recurrence has been reported for females (Mueller et al., 1999; Eaton et al., 2008). However, in their review, Hardeveld and colleagues (2010) concluded that the most important predictors for relapse and recurrence were number of previous episodes and subclinical residual symptoms. Gender and other demographic variables such as civil status and socioeconomic status did not predict course (Hardeveld et al., 2010).

As will be thoroughly discussed in the present thesis, neuropsychological studies have found MDD patients to show impairment in cognitive functioning (Austin et al., 2001). Further, although limited, there are findings that suggest that these impairments may persist despite symptom reduction and remission (Hasselbalch et al., 2011; Hammar & Årdal, 2009). Impaired cognitive functioning may be an important factor to consider when identifying vulnerability factors for relapse and recurrence in MDD (Hammar & Årdal, 2009; Gotlib & Joormann, 2010; Majer et al., 2004).

1.1.6 The definitions of the concepts; response, symptom reduction, remission recovery, relapse and recurrence.

Inconsistencies in the conceptualizations of the concepts used to describe the course of MDD may provide divergent results in research and incorrect inferences in clinical practice (Frank et al., 1991; Rush et al., 2006). In attempts to provide consistency, suggested operational criteria for outcomes in depression, have been postulated (Frank et al., 1991; Rush et al., 2006). *Response* refers to a clinically significant degree of symptom reduction following treatment (Frank et al., 1991) and may be termed as being in *symptom reduction*. *Remission* is achieved after a minimum three-week period during which minimal symptom status is maintained. Suggested cut of score in the definition of remission is < 10 on the Montgomery Åsberg Depression Rating Scale (MADRS) (Hawley, Gale & Sivakumaran, 2002) and < 7 on the Hamilton Depression Rating Scale (HDRS) (Rush et al., 2006). Remission can only be lost by a relapse of depressive symptoms. A *relapse* occurs before recovery and is operationally defined as a return to a fully symptomatic state of the preceding major depressive episode. In order to be defined as a relapse, the symptoms must sustain for a minimum of two weeks. *Recovery* from MDD is ascribed after at least 4 months following the onset of remission (Rush et al., 2006). Frank et al (1991) suggests that the subject must be 6 months in remission to achieve recovery. Recovery is only lost by a recurrence of a new episode of MDD. A *recurrence* is termed when the subject enters a new episode of MDD.

1.2 Cognitive functioning.

Cognitive functioning has been conceptualized as our ability to use and integrate basic capacities such as perception, attention, language, actions, memory and thought (McCarthy and Warrington, 1990). Within the neuropsychological field, cognitive function is understood as the information handling aspects of behavior and has been described as separated, basic mental functions of input, storage, processing and output, which can be conscious or unconscious (Lezak, Howieson, Bigler & Tranel, 2012). Thus, cognitive functioning can be understood as encompassing several basic

and more advanced processes, making the individual able to adapt to changing environments. Impairment in aspects of cognitive functioning may therefore affect the individual thoughts and behavior and have implications for everyday functioning.

1.2.1 Executive functioning (EF)

Unlike the cognitive domains of memory and attention, there is no uniform intuitive concept for EF (Elliott, 2003). EF is a neuropsychological construct generally understood as "higher-level" cognitive processes that control and regulate lower level cognitive processes such as perception, attention, motor- and psychomotor responses, guiding behavior towards a goal (Alvarez & Emory, 2006; Delis, Kaplan & Kramer, 2001a). EF is understood as top-down mental processes and are thus recognized to be more effortful compared to more automatic basic processes (Diamond, 2013; Delis et al., 2001a). EF is also termed cognitive control, in that the cognitive functions that encompass EF are essential in self-control and self- regulation (Miyake & Friedman, 2012; Hugdahl et al., 2009). Lezak (1983) and Lezak et al. (2012) describe EF as a global cognitive function that determines how behavior is expressed. EF thus builds on the more basic cognitive functions, allowing the individual to respond flexible and adaptive to the environment (Lezak et al., 2012). Impaired EF may thus have severe consequences for the individual in their everyday functioning.

Inhibition, updating, mental flexibility, working memory, semantic- and phonemic fluency and planning- and problem-solving are all recognized to be essential EF (Snyder, 2012; Delis et al., 2001a). However, controversies exist with regard to which of the EF components is the most important and the precise structure and interaction between these components (Diamond, 2013; Jurado & Rosselli, 2007; Miyake & Friedman, 2004). Core EF has been identified to be inhibition and switching, working memory, and sustained and selective attention (Alvarez & Emory, 2006). Focusing on the structure and interaction within EF, there are controversies regarding whether EF should be viewed as one unitary concept, or as a concept consisting of different cognitive functions (Diamond, 2013; Jurado & Rosselli, 2007; Miyake & Friedman, 2004). Including shifting, updating and inhibition, Miyake, Friedman, Emerson,

Witzki & Howerter (2000), and Miyake & Friedman (2012), concluded that although these components are clearly distinct components and can be measured and evaluated in terms of what is specific for each function, they also share some common underlying functions.

Neuroimaging methods and observations of patients with frontal lesions have identified the frontal lobes, and especially the prefrontal cortex to be an important functional and anatomical structure governing EF (Stuss & Levine, 2002; Jurado & Rosselli, 2007). Researchers have mainly suggested four structures of the prefrontal cortex to be essential in EF; the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex (VPFC), the anterior cingulate cortex (ACC) and the orbifrontal cortex (Alvarez & Emory, 2006; Stuss & Levine, 2002). These frontal regions have been found to be both specific and general for different components of EF (Nee, Wager & Jonides, 2007; Wager, Jonides & Reading, 2004). However, reviews and meta- analytic studies conclude that there are findings suggesting that EF is depended not only on these structural components, but on associated cerebral networks including other brain regions, both subcortical structures and posterior cortex (Alvarez & Emory, 2006; Jurado & Rosselli, 2007; Elliott, 2003).

1.2.2 The Delis- Kaplan Executive Function System.

The Delis - Kaplan Executive Function System (D-KEFS), (Delis et al., 2001a) provides a set of standardized neuropsychological tests designed to measure several components encompassing EF. The D-KEFS includes a set of nine tests which are designed to measure a broad range of verbal – and nonverbal EF, such as inhibition, mental flexibility, problem solving and planning, phonemic- and semantic fluency, concept formation, abstract thinking and creativity. The objective of the D-KEFS was to provide a tool which would assess the complexity and multifactorial domain of EF in a more detailed manner. Thus, in addition to developing new tests, the D-KEFS builds on previously well used and standardized neuropsychological tests and have added new conditions to better differentiate performance. Some of the tests are designed to contain both conditions that demands basic cognitive skills, such as

attention, perception, speed of processing, motor speed and basic language abilities, and conditions that demands more higher- level cognitive skills, such as EF. In addition, the D-KEFS provides calculation and examination of contrast scaled scores which give a more detailed picture concerning an impaired performance within a specific condition (Delis et al., 2001a).

1.3 Cognitive functioning in MDD.

The neuropsychological literature concerning cognitive functioning in MDD have found this patient group to be impaired within several cognitive domains, including attention, verbal - and visual memory, psychomotor speed and EF (Rogers et al., 2004; Austin et al., 2001; Hammar & Årdal, 2009; Elliott, 2003; Porter et al., 2007; Ravnkilde et al., 2002). However, although well documented, this field of research shows divergent results, with no clear consensus regarding pattern or profile of cognitive impairment in this patient group (Austin et al., 2001; Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari & Lönnquist, 2008). Three different hypotheses which all attempt to understand the cognitive profile of MDD patients has been suggested. The global- diffuse hypothesis states that MDD patients have a generally lowered or impaired cognitive profile seen across cognitive domain (Veiel 1997; Landrø, Stiles & Sletvold, 2001). A second hypothesis states that the neuropsychological profile of MDD patients is domain-specific, with impairment in mainly the cognitive domains of EF and memory (Elliott, 2002; Austin et al., 2001). The third position, the cognitive –effort hypothesis, states that MDD patients show mainly impairment on tasks requiring considerable cognitive resources. Thus, performance in more automatic information processing is not affected (Hasher & Zacks, 1979; Hammar, 2003). There is support for all hypotheses in the literature, showing that this field of research is complex. Not all MDD patients are found to have cognitive impairment (Stordal et al., 2005). Thus, factors that are recognized to be important for future research is the heterogeneity in cognitive performance seen in this patient group (Stordal et al, 2005; Naismith et al., 2003) and the relationship between cognitive function and clinical symptomatology (Elliott, 1998; Elliott, 2002).

There may be specific subtypes of depressed patients with different neuropsychological profiles (Porter et al., 2007; Naismith et al., 2003). Another important issue related to the profile of cognitive impairment in MDD is the question if these impairments improve in accordance with symptom decline or if they persist despite symptom reduction and remission.

1.3.1 Cognitive functioning in the acute phase of MDD.

MDD patients have been found to be impaired in measures of attention in the acute phase of illness (Landrø et al., 2001; Lyche, Jonassen, Stiles, Ulleberg & Landrø, 2011b; Hammar, Lund & Hughdahl, 2003a), although contradicting results show that MDD patients perform equal to control subjects in these measures (Harvey et al., 2004; Halvorsen et al., 2012). Research reports have also documented impaired memory functions in the acute phase of illness (Airaksinen, Larsson, Lundberg & Forsell, 2004; Burt, Zembar & Niederehe, 1995; Hickie et al., 2005; Ilsley, Moffoot, Carroll, 1995; Basso & Bornstein, 1999; Kizilbash, Vanderploeg & Curtiss, 2002; Fossati, Coyette, Ergis, Allialaire, 2002; Fossati et al., 2004; Bearden et al., 2006). Other studies show intact memory performance in this patient group (Fossati, Amar, Raoux, Ergis, Allilaire, 1999; Castaneada et al., 2008; Grant, Thase & Sweeney, 2001; Wang et al., 2006; Rund et al., 2006). Studies have also found intact verbal but impaired visual memory in MDD (Deptula, Manevitz, & Yozawitz, 1991; Porter, Gallagher, Thompson, & Young, 2003, Kalska, Punamäki, Mäkinen-Pelli, Saarinen, 1999; Hammar, Isaksen, Schmid, Årdal & Strand, 2011) showing that there are aspects of memory performance that may be more affected than others.

Reduced speed of processing are also documented in MDD patients (Den Hartog, Derix, Van Bemmel, Kremer, & Jolles, 2003; Egeland et al., 2003; Rund et al., 2006; Tsourtos, Thompson, & Stough, 2002; Halvorsen et al., 2012; Ilsley et al.,1995). Reduced speed of processing has been suggested to account for impaired cognitive function across domains (Den Hartog et al., 2003). However, others find intact processing speed in MDD patients despite impaired performance in other cognitive functions (Hammar et al., 2011; Purcell, Maruff, Kyrios & Pantelis, 1997; Porter et

al., 2003; Airaksinen et al., 2004), showing that there is no clear evidence of reduced speed of processing affecting cognitive performance in general.

