A study of
recurrent unipolar major depression
and executive functions

by

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Contents

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Abbreviations

BOP	Bergen-Oslo Project
BPRS/BPRS-E	Brief Psychiatric Rating Scale Expanded
CalCAP	California Computerized Assessment Package
catc	categories completed from the WCST
categor	categorical verbal fluency from the COWAT
C.I.	Confidence Interval
COWAT	Controlled Oral Word Association Test
CRT	Complex Reaction Time test from the CalCAP
CVLT	California Verbal Learning Test
d	Choen's *d*
DB/db	Digit Span Backward subtest from the WAIS-R
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECT	Electro Convulsive Therapy
EF/EFs	Executive Functions
FTMS/ftms	Failure To Maintain Set from the WCST
fMRI	functional Magnetic Resonance Imaging
GAF	Global Assessment of Functioning scale (DSM-IV)
HDRS	Hamilton Depression Rating Scale
HPA	Hypothalamic-Pituitary-Adrenal
ICC	Intra-Class Correlation

LDFR	Long Delay Free Recall from the CVLT
LGP	Level of General Psychopathology
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
PANSS	Positive And Negative Syndrome Scale
PANSS-G	General psychopathology subscale from the PANSS
PASAT	Paced Auditory Serial Addition Test
pasat2	2-seconds inter-stimulus interval subtest from the PASAT
pasat3	3- seconds inter-stimulus interval subtest from the PASAT
PC	Picture Completion subtest from the WAIS-R
PET	Positron Emission Tomography
perserr	perseverative errors from the WCST
phonem	phonemic verbal fluency from the COWAT
R^2	square of the regression coefficient
r	Pearsons' correlation coefficient
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SD/S.D./s	Standard Deviation
SeqRT1	Sequential Reaction Time 1 from the CalCAP
SeqRT2	Sequential Reaction Time 2 from the CalCAP
SIM	Similarities subtest from the WAIS-R
SiRT	Simple Reaction Time test from the CalCAP
SSRIs	Selective Serotonin Re-uptake Inhibitors
Stroop	Stroop Colour and Word Test
Stroop c-w/STROCW	Colour-Word subtask from the Stroop

ToL/tol	Tower of London test
VSVT	Victoria Symptom Validity Test
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WCST	Wisconsin Card Sorting Test
WHO	World Health Organisation

ToL/tol   Tower of London test

VSVT   Victoria Symptom Validity Test

WAIS-R   Wechsler Adult Intelligence Scale-Revised

List of papers

This thesis is based on the following papers which will be referred to in the text by their Roman numerals:

I Stordal KI, Lundervold AJ, Egeland J, Mykletun A, Asbjørnsen A, Landrø NI, Roness A, Rund BR, Sundet K, Oedegaard KJ, Lund A. Impairment across executive functions in recurrent major depression. Nord J Psychiatry 2004; 58: 41-47.

II Stordal KI, Lundervold AJ, Mykletun A, Asbjørnsen A, Biringer E, Egeland J, Hammar Å, Landrø NI, Roness A, Rund BR, Sundet K, Lund A. Frequency and characteristics of recurrent major depressed patients with unimpaired executive functions. World J Biol Psychiatry 2005; 6(1): 36-44.

III Stordal KI, Mykletun A, Asbjørnsen A, Egeland J, Landrø NI, Roness A, Rund BR, Sundet KS, Lundervold AJ, Lund A. General psychopathology is more important for executive functioning than diagnosis. Acta Psychiatr Scand 2005; 111: 22-28.

IV Egeland J, Lund A, Landrø NI, Rund BR, Sundet K, Asbjørnsen A, Mjellem N, Roness A, Stordal KI. Cortisol level predicts executive and memory function in depression, symptom-level predicts psychomotor speed. Acta Psychiatr Scand 2005; 112: 434-441.

Summary

Background

Unipolar major depression is a prevalent disorder and is in the World Health Organisation's (WHO) top five on their global burden of disease-list. For more than three decades, assessment of neurocognitive functioning in patients with mental disorders by use of neuropsychological tests has been performed for research purposes. Patients with schizophrenia have been extensively studied, but a substantial amount of research has also been performed on depressed patients.

In patients with unipolar major depression, performance below that of healthy controls has been shown on tests measuring memory, attention, psychomotor speed and executive functions. Executive Functions (EF) are higher order neurocognitive functions that control and integrate other neurocognitive functions; dysfunctions have been associated with frontal lobe dysfunction. Still, there is a lack of studies investigating EF in the most prevalent form of unipolar major depression, patients with recurrent subtype.