1.3.2 Executive functioning in the acute phase of MDD

A large amount of research papers find MDD patients to be impaired in EF in the acute phase of illness (Elliott, 1998; Porter et al., 2003; Snyder, 2012). MDD patients have been found to be impaired in several of the cognitive functions that encompass this domain, including planning – and problem-solving (Naismith et al., 2003; Cella, Dymond & Cooper, 2010), working memory (Rose & Ebmeier, 2006; Halvorsen et al., 2012; Taylor Tavares et al., 2007; Stordal et al., 2004), mental flexibility or set shifting (Austin et al., 1999; Purcell et al., 1997; Naismith et al., 2003; Harvey et al., 2004; Taylor Tavares et al., 2007; Fossati, Guillaume, Ergis & Allilaire, 2003; Fossati et al., 1999; Airaksinen et al., 2004), verbal fluency (Henry & Crawford, 2005; Gohier et al., 2009; Fossati et al, 1999; Stordal et al., 2004; Naismith et al., 2003;Fossati et al., 2003; Okada, Okamoto, Morinobu, Yamawaki & Yokota, 2003; Calev, Nigal & Chazan, 1989) and inhibition (Harvey et al., 2004; Gohier et al., 2009; Hammar et al, 2011; Markela- Lerenc, Kaiser, Fiedler, Weisbrod & Mundt, 2006; Stordal et al., 2004; Rund et al., 2006). Despite some studies reporting intact performance in most EF measures MDD (Halvorsen et al., 2012; Grant et al., 2001;Vythilingam et al., 2004), the literature in general find EF to be impaired, suggesting that EF may represent core cognitive dysfunctions in MDD (Snyder, 2012; Elliott, 2002). Impairment in EF has also been found to affect performance in other cognitive domains such as attention and memory due to the importance of intact EF in the encoding and retrieval of information (Fossati et al., 2002; Fossati et al., 2003; Taconnat et al., 2010). This may be a reasonable suggestion, given that performance in other cognitive domains more or less has been postulated to rely on intact EF (Miyake & Friedman, 2012). However, studies are divergent with regard to the pattern and extent of EF impairment. Researchers have found MDD patients to have a general impairment across EF (Snyder, 2012; Stordal et al., 2004; Rogers et al., 2004; Majer et al., 2004), yet others find more specific impairment in some functions within

EF, such as inhibition (Harvey et al., 2004; Rund et al., 2006; Hammar et al., 2011), semantic fluency (Fossati et al., 1999; Fossati et al., 2003; Hammar et al., 2011; Calev et al., 1989) and within measures of mental flexibility (Purcell et al., 1997; Harvey et al., 2004; Austin et al., 1999; Fossati et al., 2003; Grant et al., 2001).

1.3.3 State versus trait factors in MDD

Important for the understanding of cognitive function in MDD is to investigate whether the cognitive impairment is *state* dependent and thus are evident only in the depressive state, or if these impairments result from an underlying neurobiological stable impairment, a *trait* (Douglas & Porter, 2009; Austin et al., 2001; Elliott 1998). Findings of prolonged impairment may indicate that cognitive impairment represents a stable trait in this patient group, or that these impairments normalize at a later pace compared to depressive symptoms (Hammar & Årdal, 2012; Hammar & Årdal, 2009). Seen from a trait perspective, a stable cognitive dysfunction can be recognized as a vulnerability factor for the first onset, and the persistent and relapsing nature of MDD (Weiland- Fiedler et al., 2004; Reppermund et al., 2007; Majer et al., 2004). To explore the course of cognitive function in MDD, and hence the question of state or trait dependence, studies have investigated cognitive function including patients in the remitted state, or have longitudinally followed patients from the acute phase of illness and through phases of symptom reduction and remission.

1.3.4 Cognitive functioning in a long term perspective

Studies investigating MDD patients in the remitted state have found impairment in both attention (Weiland- Fiedler et al., 2004) and memory functions (Merens, Booij, Van Der Does, 2008; Behnken et al., 2010). One study found evidence of impaired attention and EF in remitted patients (Paelecke- Habermann, Pohl & Leplow, 2005). Impairment in attention, processing speed, verbal memory and EF has also been found in the remitted state (Preiss et al., 2009; Paradiso et al., 1997). Contrary to these findings, intact memory functions in the remitted state have been reported (Smith, Muir & Blackwood, 2006). However, due to the cross sectional designs of these

studies, knowledge about cognitive function in the acute phase is missing, making it difficult to draw inferences concerning the course of cognitive impairment across symptomatic phases.

Longitudinal studies following patients from the acute phase of illness have found persistent impairment in verbal fluency and verbal memory despite significant symptom reduction (Neu et al., 2005; Airaksinen et al., 2006). Impaired immediate recall, but intact verbal learning and memory was found in both in the acute and remitted phases of MDD, indicating that patients benefitted from repetitions and structure (Hammar et al., 2011; Hammar & Årdal, 2013). These results suggest that poor performance could be related to a deficit in attention across symptomatic phases (Hammar et al., 2011; Hammar & Årdal, 2013). However, studies have reported normalization of verbal (Biringer et al., 2007) and visual memory (Hammar & Schmid, 2013) in line with symptom reduction. One study found both currently depressed and remitted MDD patients to show intact performance in measures of EF, attention and verbal memory, but impaired performance in measures of psychomotor speed (Halvorsen et al., 2012). MDD patients have been found to show sustained impairment in an effortful attention paradigm in a 6 month follow- up study (Hammar, Lund & Hughdahl, 2003b). However, retesting those patients 10 years later when they were in recovery revealed a normalization of performance (Hammar & Årdal, 2012). Reppermund and colleagues (2007) found a large proportion of patients, both remitted and non-remitted, to have a general impairment across cognitive domains. Further, remitted patients performed significantly better on measures of speed of processing compared to non-remitters (Reppermund et al., 2007).

1.3.5 Executive Function in a long term perspective

As shown in the previous section, some studies show a general impairment across cognitive domain, including EF (Paelecke- Habermann et al., 2005; Preiss et al., 2009; Paradiso et al., 1997). Others have found intact memory performance, but impaired performance in the EF of inhibition and mental flexibility in the remitted state (Smith et al., 2006).The finding of impaired mental flexibility is supported by

others (Yamamoto & Shimada, 2012). In general, impairment in EF and attention has been found to be more stable cognitive deficits persisting despite improved clinical status while the cognitive functions of memory, verbal fluency measures and psychomotor speed have been suggested to be more related to clinical state (Douglas & Porter, 2009; Lee, Hermens, Porter & Redoblado- Hodge, 2012; Porter et al., 2003; Paelecke- Habermann et al., 2005).

Moreover, within the EF domain, there are results indicating that inhibition and semantic fluency may be of particular importance in MDD due to the persisting impairment seen in these functions across studies. MDD patients have been found to be impaired in these functions in the remitted state (Paelecke-Habermann et al., 2005; Paradiso et al., 1997; Smith et al., 2006; Nakano et al., 2008; Okada et al., 2009). Supporting findings from the remitted state, longitudinal studies have found persistent impairment in semantic fluency (Neu et al., 2005; Reiches & Neu, 2000). Following patients for two years, Biringer and colleagues (2005) found a significant improvement in several measures of EF in line with significant reduction in depressive symptomatology. However, this pattern was not evident for performance in inhibition and semantic fluency, with patients still performing significantly poorer compared to the control group on these measures (Biringer et al., 2005). Other longitudinal studies of various lengths also find persistent impairment in inhibition despite symptom reduction and remission (Hammar et al., 2010; Årdal & Hammar, 2011; Trichard et al., 1995). Trichard et al. (1995) found semantic fluency performance to normalize in accordance with symptom decline, while performance in inhibition remained impaired (Trichard et al., 1995). Thus, although there is evidence of intact semantic fluency in the acute phase of illness (Austin et al, 1999) and intact inhibition and semantic fluency performance in phases of remission (Merens, et al., 2008; Halvorsen et al, 2012), there are findings in the literature that suggest a relatively firm pattern of sustained impairment in inhibition and semantic fluency. However, a general consensus regarding cognitive functioning in a long term perspective is still absent (Hasselbalch et al., 2011; Hammar & Årdal, 2009). More longitudinal studies are needed. Studies that include patients only in the remitted state

are limited in order to draw conclusions relative to cognitive function in the acute phase of illness.

1.3.6 Inhibition in MDD

Inhibition involves being able to suppress strong internal predispositions or external stimuli in order to control attention, behavior, thoughts and emotions (Diamond, 2012). Inhibition is conceptualized as a function in which the individual is suppressing an automatic response in order to make a less automatic but task relevant response (Miyake et al., 2000). In the literature of EF in MDD, inhibition has been measured using a variety of different neuropsychological tests and also experimental paradigms. The most common neuropsychological measure of inhibition is the Stroop task (Snyder, 2012). The original Stroop test was developed by J. R. Stroop (1935). The basic feature of this confliction color - word task is the measurement of the individual's ability to suppress or override the automatic response of reading in order to name the ink color the word is written in. This incongruent condition is a measure of inhibition and is further compared to the more automatic tasks of only naming the ink color of printed color dots and reading words printed in black (Snyder, 2012; Delis et al., 2001a). Since its development, the Stroop test has been subject for further development (Lund- Johansen, Hugdahl & Wester, 1996; Delis et al., 2001a). In example, in the D-KEFS Color- Word Interference Test, a fourth task, were the individual's ability to mentally switch between the ability to inhibit and the more basic function of reading the words, is added (Delis et al., 2001a).

As described earlier, there are findings showing evidence of impaired inhibition being a cognitive dysfunction of relevance in MDD. Further, MDD is associated with structural and functional abnormalities in the prefrontal cortex and other cortical and subcortical structures which are also found to be essential for EF functioning in general (Rogers et al, 2004; Levin, Heller, Mohanty, Herrington & Miller, 2007), and inhibition function in particular (Nee et al., 2007; Matthews et al., 2009). However, there are still controversies regarding the exact nature and clinical implications of impaired inhibition in MDD. Inhibition has been found to be important in the study of

how MDD patients process emotional stimuli (Peckham, McHugh & Otto, 2010). The ability to override automatic responses and inhibit the processing of irrelevant material that captures attention has been suggested to be essential for the ability to suppress negative thoughts in patients with MDD (Joorman, Yoon, & Zetsche, 2007; Gohier et al., 2009). Depressed patients are found to have difficulties disengaging from negative material (Joorman & Gotlib, 2008), thus inhibition may be a cognitive function explaining this inability, making individuals prone to ruminative tendencies,which is reported to be a stable trait in MDD (Nolen- Hoeksema, 1991; Nolen –Hoeksema et al., 2008). Thus, inhibition is viewed as essential for emotional regulation in MDD (Gotlib & Joormann, 2010; Joormann & Gotlib, 2010). Moreover, poor inhibition has been found to be significantly poorer in MDD patients that have had past suicide attempts (Keilp, Gorlyn, Oquendo, Burke & Mann, 2008), and has been found in addition to other EF, to be predictive of nonresponse to the effect of treatment with the SSRI fluoxetine (Dunkin, et al., 2000).

1.3.7 Verbal fluency in MDD

Performance in verbal fluency reflect the individual's ability to efficiently generate words that starts with a particular letter (phonemic fluency) or words belonging to a semantic category (semantic fluency) in a limited amount of time (Delis et al., 2001a). As described, studies find MDD patients to be impaired in both semantic- and phonemic fluency, with a somewhat higher prevalence found for semantic fluency performance (Henry & Crawford, 2005; Snyder, 2012). Further, there is support for reduced activation in the frontal lobes during verbal fluency in MDD, with a possible higher sensitivity for semantic fluency (Klumpp & Deldin, 2010). The impact of poor verbal fluency and the mechanisms behind performance are however debated in the literature. In their meta-analytic study of verbal fluency in MDD patients, Henry & Crawford (2005) argue that phonemic- and semantic fluency differs with regard to retrieval processes involved. They propose that semantic fluency depends upon the integrity of semantic associations in memory and the accessibility to these semantic associations, while phonemic fluency requires search strategies based primarily on

lexical representations (Henry & Crawford, 2005). Supporting these suggestions other researchers have proposed that semantic fluency are more effortful compared to phonemic fluency (Calev et al., 1989). Others have proposed that poor semantic fluency is caused by a poorly integrated semantic network (Fossati et al., 2003), or are merely a result of disorganized retrieval strategies and word generation in MDD (Neu et al., 2005). Studies also find that verbal fluency performance may be dependent on other EF such as initiation and especially for semantic fluency; mental flexibility that are thought to help in the process of retrieving information (Lafont et al., 1998; Troyer, Moscovitch & Winocur, 1997; Fossati et al., 2003; Klumpp & Deldin, 2010).

1.3.8 Cognitive functioning in recurrent MDD

Knowledge concerning neuropsychological functioning in MDD is today mostly derived through studies based on populations of patients having experienced more than one episode of MDD, suffering from recurrent MDD. Research has shown that there is a positive correlation between number of depressive episodes and cognitive impairment (Kessing, 1998; Kessing, Dam, Jørgensen, Bolwig, 1996; Karabekiroglu, Topcuoglu, Gimzal Gonentur & Karabekiroglu, 2010) indicating that number of depressive episodes has a negative influence on cognitive functioning (Fossati et al., 2004). An important question is whether the cognitive impairment seen in recurrent MDD patients is present in patients experiencing a first episode of MDD. Despite some contradicting findings (Halvorsen et al., 2012; Halvorsen, Waterloo, Sundet, Eisemann & Wang, 2011), patients with recurrent MDD have been found to be more impaired in cognitive function compared to patients with first episode of MDD (Kessing, 1998; Basso & Bornstein, 1999; Fossati et al., 2004; Karabekiroglu et al., 2010). These finding has led to questions concerning whether multiple episodes of MDD may result in a scarring effect causing extensive changes in neurobiology and thus more severe cognitive dysfunctioning (Fossati et al., 2004; De Raedt & Koster, 2010).

1.4 Cognitive function in first episode MDD – acute phase

Researches that have investigated cognitive functioning in patients experiencing a first episode of MDD have found this group to perform equal to control subjects (Wang et al, 2006; Hammar, Kildal & Schmid, 2012) and significantly better compared to groups of recurrent MDD patients (Fossati et al 2004; Basso & Bornstein, 1999) on measures of attention and verbal memory in the acute phase of illness. One study, including both first episode and recurrent MDD patients in the acute phase of illness, Castaneda and colleagues (2008) found evidence of intact cognitive functioning across the cognitive domains of attention, memory, EF and psychomotor speed. In addition, this study reports no evidence of depression severity or number of depressive episodes having an effect on cognitive performance (Castaneda et al., 2008). Also including mixed groups, intact performance in attention, memory, psychomotor speed and in most measures of EF, except a measure of problem-solving and mental flexibility were reported in MDD (Grant et al., 2001). In contrast to findings of intact performance in several cognitive domains in this patient group, one study report first episode MDD patients to be impaired in measures of attention, psychomotor speed, visual- and verbal memory and in the EF of mental flexibility, semantic fluency and working memory (Kaymak et al., 2010). This study also reported reduced hippocampal volume in this patient group, however reduced volume did only correlate with poor memory performance (Kaymak et al., 2010). Other studies have also found changed neural activation and dysfunction in first episode MDD (van Wingen et al., 2011; MacQueen et al., 2003).

Focusing on EF, studies investigating first episode MDD patients in the acute phase of illness have found this subgroup to be impaired in inhibition and mental flexibility (Karabekiroglu et al., 2010; Ilonen, et al, 2000). In the study by Karabekiroglu et al., (2010), no difference in performance on the inhibition condition between first episode- and recurrent patients was found. Moreover, the recurrent group performed significantly worse in phonemic fluency, this pattern was not seen for the first episode group (Karabekiroglu et al., 2010). First episode patients have been found to be

impulsive in decision making and have greater attention towards sad stimuli compared to healthy controls, but intact performance on tasks measuring mental flexibility (Kyte, Goodyer & Sahakian, 2005).

In a meta- analytic study of cognitive functioning in the acute phase of illness, including many of the already mentioned studies, Lee and colleagues (2012) reported no impairment in measures of verbal –and working memory. However, first episode patients were impaired on measures of psychomotor speed, visual memory function, and in all other aspects of EF. Impairment in psychomotor speed and visual memory was associated with clinical state, whereas impairment in EF and attention were not (Lee et al., 2012). It is important to mention that in this study, of the 15 samples included, 9 included mixed subgroups of recurrent- and first episode MDD patients. This mix of subgroups may have confounded the results in that the performance in general may be affected by the performance of the recurrent patients, thus indeed being a result of recurrence.

1.4.1 Cognitive functioning in first episode MDD in a long term perspective

One study including mixed groups of first episode- and recurrent MDD patients in the remitted state of MDD, found patients to be impaired in verbal memory, but unimpaired in EF (Westheide, et al, 2007). Another study following patients in a longitudinal perspective showed that in contrast to recurrent patients, first episode patients showed improvement in memory functioning in line with clinical improvement (Nandrino, Pezard, Poste, Reveillere & Baune, 2002). In a longitudinal study following groups consisting of both first episode- and recurrent patients from initial episode, a general impairment across cognitive domains, including measures of EF was reported (Reppermund, Ising, Lucae & Zihl, 2009).

In sum, findings concerning cognitive impairment in first episode MDD are limited, and clearly show mixed results. There are some indications suggesting that this patient group may be impaired in cognitive functions, especially within the EF domain. However, more research is needed in order to draw inferences concerning

these findings. There is also a lack of longitudinal studies including patients with a first episode of MDD. Longitudinal designs will provide more detailed knowledge concerning the relationship between cognitive functioning and course of illness.

1.4.2 Executive function and illness course in MDD.

Few studies have investigated the implications of poor EF and the direct relationship between EF and illness course in MDD. This is somewhat surprising given the many research reports finding persistent EF impairment in MDD. In recent years, in addition to the diagnostic symptom evaluation in MDD, a broader focus has been on general daily life functioning in MDD (Doesschate, Koeter, Bochting & Schene, 2010). Research has found that MDD patients show reduced general daily life functioning both in the acute phase (Papakostas et al., 2004) and in phases of remission and recovery (Årdal, Lund & Hammar, 2012; Doesschate et al., 2010). There are further studies that report a positive correlation between daily life functioning and cognitive performance (McCall & Dunn, 2003) and cognitive functioning in the acute phase has been found to predict functional outcome 6 months later (Jaeger, Berns, Uzelac & Davis- Conway, 2006). Poor EF has been found to correlate with treatment seeking in depression (Castaneda et al., 2010). Impaired EF has been found to predict worse clinical symptom severity and functional outcome, both social- and occupational functioning (Withall, Harris & Cumming, 2009). Impaired mental flexibility has been found to correlate with poor treatment response and risk for relapse (Majer et al., 2004). One study reported that non- responders to antidepressant treatment with SSRI performed significantly worse than responders in pre-treatment measures of executive function, with especially impairment in perseverative- and inhibitory responses (Dunkin, et al., 2000). Geriatric MDD patients with impaired initiation and perseveration scores were found to show increased rate of relapse and recurrence (Alexopoulos et al., 2000). Contrary, one study found no association between poor EF and course of MDD (Reppermund et al., 2009). In sum, although limited, these results indicate that impaired EF may have a profound effect

on the individual with regard to general social- and occupational functioning, treatment response, and be a factor contributing to risk of relapse and recurrence.

1.5 Executive functioning and the relation to clinical and demographic factors

As described previously, there are diverse findings regarding cognitive impairment in MDD both in the acute phase and in a long term perspective. Although several studies report that EF is of particular importance in MDD, there is still no clear pattern of EF impairment in this patient group. The diverse findings characterizing this area of research may be a result of differences between studies concerning methodological design and the fact that depression is a heterogenic disorder both concerning causes and clinical symptom expression (Porter et al., 2007; Austin, et al., 2001; McClintock, Husain, Greer & Cullum, 2010). Clinical and demographic factors such as severity of depression, number of previous episodes, hospitalization, use of medication, presence of comorbid disorders and age have all been shown to influence cognitive performance in general, and EF in particular (Snyder, 2012). Not all depressed patients have impaired cognitive functioning, showing that there may be different subtypes of depressed patients, with different cognitive profiles (Airaksinen et al., 2004; Stordal et al, 2004; Hammar & Årdal, 2009). A large number of studies have included a mix of patients with different diagnostic subtypes such as unipolar and/or bipolar depressives, with or without psychotic symptoms, and first versus recurrent MDD. Thus, the impact these different symptomatic patterns may have on cognitive performance is important to address (Douglas & Porter, 2009). This has led researchers to argue for the inclusion of more homogenous patient groups differentiated by strict inclusion- and exclusion criteria (Porter et al., 2007; Hammar & Årdal, 2009). Important factors that are found to affect cognitive performance in general and that are of relevance in the present thesis is severity of illness, comorbid disorders, age, gender and the use of antidepressant medication.

1.5.1 Severity of illness

There are evidence of a relationship between severity of depression and EF performance, although results yield considerable diversity (McDermott & Ebmeier, 2009; McClintock et al., 2010), making these questions still unanswered. Studies have reported no relationship between depression severity and EF performance (Harvey et al., 2004; Hammar et al., 2011; Porter et al., 2007), while others report the opposite (Airaksinen et al., 2004; Paelecke-Habermann et al., 2005; Porter et al., 2003; Grant el at., 2001). As described in previous sections of the thesis, investigating patients longitudinally, studies find persistent EF impairment despite symptom severity decline (Neu et al., 2005; Reiches & Neu, 2000; Årdal & Hammar, 2011; Hammar et al., 2010). However, the relationship between severity and EF is complicated, and thus may yield for specific EF functions only (Trichard et al. 1995; Biringer et al., 2005). Also previously mentioned, there are findings suggesting that impaired EF is a more stable trait characteristic compared to memory function and performance in processing speed, which are more sensitive for symptom reduction (Douglas & Porter, 2009; Lee et al., 2011).

1.5.2 Comorbidity

High rates of comorbid disorders in MDD, and especially the high percentage of patients that presents comorbid anxiety (Kessler, Chiu, Demler, Walters, 2005) is important to acknowledge in research. Studies have found that MDD patients with comorbid anxiety perform poorer on measures of cognitive functioning in general (Kizilbash et al., 2002; Lyche, Jonassen, Stiles, Ulleberg, & Landrø, 2011a). The same pattern is evident in studies that focused on EF (Basso, et al., 2007; Lyche et al., 2011b; Lyche, Jonassen, Stiles, Ulleberg & Landrø, 2010), suggesting that this combination of symptoms have more adverse effect on EF. However, one study found no impact of co- morbid disorders on cognitive functioning in general and in EF (Castaneda et al., 2010).