This thesis is based on four original research papers published in referee based international journals. In paper I, we question whether executive dysfunctions also are present in patients with recurrent unipolar major depression compared to healthy controls. The investigation includes pattern and severity of executive dysfunction. In paper II, we consider whether all patients with recurrent unipolar major depression have impairment of EF. Mental disorders can be regarded as both categorical and dimensional conditions: according to the continuum model unipolar major depression and schizophrenia can be viewed as different levels of general psychopathology (LGP).

Paper III explores the continuum model of mental disorders. We investigate whether LGP explains more of the variance in EF than diagnosis (unipolar major depression versus schizophrenia). Elevated levels of the stress hormone cortisol are often found among depressed patients, and there is evidence that prolonged hypercortisolemia can be neurotoxic. Specifically, recurrent depression episodes may lead to progressive brain damage. It is uncertain if executive dysfunctions in recurrent unipolar major depression are associated with elevated cortisol levels. Therefore, the aim of paper IV was to explore whether level of saliva cortisol is correlated with level of executive dysfunctions in recurrent unipolar major depression.

Method

Data were collected in the context of a Norwegian, cross-sectional, multi-centre study, the BOP, starting in 1998. In the BOP, patients with either a diagnosis of unipolar major depressive disorder (MDD), recurrent type (N=50) or schizophrenia (N=53) and healthy controls (N=50) were included. The patients were diagnosed by the Structured Clinical Interview for DSM-IV Axis I Disorders. Depressed patients scoring above 18 points on both the Hamilton Depression Rating Scale and Montgomery-Åsberg Depression Rating Scale were included. Other inclusion criteria were: age between 20 and 50, Norwegian language and normal vision and hearing. Patients were excluded if they had a history of head trauma, neurological disorder or developmental dysfunction, present alcohol or substance abuse, other medical conditions likely to affect neurocognitive functions or if they recently had received electro convulsive treatment. The clinical psychiatric evaluation was performed by five trained psychiatrists. In the BOP, a broad neuropsychological test battery was used to measure several domains of neurocognitive function. In this thesis, mainly tests assessing components of EF are used. The tests were administered by a licensed clinical neuropsychologists, a graduate

psychology student or a medical doctor (Kirsten Irene Stordal) supervised by a neuropsychologists.

Results

There was a tendency for patients with recurrent MDD to perform below healthy controls on all measures of EF (Paper I). A significant group difference was found for eight of ten measures. The executive dysfunctions were within -1.0 SD from the mean of the control group. While the components verbal fluency, inhibition, set-maintenance and working memory were affected in recurrent MDD, set-shifting and planning seemed to be spared. Whether this dysfunction could be found in all patients with recurrent episodes of depression, was uncertain. This was explored in the following paper, the result being that more than half of the patients with recurrent MDD had unimpaired EF when unimpairment was defined as performance above -1.0 SD of the sample mean of the control group on more than one component of EF (Paper II). The sub-group of patients without impairment of EF was characterised by higher intellectual abilities and fewer episodes of depression than the subgroup with EF impairment. In paper III we found EF impairment to be more strongly related to LGP than to diagnosis (MDD versus schizophrenia). In the last paper an inverse correlation between saliva cortisol and EF was found (Paper IV).

Discussion

All the papers add to current knowledge in this field: The first paper in that patients with recurrent MDD have mild executive dysfunctions, and that seemingly all components of EF are affected. The second paper shows that more than half of patients with recurrent MDD have unimpaired EF when depressed, and that this subgroup has higher intellectual abilities and a history of fewer depression episodes. The novel

finding in the third paper is that EF impairment is more strongly related to LGP than diagnosis (comparing MDD and schizophrenia). This finding is in line with the continuum hypothesis in psychiatry. In recurrent MDD, the level of performance on tests assessing EF seems to be inversely correlated with the level of saliva cortisol. Thus, this fourth study directly and indirectly gave support to the cortisol hypothesis.