1.5.3 Age and gender

Although not systematically investigated, there are findings showing that older MDD patients have a poorer performance in EF compared to younger subgroups (Nakano et al., 2008) and reviews have concluded that elderly patient groups are more impaired on cognitive function in general compared to younger patients (Porter et al., 2007; Elliott, 1998). Thus, poor EF in MDD may be confounded by the naturally occurring factors of aging (Snyder, 2012). One study contradicting this statement find no difference in EF performance between younger (<60 years) and older (>60 years) adults (Thomas et al., 2009).

Despite findings of higher prevalence and recurrence rates of depression in females (Kringlen et al., 2001; Lewinsohn et al., 1998; Kessler et al., 2005; Eaton, et al., 2008; Piccinelli & Wilkinson, 2000), there exist no indications of gender effects concerning MDD and cognitive functioning, and EF in particular (Porter et al., 2007; Hasselbalch et al., 2011). One reason for the lack of knowledge concerning gender effects on cognitive function in MDD may be that a large amount of research has a substantially higher number of women compared to men included.

1.5.4 Medication

The use of medication has been shown to both enhance (Harmer, Goodwin & Cowen, 2009) – and have negative effect (McClintock et al., 2010) on cognitive performance in MDD. Thus the effect of medication should be evaluated in research addressing EF in MDD. However, EF impairment has been reported in drug naive subgroups (Porter et al., 2003) and medication status have been found to have minimal effect on EF (Taylor Tavares et al., 2007). Although still not fully understood, the effects of modern antidepressant medication, such as Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin Noradrenalin Reuptake Inhibitors (SNRI), on cognitive performance in general are recognized as being minimal (Biringer, Rongve, & Lund, 2009). The sedative - and reported adverse effect of Tricyclic Antidepressants (TCA)

on cognitive function (Amado-Boccara, Gougoulis, Poirier Littrè, Galinowski & Lôo, 1995) is thus not shared by SSRI and SNRI.

In sum, it is important in studies of EF in MDD to describe the clinical sample investigated concerning severity, prevalence of comorbidity, medication use, age and gender, in order to control for the confounding effect these factors may have on the results.

1.5.5 Summary

The studies that concerns cognitive functioning in MDD show impairment in several cognitive domains, both in the acute phase, and in phases of symptom reduction and remission. There are further findings suggesting that impairment in EF, and especially inhibition and semantic fluency, may be of particular importance in MDD. These functions have been found to be impaired across symptom course. However, there is still a lack of longitudinal studies investigating EF in MDD. Further, knowledge concerning EF in first episode MDD is lacking. Thus, in order to draw inferences about the pattern and course of EF in MDD, studies should follow patients longitudinally. In addition, studies should aim at including patients that experience their first episode to gain knowledge of EF initial in the disorder.

2.0 Aims and research questions

The aim of the present thesis was to investigate EF longitudinally in recurrent- and first episode MDD patients. The present thesis sought to gain more knowledge about EF in the course of MDD in order to provide a better understanding of the nature and pattern of EF impairment that characterize this patient group. A sample of patients with recurrent MDD and a sample of first-episode MDD were included. The following research questions were investigated:

1) The research aim in paper I was to investigate a group of recurrent MDD in a 9 month follow –up study. The study pursued the results from the acute phase of illness and investigated if the impairment in specific EF seen in the acute phase persisted despite significant reduction in depressive symptoms. The background for this research question was the limited number of longitudinal studies investigating EF in MDD.

2) The research aim in paper II was to investigate EF in the acute phase of first episode MDD. The paper addressed the question if the impairment in specific EF found in recurrent MDD in the acute phase of illness is evident in the first episode. The background for this research question was the limited knowledge of EF initially in the disorder.

3) The research aim in paper III was to investigate the group of first episode MDD patients in a 1 year follow-up study. The research questions were twofold; first, the study pursued the results from the acute phase of illness and investigated if the EF impairment seen in the acute phase persisted despite significant reduction in depressive symptoms. Secondly, the study investigated if there was an association between EF and the experience of relapse of the disorder within the first year after initial episode.

3.0 Methods

3.1 Design and participants

The participants included in the present studies were recruited from two different projects which focused on cognitive functioning in patients diagnosed with MDD. In both projects the participants were followed longitudinally and were investigated with a comprehensive neuropsychological test battery at two occasions. All participants included in the two projects were Norwegian native speakers and vision and hearing were normal or corrected to normal.

In the first project, patients were recruited from the Department of Affective Disorders at Haukeland University Hospital, Division of Psychiatry, through collaboration between Haukeland Hospital Trust and The University of Bergen, Norway. At inclusion, patients were hospitalized. The control subjects were recruited among employees in the health care sector and among acquaintances of the employees of the Department of Biological and Medical Psychology; University of Bergen (UiB).These participants were included in the first paper of the present thesis.

In the second project the patients were included through cooperation with medical practitioners in the primary health care sector in Bergen and through cooperation with psychologists working in primary Psychiatric Healthcare for students (SPH). The SPH are run by the Student Welfare Organization in Bergen (SiB), University of Bergen (UiB). Patients were evaluated concerning their symptoms and severity, and given information about the present project, by their medical practitioner or psychologist. If evaluated to be suitable for participation based on the inclusion and exclusion criteria, patients were contacted by a clinical psychologist in the present project. Four patients were included through advertisement in the local newspaper, Bergens Tidende (BT), with directly contacting the clinical psychologist in the present project. The control subjects were recruited among students at the UiB, Bergen University College (HiB) and among acquaintances of the employees of the Department of Biological and

Medical Psychology, UiB. These participants were included in the second and third paper of the present thesis.

The two projects were performed in accordance with the Helsinki Declaration of the World Medical Association Assembly. The Regional Committees for Medical and Health Research Ethics and The Norwegian Data Protection Authority approved the projects.

The recurrent MDD group (Paper I).

This study was a 9 month follow- up study of patients meeting the DSM-IV criteria (APA, 2000) for a unipolar recurrent MDD diagnosis, using the MINI International Neuropsychiatric Interview (M.I.N.I), (Leiknes, Leganger, Malt, & Malt, 1999). This patient group was included in a study by Hammar & colleagues (2011) to investigate EF in the acute phase of illness. At inclusion to this study, in the acute phase of illness (T1), 24 patients (18 females and 6 males) between 17 and 56 years of age were recruited. Inclusion criteria were a minimum of one previous episode of MDD, and a score of 20 or above on the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) and 18 or above at the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), indicating moderate to severe depression. Exclusion criteria were a history of known brain damage, alcohol and/or substance abuse and/or psychosis, severe somatic illness or treatment with electro convulsive therapy (ECT). At T1, eight patients met the criteria for a co-morbid anxiety disorder. At T1 all patients informed that they were prescribed antidepressant medication. All, except four patients that were prescribed tricyclic antidepressants (TCA), used selective serotonin reuptake inhibitors (SSRI). At T1 a control group of 24 healthy subjects between 18 and 56 years of age were included, individually matched to the patient group on gender, and +/- 2 years on age and years of education. The control subjects were interviewed at inclusion concerning history of any mental and/or somatic illness. Exclusion criteria for the control group were a history of any mental disorder, severe somatic illness, brain damage, alcohol and/or substance abuse.

At the nine month follow- up assessment (T2), 20 patients and 19 control subjects were included. Drop- out for four patients and five control subjects resulted in missed data on these subjects. In addition, due to depressive and anxiety symptoms, one patient was only able to complete one test at the follow up assessment, the Color-Word Interference Test. At T2, the mean score on MADRS and HDRS indicated that the patient group was in symptom reduction at T2. At T2, all patients reported to use antidepressant medication. Three of the patients used TCA and the remaining used SSRI (see Table 1 for clinical and demographic variables for the patient group and control group at T1 and T2).

Table 1.
Recurrent group
Clinical and demographic data for patient group and the control group at T1 and T2.
Mean (M)Standard deviation (SD).

	T1*,acute phase		T2, symptom reduction	
	Patient Group N=24	Control Group N= 24	Patient Group N= 20	Control Group N=19
	M(SD)	M(SD)	M(SD)	M(SD)
Age	38.08(11.44)	37.12(11.46)	38.85(11.46)	38.15(10.84)
Years of education	12.42(1.86)	12.88(2.11)	12.45(2.21)	12.85(2.32)
Male/Female	6/18	6/18	3/17	5/14
IQ at inclusion (T1)	105.58(10.86)	110.5(7.97)	***	***
MADRS	27.08(5.19)	**	14.65(6.04)	**
HDRS	22.38(4.53)	**	11.75(4.61)	**
Hospitalizations	2.41(1.60)	**	****	
Weeks in hospital	9(15.15)	**	****	

** Data previously published in Hammar, Å., Strand, m., Årdal, G., Schmid, M., Lund, A., & Elliott, R. (2011). Testing the cognitive effort hypothesis of cognitive impairment in major depression. Nordic Journal of Psychiatry, 65, 74-80. doi:10.3109/08039488.2010.494311*

**Control group: no history of mental illness.

*** IQ (WASI) measured at T1. No significant difference between groups in total IQ (Hammar et al, 2011).

***** Measured at T1*

The first episode MDD group (Paper II and III).

In the acute phase (T1), 30 patients (16 males and 14 females) between 19 and 42 years of age, diagnosed with their first episode of unipolar MDD (APA, 2000), using the M.I.N.I (Leiknes et al., 1999) were included. Inclusion criterion was a minimum score of 20 on the MADRS (Montgomery & Åsberg, 1979) indicating moderate to severe depression. Exclusion criteria were a previous diagnosis of MDD or other mental disorder, known brain damage, severe somatic disorders, substance abuse, psychotic symptoms and treatment with ECT.

All patients were outpatients, receiving medical treatment (13, 3%), psychological treatment (30%), or both (33, 3%) for the first time, or no treatment at all (23, 3%). Two patients reported symptoms of panic disorder, and met criteria of a co-morbid diagnosis of panic disorder with agoraphobia. 14 patients were prescribed antidepressant medication; 12 were prescribed Selective Serotonin Reuptake Inhibitors (SSRI), one used Serotonin Noradrenaline Reuptake Inhibitor (SNRI), and one used a tetracyclic antidepressant (TeCA). 30 control subjects between 20 and 40 years of age, individually matched to the patient group on gender and matched on a +/- 2 years on age and years of education were included. The control subjects were interviewed at inclusion concerning history of any mental and/or somatic illness. Exclusion criteria for the control group were a history of brain damage, any severe somatic disorder or mental disorders and substance abuse (See Table 2 for clinical and demographic variables for the patient- and control group).

At the follow-up assessment (T2) 28 patients and their individually matched control subjects were included. Two patients were not included due to drop-out. The study coordinators were not able to regain contact with one patient, and one patient did not want to participate in the follow-up assessment. Respectively, data from their corresponding control subjects were not included. At T2, mean MADRS score indicated that most of the patients were in remission (see Table 2 for clinical and demographic variables for patient- and control group). Five patients were no longer receiving antidepressant medication, and one patient had started antidepressant

medication. Ten patients were prescribed Selective Serotonin Reuptake Inhibitors (SSRI) and one used Serotonin Noradrenaline Reuptake Inhibitor (SNRI). In total, 18 patients received medical and/or psychological treatment at T2 (see Table 3 for more detailed information regarding treatment).

Table 2.
First episode group
Clinical and demographic data for patient group and the control group at T1 and T2.
Mean (M)Standard deviation (SD).

	T1, acute phase		T2, remission	
	Patient Group N=30	Control Group N= 30	Patient Group N= 28	Control Group N=28
	M(SD)	M(SD)	M(SD)	M(SD)
Age	26.2(5.94)	26.17(5.69)	26.93(5.33)	26.93(5.18)
Years of education	13.97(1.71)	14.03(1.65)	14.29(1.76)	14.79(1.69)
Male/Female	16/14	16/14	14/14	14/14
IQ at inclusion (T1)	118.53(8.12)	120.97(8.23)	***	***
MADRS	24.6(3.73)	**	9.96(6.01)	**
Months depressed*	1.67(1.54)	**	*	**

* Moths depressed measured at inclusion.
**Control group: no history of mental illness.
*** IQ (WASI) measured at T1. No significant difference between groups in total IQ.

Due to questions regarding EF in the course of MDD, patients were interviewed retrospectively according to their illness course using a drawn timeline since inclusion, and categorized according to the experience of relapse of their illness during the previous year. The evaluation of relapse and remission was made based on the suggested operational criteria for outcomes in depression by Frank et al. (1991) and Rush et al. (2006). In the present thesis remission were also evaluated according to if the subject in remission described a period during which he or she experienced a better general every day functioning. Relapse were also evaluated according to if the subject described difficulties in everyday functioning, such as performing at an optimal level in areas such as school, work or social functioning, when experiencing a relapse. This categorization of patients resulted in three different subgroups of MDD,

a Relapse Group (RLG), (N=11), a No Relapse Group (NRG), (N=12) and a No Change Group (NCG), (N=5). This latter group reported that they did not experience any significant changes in their symptoms since inclusion. Differentiation between these three groups according to their MADRS scores showed that the RLG and the NRG were in remission, and that the NCG still was moderately depressed at T2 (sees Table 3 for clinical and demographic variables for the four subgroups, RLG, NRG, NCG and CG).

Table 3.
First episode group.
Clinical and demographic data for the Relapse Group (RLG), the No Relapse Group (NRG), the No Change Group (NCG) and the Control Group (CG) at T1 and T2.
Mean (M), Standard deviation (SD).

	RLG (N=11)	NRG (N=12)	NCG (N=5)	CG (N=30)
T1, acute phase	M(SD)	M(SD)	M(SD)	M(SD)
Age	25.09(6.47)	25.25(4.09)	29.6(4.88)	26.17(5.69)
Education	14.27(1.62)	14.25(1.96)	13(1.41)	14.03(1.65)
Males/Females	3/8	10/2	1/4	14/14
IQ at T1**	115.46(6.53)	119.08(9.65)	123.4(7.57)	120.97(8.23)
Months depressed	1.64(1.57)	2.08(2.07)	2(0.71)	*
MADRS score***	25(4.36)	23(2.49)	28(3.16)	*
Treatment	Frequency(percent)			
Psychological	2(18.2%)	5(41.7%)	1(20%)	*
Medical	1(9.1%)	1(8.3%)	2(40%)	*
Both psych/med.	6 (54.5%)	4(33.3%)	0	*
No treatment	2(18.2%)	2(16.7%)	2(40%)	*
T2, follow-up				
MADRS score****	9.09(5.19)	7.42(3.53)	18(6.33)	*
Treatment	Frequency/percent			
Psychological	3(27.3%)	1(8.3%)	1(20%)	*
Medical	1(9.1%)	0	1(20%)	*
Both psych/med.	4(36.4%)	6(50%)	1(20%)	*
No treatment	3(27.3%)	5(41.7%)	2(40%)	*

* control group, no history of mental illness.
** The NCG significanly higher mean IQ score compared to the RLG
*** The NCG significanly higer MADRS score compared to the NRG at T1 and T2.
****The NCG significanly higer MADRS score compared to the RLG at T2.

3.1.2 Clinical measures

The M.I.N.I, Norwegian Version (Leiknes et al., 1999) was administrated for both patient groups in the diagnostic evaluation. The M.I.N.I is a structural clinical interview for axis I psychiatric diagnoses in the DSM-IV (APA, 2000). The M.I.N.I was administrated at inclusion (T1) and performed by a trained clinical psychologist. To asses severity of depression the Montgomery Åsberg Depression Rating Scale (MADRS), (Montgomery & Åsberg, 1979) and/or the Hamilton Depression Rating Scale (HDRS), (Hamilton, 1960) were administrated. The MADRS consists of 10 items each rating symptom severity of depression. A score between 0 and 12 are classified as a condition not in the requirement of treatment. A score between 13 and 19 is classified as mild depression, with the requirement of treatment. A score between 20 and 34 is classified as a moderate to severe depression with the requirement of treatment, and a score of 35 or higher (max 60) is classified as a severe depression (Montgomery & Åsberg, 1979). The HDRS consists of 17 items each rating symptoms of depression. A score of 7 or less is classified as normal, a score between 8 and 13 are classified as mild depression, a score between 14 and 18 as moderate depression, a score of and between 19 to 22 as severe depression and a score above 23 are classified as very severe depression (APA, 2000). Screening patients for severity of depression was done both at the inclusion (T1) and at the follow-up assessment (T2), and performed by a trained psychologist. For the recurrent group both the MADRS and the HDRS were administrated. For the first episode group only the MADRS was used.

3.1.3 Neuropsychological assessment

To control for the effect of general intellectual abilities (IQ), the Wechsler's Abbreviated Scales of Intelligence (WASI), (Wechsler, 1999) were administrated at T1. For the recurrent group (Paper I) IQ was derived using the four-subtest form of the WASI. For the first episode group (Paper II and III) IQ was derived using the two-subtest form of the WASI (Wechsler, 1999).

In the three studies comprising the present thesis, selected tests from the Delis – Kaplan Executive Function System (D-KEFS), (Delis et al., 2001a) were administrated to investigate EF: the Color Word Interference Test (CWIT), the Verbal Fluency Test (VFT), the Trail Making Test (TMT) and the Tower Test (TT). These tests are adaptations of well-known neuropsychological tests often used in the literature (Delis et al., 2001a). In paper I, based on findings from the acute phase, the CWIT and VFT was analyzed at the follow up (T2). In paper II and III, all four tests were analyzed at inclusion (T1), and based on results from the acute phase, the CWIT, VFT and TMT were analyzed at follow-up (T2).

The neuropsychological tests were part of a large test battery, including other standardized and experimental tests. All testing was carried out by a trained test technician and performed during regular work hours. The neuropsychological assessment took approximately four hours to complete.

The D-KEFS Color-Word Interference Test (CWIT)

The CWIT consists of the four following conditions: 1) Color Naming (C), 2) Word Reading (W), 3) Inhibition (the classic Stroop condition) (CW), and 4) Inhibition/Switching (IS). In each condition the subject is presented with an A4 page displaying the stimuli (color patches and words) and is asked to perform the tasks as fast as possible.

In condition one, the Color Naming condition (C), the subject is presented with a sheet consisting of color patches in red, blue and green and is to name the ink colors successively stating from the left top corner of the page. In condition two, the Word Reading condition (W), the subject has to read the words (red, blue and green) written in black as fast as they can. In both the C and W conditions basic cognitive skills such as naming speed and reading speed are measured. In condition three, the Inhibition condition (CW), the subject is presented with words written in the colors red, blue and green. In this condition the subject has to inhibit the automatic response of reading the colored words and instead name the incongruent ink color the words are written in.

Thus, the ability to inhibit the automatic response of reading is measured. In condition four, the Inhibition/Switching condition (IS), the subject has to do the same as in the inhibition condition, except reading the words when the colored words are presented within a frame. In condition four the ability to inhibit an automatic response of reading and the ability to shift mental set (mental flexibility) are measured. In all four conditions seconds to complete the trial is derived. In addition, contrast scores and errors scores (errors and self-corrected errors) for each condition are derived.

The D-KEFS Verbal Fluency Test (VFT).

The VFT consists of three conditions. Condition one, Letter Fluency (LF) comprises three trials (F, A, S) were the subjects have to generate phonemically lexical items beginning with F, A or S as quickly as possible within a 60 second time limit for each trial. Condition two, Category Fluency (CF) comprises two trials (animals and boys' names) where the subjects have to retrieve multiple words belonging to the same semantic category as quickly as possible within a 60 second time limit for each trial. Condition three, Category Switching (CS) consists of one trial where the subjects are to switch successively between categories, naming fruits and furniture, within a 60 second time limit. All three conditions (LF, CF and CS) depend on cognitive skills such as speed of processing, vocabulary knowledge, initiation, spelling ability and attention. For the specific conditions, cognitive functions that are measured are systematic retrieval of phonemically similar lexical items (LF), rapid retrieval of multiple words belonging to the same semantic category (CF) and cognitive flexibility (CS). In all three conditions number of a total correct words produced in each condition is derived. In addition, contrast scores and two sets of errors; set-loss errors and repetition errors are derived.

The D-KEFS Trail Making Test (TMT)

The TMT consists of five conditions, and in each condition of the TMT, except for condition five, Motor Speed (MS), where the subject is to draw over a dotted line as fast as possible, the subject is presented with an A3 sheet of paper filled with

randomly placed numbers and letters. In condition one, Visual scanning (VS), the subject has to visually identify and mark every Number 3 which are present among other stimuli as quickly as possible. In the second condition, the Number Sequencing (NS) and third condition, Letter Sequencing (LS) the subject has to as quickly as possible draw a line from 1 to 16 (NS) and from a to p (LS). In the fourth condition, the Number- Letter Switching condition (NLS) the subject has to draw a line as quickly as possible switching between numbers and letters (1- A, 2- B, 3- C etc.) as fast as possible. The primary executive function task in TMT is the fourth condition (NLS), which measure mental flexibility. The other four conditions measure more basic cognitive skills such as visual scanning, attention, motor speed, numerical- and alphabetical processing. In all five conditions seconds to complete the conditions is derived. In addition, contrast scores and errors scores: omission – and commission errors and set-loss - and sequencing errors are derived.

The D-KEFS Tower Test (TT).

The TT consists of nine trials with increasing difficulty. The subject is asked to build towers on pegs using disks varying in size from small to large. The subject has to build designated towers presented to them on the stimulus booklet within a time limit specified for each trail, using as few moves as possible, and following specific rules. The TT computes a total achievement score (TAS) which comprises the total scores obtained across the nine trials. In addition, optional process measures such as Mean first move time, Time- per- move Ratio, Move accuracy Ratio, Total Rule Violations and Rule- Violations- Per- Item Ratio can be derived. The TT is recognized as a challenging executive task and investigates the ability of spatial planning, rule learning, inhibition and the ability to establish and maintain a cognitive set. Basic cognitive tasks such as visual attention and visual-spatial skills are also needed to complete the task. Contrast measures are not derived in the TT.

3.1.4 Contrast scores in the D-KEFS

The D-KEFS provides an opportunity to examine contrast scaled scores for the CWIT, the VFT and the TMT. The contrast scaled scores are provided to gain a more detailed picture concerning an impaired performance in the different conditions. In example, if a subject has a poor performance in all or most of the conditions in the CWIT test, the poor performance in the inhibition – and the inhibition/switching conditions could be a result of reading difficulties and/or poor processing speed (word reading and color naming). The contrast scaled score is derived by subtracting the completion-time scaled score for one of the more basic cognitive abilities, such as naming colors or reading words, from the completion-time scaled score for one of the executive function (EF) tasks, such as inhibition or inhibition/switching. The scaled score difference provides the opportunity to derive a contrast scaled score which gives information about the causes of an impaired score. The contrast scaled scores have a mean of 10, and a standard deviation of 3. A contrast scaled score between 8 and 12 reflects an equivalent level of performance on the EF task and on the more basic cognitive task. A contrast scaled score of 13 or higher reflects a better performance on the EF task relative to the more basic component task, and a contrast scaled score of 7 or lower indicates worse performance on the EF task.

3.1.5 Data recorded from the D-KEFS

Data recorded from the four D-KEFS tests were raw scores (seconds to complete trial, number of words produced, Total Achievement Score, number of Errors). To examine contrast scores in the present thesis either contrast scaled scores was derived for the patient group (paper I) or contrast scores were calculated for all subjects using raw scores, (paper II and III).

3.1.6 Statistical analyses

The statistical analysis of the data was carried out using the Statistical Package for the Social Sciences (SPSS) version 19 and 20. Independent Samples t -Tests were computed to compare the groups for demographic and clinical variables, and error

analysis. Paired Sample t- Test was administered to assess change in cognitive performance across time. Bivariate correlation was computed to investigate the relationship between cognitive function and depression severity, and partial correlations were conducted to explore the consistency in test performance across time. Repeated measures between-groups analyses of variance were conducted for the EF performance across time. The basic design was Group (depressed patients and control subjects) x Test occasion (Test 1 and Test 2) x Test (condition). Multivariate - and univariate between-groups analysis of variance was conducted to investigate differences between the patient group and control group in EF. A multivariate analysis of variance with post hoc comparisons (Tukey HSD) was conducted to explore the differences in cognitive functioning between the subgroups of MDD. A logistic regression analysis was computed to explore the predictive value of poor inhibition and inhibition/switching performance on tendency to relapse in the patient group.

4.0 Summary of papers

Paper I

Paper I pursued findings from a study of Executive Functioning (EF) in the acute phase of illness in a group of recurrent MDD patients (T1), (Hammar et al., 2011). Administrating all four tests from the D- KEFS, Hammar and colleagues (2011) concluded upon a specific impairment in the EF functions of inhibition and semantic fluency.

Paper I investigated if the impairment seen in inhibition and semantic fluency persisted or normalized in relation to symptom reduction, in a 9 month follow- up study (T2). We hypothesized in accordance with previous longitudinal studies finding persistent impairment in inhibition and semantic fluency, that the patient group would still be impaired compared to the control group at the follow-up assessment. 20 patients with recurrent MDD, currently in symptom reduction, and 19 healthy control subjects were included and retested. The results showed that the patient group still performed poorer compared to the control group in the EF of inhibition, inhibition/switching and semantic fluency. Further, the results showed that the patient group performed poorer in one measure of processing speed, color naming. However, a calculation of mean contrast scaled scores for the patient group showed that poor processing speed did not solely account for the poor performance in inhibition and inhibition/switching. The patient group did not perform poorer compared to the control group in measures of phonemic fluency and mental flexibility in general. The results also showed that for the patient group there was a strong correlation between performance in inhibition across T1 and T2.This pattern of performance was not evident for performance in semantic fluency. Moreover, the results showed no correlation between depression severity and cognitive performance. In conclusion, there is a prolonged impairment across time in inhibition and semantic fluency in recurrent MDD. Further, in a 9 month perspective, the findings suggest that inhibition may represent a stable trait marker in recurrent MDD.

Paper II

Paper II investigated EF in first episode MDD. We hypothesized, based on the previous literature suggesting a relatively stable impairment in inhibition and semantic fluency in MDD that the group of first episode MDD patients would be impaired compared to the control group on these EFs. Paper II investigated the inhibition, phonemic- and semantic fluency, mental flexibility and planning- and problem solving, in a group of 30 patients with a first episode of MDD in the acute phase of illness and a group of 30 healthy control subjects. The results showed that the patient group performed significantly poorer compared to the control group on inhibition, inhibition/switching and semantic fluency. The patient group did not show equivalent difficulties in phonemic fluency, planning and problem solving, or in the other EF measures of mental flexibility. However, the patient group performed significantly poorer on three conditions that relay on speed of mental processing, namely, color naming, word reading and visual scanning. The calculation of contrast scores comparing the two groups showed that processing speed alone could not account for the impaired performance in inhibition and inhibition/switching. The results showed no correlation between depression severity and cognitive performance, but that patients that used medication performed poorer than those that did not in color naming and inhibition/switching. In conclusion, specific EF impairment in inhibition and semantic fluency was found to be present in first episode MDD. Paper II shows that patients with a first episode of MDD may show a similar pattern of impairment in EF as previously found for subgroups of recurrent MDD.

Paper III

Paper III pursued findings from the acute phase of first episode MDD patients (Schmid & Hammar, 2013a) and investigated whether the impairment seen in inhibition and semantic fluency would persist or normalize in a one-year follow up assessment (T2), and if there was a relationship between poor inhibition and semantic fluency in the acute phase and relapse during the follow up period. Based on previous findings it was hypothesized that the patient group would still perform poorer

compared to the control group in inhibition and semantic fluency, and that poor performance would correlate with the experience of relapse. 28 patients and their individually matched control subjects were included in the follow up assessment. Most patients were in remission. The results showed that the patient group in general still performed poorer compared to the control group in inhibition, inhibition/switching and semantic fluency. However, the performance in inhibition was more severe when an additional requirement of mental flexibility was demanded. Performance was not impaired in phonemic fluency or in the other EF measures of mental flexibility. The patient group was also impaired in three measures of processing speed, namely word reading, visual scanning and number sequencing. However, a calculation of contrast scores showed that processing speed could not solely account for the poor performance in EF. In addition, patients that used medication performed poorer in one processing speed measure; the number sequencing condition, and better on the semantic fluency condition, compared to those that did not.

Results showed that patients in the relapse group and the no relapse group were in remission, while the no change group still had symptom severity indicating mild to moderate depression. The no change group differed from the two other groups showing higher mean severity score at T1 and T2 and higher mean IQ score. Although there were no gender differences in EF performance in general, there was a substantial higher distribution of females in the relapse group. Moreover, results showed that the relapse group performed significantly poorer compared to the no-relapse group and the control group in inhibition/switching in the acute phase, and that poor performance in the inhibition/switching condition in the acute phase of illness may predict the experience of a relapse. There were no significant differences between the four subgroups in semantic fluency performance. The relapse group showed an improvement in some measures of processing speed, and in phonemic – and switching fluency. The no relapse group also showed improvement in some measures of processing speed and in inhibition performance across time.

No improvement was found for the no change group. In conclusion, patients diagnosed with their first episode of MDD show, independent of symptom severity, a prolonged impairment in inhibition, inhibition /switching and semantic fluency. Further, impairment in inhibition/switching may be a vulnerability factor for the experience of relapse.

5.0 Discussion

5.1 Summary of findings

The main findings in the present thesis supported the hypothesis of inhibition and semantic fluency representing a stable and persistent impairment in MDD across illness course. The findings demonstrate that both groups of recurrent- (Schmid, Strand, Årdal, Lund & Hammar, 2011) and first episode (Schmid & Hammar, 2013a; Schmid & Hammar, 2013b) MDD patient have a specific impairment in the ability to inhibit, in inhibition while simultaneously mental flexibility is required, and in semantic fluency compared to the healthy control groups. Performance in more basic cognitive tasks such as motor performance, attention, initiation, spelling ability, vocabulary knowledge and other EF measures such as phonemic fluency, planning and problem-solving or in other tests requiring mental flexibility were not impaired. Further, the thesis found no support for poor processing speed to reflect a general challenge in MDD, affecting performance across the EF measures. There was however some results indicating an effect of antidepressant use on cognitive performance. Further, results showed that there was a stable individual performance in the ability to inhibit in the recurrent patient group, and for both the functions of inhibition and semantic fluency performance in the first episode group across time, suggesting that the inability to inhibit may be a stable individual trait in both patient groups, and that there are some evidence of the same stability concerning the poor performance in semantic fluency.

Dividing the group of first episode MDD patients in subgroups according to the experience of relapse within the follow- up period in Paper III (Schmid & Hammar, 2013b), the findings in the present thesis suggest that there may be different subgroups in MDD which show different course of illness and that these subgroups also may differ concerning EF. The present thesis found support for the hypothesis that patients who experienced a relapse would be more impaired in inhibition in the acute phase of illness compared to patients that did not experience a relapse.

However, the inability to inhibit was most affected when additionally the function of mental flexibility was required, and performance in inhibition/switching was found to be predictive for the tendency to experience relapse. Not supporting the hypothesis, the relationship seen between relapse and poor performance in inhibition/switching was not evident for performance in semantic fluency. In sum, the results show that poor inhibition/switching in first episode MDD in the acute phase to a larger degree characterizes the function of those patients that are vulnerable for the experience of relapse.

5.1.2 Executive Functioning in MDD- specific EF impairment.

The results in the present thesis support the theoretical hypothesis stating that EF is of importance concerning the cognitive profile in MDD (Elliott, 2003; Austin et al., 2001; Snyder, 2012). However, investigating several functions within the EF domain, such as phonemic- and semantic fluency, inhibition, mental flexibility and planning and problem-solving, the thesis found support for a more specific impairment, namely impaired inhibition and semantic fluency. These findings support previous studies reporting impaired inhibition performance in the acute phase of illness (Harvey et al., 2004; Gohier et al., 2009; Hammar et al, 2011; Markela- Lerenc, et al., 2006; Stordal et al., 2004; Rund et al., 2006) and in phases of symptom reduction and remission (Nakano et al., 2008; Smith et al., 2006; Paradiso et al., 1997; Paelecke-Habermann, et al., 2005). The present results are also in accordance with other longitudinal studies finding impaired inhibition across illness course (Hammar et al., 2010; Årdal & Hammar, 2011; Biringer et al., 2005; Trichard et al., 1995), thus the thesis show that impaired inhibition is of importance in MDD, probably accounting for many of the difficulties these patients experience.

The findings of impaired semantic fluency is also confirmed by other studies (Henry & Crawford, 2005; Ravnkilde et al., 2002; Gohier et al., 2009; Fossati et al, 1999; Stordal et al., 2004; Naismith et al., 2003; Fossati et al., 2003; Paelecke-Habermann et al., 2005; Okada et al., 2003; Okada et al., 2009; Calev et al., 1989; Hammar et al., 2011). The thesis supports the longitudinal studies reporting persistent impairment in

semantic fluency across time (Neu et al., 2005; Reiches & Neu, 2000; Biringer et al., 2005)). Regarding verbal fluency performance in MDD, the findings in the present thesis are in accordance with previous studies finding intact phonemic fluency performance in MDD (Nakano et al., 2008) and impaired semantic – but intact phonemic fluency in MDD (Fossati et al., 1999; Fossati eta al., 2003; Hammar et al., 2011; Calev et al., 1989). These findings support the assumption that semantic- and phonemic fluency may depend on different retrieval mechanisms that require different cognitive resources (Henry & Crawford, 2005; Fossati et al., 2003; Snyder, 2012). As described in the introduction section, impaired semantic fluency in depression has been found to be influenced by an additional difficulty to mentally switch between subcategories (Lafont et al., 1998; Fossati et al., 2003; Fossati et al., 1999), which may contribute to the poorer performance in semantic fluency compared to phonemic fluency in depression. In addition, due to the pronounced impairment seen in inhibition in this patient group, one can assume that due to the divergence of negative thoughts and ruminative tendencies often found in MDD (Nolen-Hoeksema, 1991; Nolen-Hoeksema, 2000; Nolen-Hoeksema et al., 2008) impaired ability to inhibit may cause difficulties allocating resources to the sematic fluency task. In the phonemic fluency task, patients may benefit from the structure that vocal cues provide, making them less vulnerable for the tendency to ruminate. However, the present thesis can only speculate concerning the influence of inhibition. More studies are needed to address the mechanisms behind semantic- and phonemic fluency function in MDD since there is support in the literature for semantic fluency being a cognitive function of importance.

The findings in the present thesis showing a specific impairment within the EF domain contradict other studies and meta- analysis supporting a more general impairment across EF in MDD (Snyder, 2012; Naismith et al., 2003; Stordal et al., 2004; Ravnkilde, et al., 2002; Harvey et al., 2004) and studies that report MDD patients to perform equal to control subjects across EF (Halvorsen et al., 2012; Vythilingam et al., 2004), including inhibition (Merens, et al., 2008) and semantic fluency performance (Austin et al., 1999; Harvey et al., 2004). Concerning mental

flexibility, it is important to highlight that although there are reports of intact mental flexibility in MDD patients (Kyte et al., 2005; Hammar et al., 2011), the majority of studies investigating this ability find MDD patient to be impaired (Austin et al., 1999; Purcell et al., 1997; Taylor Tavares et al., 2007; Fossati, et al., 2003; Fossati, et al., 1999; Airaksinen et al., 2004). Impaired mental flexibility is further found to interact with performance requiring other cognitive resources and contribute to poor performance (Fossati et al., 1999; Fossati et al., 2003; Lafont et al., 1998), which indicates that this cognitive function are of importance in MDD. In the present thesis both depressed patient groups demonstrated poorer performance on the task that requires both inhibition and mental flexibility, showing that this combination may be of particular difficulty, and it can be discussed whether the other measures of mental flexibility in the present thesis may not be sensitive enough to detect this disability in MDD. In example, low reliability scores are reported for the third condition of the verbal fluency test, category switching (Delis, Kaplan & Kramer, 2001b). However, the relative consistent performance in EF across time and subgroups in the present thesis rather suggests that poor performance in inhibition/switching may not reflect impaired mental flexibility in general.

The present thesis also demonstrates that planning and problem-solving are not impaired in the acute phase of illness in MDD. However, planning and problem-solving abilities are found to be poor in MDD patients (Snyder, 2012; Naismith et al., 2003; Cella et al., 2010). In contrast, there are also studies that report no such impairment (Purcell et al., 1997; Porter et al., 2003; Hammar et al., 2011), indicating that this EF is not that pronounced in MDD patients. Studies have found MDD patients to be impaired in inhibition, verbal fluency and in working memory, but that patients did not perform impaired in mental flexibility, planning and problem-solving (Stordal et al., 2004; Hammar et al., 2011). Another study reported MDD patients with late onset depression (> 50 years) to be impaired in planning and problem-solving, while patients with early onset performed equal to controls, suggesting that age at onset may be an important factor regarding planning and problem-solving ability (Naismith et al., 2003).

The contradicting results evident in the literature may be caused by methodological differences between studies with regard to which EF are measured and which tests of EF are administrated. Some studies have only administrated one test of EF (Preiss et al., 2009; Markela- Lerenc et al., 2006; Årdal & Hammar, 2011; Hammar et al., 2009) which makes differentiating between performances within EF difficult. The present thesis has an advantage in following two independent patient groups across illness course and using a consistent standardized battery of EF tests (Delis et al., 2001a). The advantages of this design are first and foremost the control of the impact the use of different tests and different methodology will have on results. Secondly, the inclusion of several measures of EF makes it possible to gain knowledge concerning which EF is most affected in MDD.

In sum, the present thesis suggests that MDD patients do not show a comprehensive impairment affecting EF in general, but finds support for a more specific impairment within EF, affecting inhibition and semantic fluency. The thesis therefore supports the view that EF should be viewed as consisting of different cognitive functions encompassing the domain, and not solely as one unitary concept.

5.1.3 Impairment in inhibition and semantic fluency and effect of poor processing speed.

When interpreting the findings of the present thesis, it is important to address the poor processing speed that was evident in some measures. Results of poor processing has often been reported in the acute phase of illness (Lee et al., 2012; Den Hartog et al., 2003; Egeland et al., 2003; Egeland et al., 2005; Tsourtos et al. 2002). Although there are findings of impaired processing speed in remission (Halvorsen et al., 2012) processing speed is generally found to be sensitive to clinical state (Egeland et al., 2005; Porter et al., 2003; Douglas & Porter, 2009; Lee et al., 2012; Neu et al., 2005; Weiland- Fiedler et al., 2004). Contrary to this last inference, the findings of impairment in measures of processing speed across time in the present thesis suggest that reduced speed of processing may persist beyond the depressive state in MDD. Reduced processing speed has been suggested to account for poor cognitive

performance in general in MDD (Den Hartog et al., 2003). However, supporting other studies in the literature (Snyder, 2012; Hammar et al., 2011; Purcell et al., 1997; Porter et al., 2003; Airaksinen et al., 2004) the thesis could not find indications of poor processing speed affecting cognitive performance in general. This interpretation was based on two inferences. First, by controlling the effect poor processing speed may have on inhibition and inhibition/switching by the use of contrast measures. Secondly, a general processing speed deficit would probably affect performance across EF and not just be evident in specific measures. Summarized, the present thesis shows that MDD patients may struggle with impairment in speed of processing despite significant symptom decline. However, there is no indication in the present thesis that reduced speed of processing alone can account for the impairment in EF.

5.1.4 Stable EF impairment in MDD.

The findings in the present thesis suggest that performance in inhibition and semantic fluency is not sensitive for severity of illness. Thus, impaired inhibition and semantic fluency are not a state phenomenon in MDD, but rather stable traits, persisting during phases of symptom relief and remission. These findings support previous results showing that EF represents stable traits in this patient group (Douglas & Porter, 2009; Lee et al., 2011). The individually stable performance seen in inhibition across time in both patient groups, independent of symptom severity, contributes to the interpretation of this impairment representing a stable trait. This pattern of a stable individual performance in inhibition has also been found in a 10-year follow up study of recurrent MDD patients (Årdal & Hammar, 2011), which show that poor inhibition ability are stable across a considerable length of time. However, regarding the persistent impairment seen in semantic fluency, the thesis showed that the pattern of stable individual performance across time in semantic fluency was only evident in the first episode group. In addition, the thesis found that medication use may have an enhanced effect on performance in semantic fluency, suggesting that semantic fluency performance across time may be more affected by other variables during illness course. One previous longitudinal study reported semantic fluency performance to

normalize in accordance with symptom decline, while inhibition performance remained impaired (Trichard et al., 1995). However, the lack of association between semantic fluency performance and severity of depression in the present thesis, indicate that impairment in semantic fluency may be more variable and sensitive to other factors characterizing MDD patients during illness course, such as variables related to direct effects of medical treatment.

5.1.5 Impaired inhibition and semantic fluency performance in first episode MDD.

The thesis show that impairment in inhibition and semantic fluency are present already in first episode of MDD, and it may be assumed that these impairments are not a result of a cognitive scarring effect caused by previous experienced episodes. These findings are supported by other studies investigating EF in first episode MDD patients, showing impaired EF in general (Lee et al., 2012; Kaymak et al., 2010; Kyte et al., 2005), and inhibition, semantic fluency and mental flexibility in particular (Ilonen et al, 2000; Karabekiroglu et al., 2010; Kaymak et al., 2010). Evidence of neurobiological dysfunction in this subgroup also supports the presence of impairment initial in the disorder (van Wingen et al., 2011; MacQueen et al., 2003). Studies have also reported this patient group to have intact performance in measures of memory (Wang et al., 2006) and effortful information processing (Hammar et al., 2012) in the acute phase of illness. Further, this patient group show improved memory function with symptom decline (Nandrino et al., 2002). Seen in accordance with the results in the present thesis, these findings suggest that aspects of EF may represent core cognitive dysfunctions in MDD, present in first episode and during phases of symptom decline and remission.

However, in the present thesis, due to important demographic differences and differences concerning general intellectual ability (IQ), the recurrent- and first episode patients were not compared on performance in EF. Thus, only indirect inferences could be drawn concerning interpretations of a cognitive scarring effect. As mentioned, the majority of studies in the literature have included mixed groups of patients with recurrent- and first episode MDD (Lee et al., 2012). Thus the effect of

recurrence may account for the impairment seen across groups. In order to gain more direct inferences concerning the effect number of depressive episodes have on EF; more studies are needed, following the same patient group longitudinally.

5.1.6 Subgroups of MDD and vulnerability for relapse

The results in the present thesis suggest that there may be subgroups within MDD that show different clinical – and cognitive profiles. The thesis demonstrate that within one group of first episode MDD patients there were three subgroups that developed a different course of illness with regard to the experience of relapse and level of symptom severity across time. The findings in the thesis are in accordance with the high rates of relapses estimated in this disorder (Mueller et al., 1999; Hardeveld et al., 2010) which states that approximately 50 % will experience a relapse or recurrence within only months (Riihimäki et al., 2011) or within approximately two years (Solomon et al., 2000; Stegenga, et al., 2012; Vuorilehto et al., 2009) after being in remission or recovery. The findings in the thesis are also in accordance with studies reporting that for approximately 20% of MDD patients, their symptoms persist and exceeds 24 months (Spijker et al., 2002), thus developing a more chronic course of illness.

The thesis also demonstrate that these subgroups differ with regard to EF, with poor performance in inhibition/switching being more pronounced in the relapse group, and that performance in this function were associated with higher probability of experiencing relapse. These results suggest that poor inhibition/switching may be a vulnerability trait affecting probability of experiencing a relapse. This pattern was however not evident for performance in semantic fluency, or the other EF measures, which support the assumption previously given of semantic fluency performance being sensitive for other factors characterizing the illness. In addition, the three subgroups differed with regard to improvement in cognitive functioning across time, with the relapse- and the no relapse group showing improvement in some measures of processing speed and EF, and the finding of no such improvement in the no change group. These results could be effects of symptom improvement, although the thesis

did not find any correlation between symptom severity and cognitive performance in general. However, due to small sample size and other possible confounding variables it is important that the interpretations concerning the findings differentiating the three subgroups should be made with great caution. These methodological limitations enhance the probability of making Type II error (these limitations will be discussed in more detail in section 5.2, under strengths and limitations).

As previously described studies have shown that course of illness in MDD has been associated with clinical factors such as severity of illness and presence of residual symptoms. Severity of the preceding episode has been found to be a factor contributing to the persistence of symptoms (Spijker et al., 2002: Stegenga et al., 2012). Further, severity of the preceding episode and presence of residual symptoms is found to be important predictors of relapse and recurrence (Vuorilehto et al, 2009; Riihimäki et al., 2011; Stegenga et al., 2012; Hardeveld et al., 2010). These variables were however not measured in between the acute phase and follow-up assessment in Paper III, thus the present thesis can only discuss the possible implications of these factors. The higher severity score across time in the no change group compared to the two other groups may thus suggest that severity of the preceding episode is a factor of importance concerning persistence of symptoms. The somewhat higher mean severity score seen in the relapse group compared to the no relapse group in the acute phase may also suggest that severity of the preceding episode can represent a factor influencing the tendency to relapse. More studies are needed in order to reveal the relationship between the effect of depression severity, course of illness and relationship between these clinical factors and EF.

Although victim of methodological limitations, the findings that these three subgroups of patients differ with regard to clinical course– and EF, are of importance and should be viewed as preliminary in the search for important factors contributing to the high relapse and recurrence rates in MDD. Especially since other longitudinal studies have found a correlation between EF and risk of relapse (Majer et al., 2004; Alexopoulos et al., 2000). Further, the documented implications of poor EF affecting

general functioning (Withall et al., 2009) and response to antidepressant medication (Dunkin et al., 2000) suggest that EF may influence course of illness in MDD. Although there are results showing no association between cognitive impairment and course of MDD (Reppermund et al., 2009), the findings in the present thesis suggests that the relationship between EF and course of illness should be targeted in future studies, following a large number of first episode MDD patients longitudinally with a focus on the direct effect of poor inhibition, inhibition/switching and semantic fluency.

5.1.7 Clinical implications of the present findings.

The results of the present thesis suggest that the EFs of inhibition and semantic fluency are important in the understanding of the cognitive profile in MDD. Impaired performance in these functions may account for many of the challenges this patient group experience. The implications of poor semantic fluency are complex since few studies have correlated this function to clinical characteristics of MDD. Nevertheless, given the description of this function being dependent on efficient retrieval processes (Delis et al., 2001a; Henry & Crawford, 2005; Neu et al., 2005) and affected by the ability of initiation and mental flexibility (Lafont et al., 1998; Troyer et al., 1997; Fossati et., al., 2003; Klumpp & Deldin, 2010), poor performance may have severe effects on the individual's ability to keep relevant information in working memory and to flexibly adapt to changes in context. The implications of poor inhibition have been somewhat more studied in relation to the clinical characteristics of MDD. As described, impaired inhibition have been associated with poor ability to suppress negative thought and tendency to ruminate, a tendency found to represent a trait characteristic in MDD (Joormann et al., 2007; Joormann & Gotlib, 2008; Gohier et al., 2009; Nolen- Hoeksema, 1991; Nolen –Hoeksema, et al., 2008). Ruminative tendencies and other maladaptive cognitive coping strategies such as emotional suppression and catastrophizing are more frequently found coping strategies in individuals with depressive symptoms (Garnefski & Kraaij, 2006). These patients seldom use the coping mechanism of positive reappraisal which is suggested to be an

important aspect of emotion regulation (Garnefski & Kraaij, 2006). Seen in accordance with research finding inhibition to be important for emotional regulation (Gotlib & Joormann, 2010; Joormann & Gotlib, 2010), this cognitive function may be of importance affecting patients adaptive regulation and coping mechanisms. As previously mentioned, inhibition has been found to be more impaired in patients that have had past suicide attempts (Keilp et al., 2008).

Of importance in this matter, is the finding showing that the inability to inhibit and poor functioning in semantic fluency can affect patients from an early phase of the disorder and further through illness course although they no longer fulfill the diagnostic criteria for a depressive illness. Thus, this persistent impairment may affect patients' ability to regain their former function when the symptoms of depression are reduced. For the individual, this can lead to considerable frustration, helplessness and low self-esteem which may contribute to the relapse of depressive symptoms (Snyder, 2012; Hammar & Årdal, 2009). Seen in accordance with the results of the present thesis, showing that poor inhibition with the additional requirement of switching was more pronounced in patients that experienced a relapse compared to those that did not experience relapse, one might speculate that the less pronounced impairment in this function could represent a resilience factor making the individual more responsive for treatment and providing a more adaptive regulation and managing of depressive symptoms. This may in turn make it easier to regain former function and thus make these individuals less vulnerable for experiencing a relapse of their depression. Individual differences in inhibition may be a factor affecting course of illness.

Regarding the implications for treatment in MDD, the results in the present thesis add to the growing literature suggesting that the presence of cognitive impairment across illness course warrant new therapeutic strategies, aimed at targeting and improving these dysfunctions (Murrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011; Trivedi & Greer, 2014). It is important to inform patients and clinicians concerning persistent cognitive impairment and to adjust for a more facilitated return to work, school and/or studies. At the same time, it is important to communicate that long term

effects of impaired cognitive performance may not affect a general cognitive impairment, but rather be a result of specific impairment. Further, it is important to communicate that this pattern of cognitive functions does not yield for every depressed patient. MDD is a highly heterogeneous disorder and as shown in the present thesis there may be subgroups within this disorder that show a different course of illness.

5.2 Strengths and limitations

The longitudinal design in the present thesis and the inclusion of a group with first episode MDD makes an important contribution concerning the investigation of the course of EF across illness course in MDD. However, when interpreting the findings in the present thesis it is important to address and discuss certain methodological issues.

As mentioned, strength of the present thesis is the inclusion of several measures of EF and of more basic cognitive functions such as processing speed, making it possible to differentiate between functions of most importance in MDD. The D-KEFS have been found to be a sensitive tool in the assessment of executive function deficits in numerous clinical populations (Delis, Kramer, Kaplan & Holdnack, 2004; Homack, Lee & Riccio, 2005; Shunk, Davis, Dean & Dean, 2006). However, the D-KEFS has also received criticism regarding providing moderate to low reliability scores, and poor validity for some tests included (Schmidt, 2003; Baron, 2004), especially the low reliability scores of the contrast measures (Crawford, Sutherland & Garthwaite, 2008). However, in a review, the authors respond to the validity concerns by highlighting that several of the EF tests in the battery build upon previous well validated neuropsychological tests (Delis et al., 2004).

Another strength of the present thesis is the inclusion of measures of general intellectual abilities using the WASI (Wechsler, 1999), which made it possible to control for differences in general intellectual abilities (IQ). Also, the inclusion of two independent control groups individually matched to the patient groups according to

age, education and gender are of importance controlling for the effects of these demographic variables on cognitive performance and for the effects of learning across inclusion- and follow-up. According to age, both patient groups had a mean score of < 40 years which show that the two subgroups were relatively young and the effects previously found of age on EF (Porter et al., 2007; Elliott, 1998; Naismith et al., 2003) would probably not be evident across subgroups in the present thesis.

A limitation in the thesis is the relatively low number of subjects included. In the recurrent patient group, only 20 patients were available for reassessment at follow-up. This may affect the power of the tests administrated regarding identifying possible differences in EF performance between the patient and control group. Furthermore, the subgroups that emerged based on relapse experience comprised few subjects, with the No Change Group only consisting of 5 individuals. Thus, the combination of small groups and the use of parametric statistical analysis with strict post hoc analysis and alpha levels make the probability of type II error more likely. The results concerning the differences between the three subgroups of MDD patients should therefore be regarded as preliminary. Concerning gender effects, the thesis showed no results of gender having an effect on EF in general in the patient group across time. However, when dividing the patients in subgroups according to the experience of relapse, gender effects emerged, showing that 72,7 % of the patients that experienced a relapse were female. This suggests that gender should be further explored in relation to EF. This is important due to the literature showing higher relapse – and recurrence rates for female gender (Kringlen et al., 2001; Lewinsohn et al., 1998; Kessler et al., 2005; Eaton, et al., 2008; Piccinelli & Wilkinson, 2000).

All of the patients in the recurrent group, and about half of the patients in the first episode group were prescribed antidepressant medication. The present thesis could therefore not rule out the effect of medication on EF performance. The thesis found that medication use may have had both an adverse and an enhanced effect on cognitive performance. In paper II, patients that used medication performed worse in one measure of speed of processing, color naming, and in inhibition/switching. In

paper III, patients that used medication showed a better performance in semantic fluency and worse performance in some measures of psychomotor speed. Both scenarios are supported in the literature (McClintock et al., 2010; Harmer et al., 2009; Biringer, et al., 2009; Taylor Tavares et al., 2007). However, EF impairment has also been reported in drug naive subgroups of MDD (Porter et al., 2003). In the present thesis most patients used SSRIs and SNRIs, which found to have minimal effect on cognitive performance (Biringer, et al., 2009). Medication use did not correlate with the other measures of cognitive performance, thus the present thesis could not find support for medication having an effect across cognitive performance.

The two patient groups showed few comorbid disorders, which may be considered a strength since the presence of comorbid disorder has been found to affect cognitive performance in general (Kizilbash, et al., 2002; Lyche, et al., 2011a), and EF (Basso, et al., 2007; Lyche et al., 2011b; Lyche et al., 2010). However, the control of such confounding variables may reduce generalizability. Especially since the presence of comorbid disorders are the rule more often than the exception in MDD (Kessler et al, 2005), with estimates of comorbidity of nearly 72% (Kessler et al., 2003). A limitation in the present thesis is that the MINI - International Psychiatric Structural Interview (Leiknes et al., 1999) was not administered at the follow up assessment, thus important information about potential comorbid disorders that had developed during the follow-up period may have been lost. Further, there was a lack of a clinical evaluation and standardized measure to confirm symptomatic state of patients during the follow-up interval, which makes it difficult to draw firm conclusions regarding the course of depression in between inclusion and follow-up assessment. Future longitudinal studies should have excessive measurements of depressive symptomatology during the follow up period to gain a better understanding of the relationship between EF and clinical factors.

5.3 Conclusions and future research directions

The present thesis found support for a specific and long lasting impairment within the EF domain, namely impaired inhibition and semantic fluency. In particular, the thesis

finds support for the suggestion that impaired inhibition may represent a stable trait in MDD, which characterizes to a larger degree those patients that experience a relapse of their depression. However, due to methodological concerns the results showing an association between poor inhibition and tendency to experience relapse should be replicated. The literature still needs more longitudinal studies to explore the stable pattern of inhibition and semantic fluency in MDD. Preferably, studies should aim at targeting patients before the onset of illness to gain knowledge concerning the role of EF in the development and persistence of MDD. The clinical implications of poor inhibition and poor ability in semantic fluency should be addressed in future research, with a focus on the mechanisms behind these functions and how they affect patients thinking and behavior, everyday functioning and response to treatment. Especially important in this sense is how these functions affect the individual emotional regulation and coping skills. The exploration of this relationship will provide more knowledge concerning how cognitive functioning and especially EF, may contribute to the understanding of why some patients experience recurrent MDD while others stay healthy after experiencing one episode.

6.0 Source of data

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