There is little evidence that unipolar major depression is uniquely associated with executive dysfunctions due to that 1) most components of EF are affected, 2) not all patients have executive dysfunctions, 3) executive dysfunctions are not specific to depression as they are also found in other mental disorders and in somatic disorders and 4) not all depressed patients have elevated levels of cortisol associated with executive dysfunctions. Future studies of the association between mental disorders and neurocognitive dysfunction should avoid restrictions resulting from imperfect diagnostic classifications for mental disorders, i.e. focusing on similarities in neurocognitive dysfunctions across psychiatric diagnoses rather than within one mental disorder at the time.

Introduction

Neuropsychological studies of patients with depression have been performed for several decades, and the first paper reviewing neurocognitive deficits associated with depression was published in 1975 (Miller, 1975). Today, a substantial amount of neurocognitive research has been performed on patients with depression, but still there are several unanswered questions. The present thesis will attempt to answer a selection of these questions relating to the neurocognitive domain of EF in patients with recurrent unipolar major depression.

This thesis is based on four original research papers published in referee based international journals. The thesis is organised into five main sections. First in the introduction section, the epidemiology and clinical characteristics of unipolar major depression is presented. Thereafter, literature that is mainly from the period that this study was planned and data were collected regarding the association between neurocognitive function with a special focus on EF and unipolar major depression is summed up. A subsection follows concerning whether mental disorders are categorical or dimensional conditions. Finally in the introduction section, the neurobiology of unipolar major depression is presented with a focus on models of the pathogenesis of recurrent depression and executive dysfunctions. The next section clarifies the main aim and sub-aims of the present study. In the material and methods section, the study design, the samples and the psychiatric, neuropsychological and cortisol measurements are presented as well as the statistical analyses used. In addition, relevant ethical aspects of the study are presented. In the results section, summaries of the results from the four papers are given. In the last section of the thesis, a synopsis of results is given along with a discussion of these results in light of previous findings including updated

literature. The idea of presenting "older" literature in the introduction and updated literature in the discussion is to illustrate the continued development within these areas since publication of the papers. Before discussing general methodological issues relevant to the present study, this section approaches possible functional consequences of executive dysfunctions for depressed patients and the underlying pathogenesis of executive dysfunctions. Thereafter is included the conclusions of the study and their clinical implications. Finally, suggestions for future research are given.

The literature search mainly used the PubMed/Medline, PsycINFO and EMBASE databases. The search terms were cognition, neuropsychology, neurocognition, EF, depression, major depression, unipolar major depression, MDD, recurrent depression, cortisol and saliva cortisol. The literature used for the main aims for the most part included clinical studies, but also meta-analyses and review papers when they were available. The clinical studies selected were so because they were either the best or the newest or because the method (the neuropsychological tests or operationalisation), the sample or the design was most similar to the present study.

Unipolar major depression

Mental illness is by WHO defined as absence of good mental health. Epidemiological studies have repeatedly found a 12-month prevalence of mental disorders of approximately 30 % and lifetime prevalence about 50 % (Kessler et al., 2005, Kringlen et al., 2001). Among the 10 leading causes of disability worldwide, five of them are mental disorders (Lopez and Murray, 1998). The mental disorder associated with the highest disability rate is unipolar major depression followed by alcohol abuse, bipolar disorders, schizophrenia and obsessive-compulsive disorders. Epidemiological studies

suggest that mental disorder is the single leading cause of permanent work-related disability in Norway (Mykletun and Øverland, 2006, Mykletun et al., 2006, Sivertsen et al., 2006).

Today, unipolar major depression is rated as the fourth most important contributor to the global burden of disease, and the WHO predicts that it will become the second largest cause of disability by the year of 2020 after ischemic heart disease (Lopez and Murray, 1998). A 12-month prevalence of 6.6 % and a life-time prevalence of 16.2 % were recently found according to DSM-IV criteria for Major Depressive Disorder (MDD) (Kessler et al., 2003). In comparison, the lifetime prevalence of non-affective psychoses including schizophrenia ranges from 0.4 % to 0.7 % (Kringlen et al., 2001, Kessler et al., 2005). The point-prevalence of depression has been shown to be stabile over a period of 40 years, only slightly increasing in women below 45 years (Murphy et al., 2000). Women seem to experience major depression about twice as often as men, both in 12-month and lifetime perspectives (Kringlen et al., 2001, Kessler et al., 1994, Kessler et al., 2003). MDD co-occurs with both somatic as well as other mental disorders. Three fourths of patients with lifetime MDD also met the criteria of at least one other DSM-IV disorder compared to two thirds of patients with 12-months MDD, and the most commonly occurring co-morbid disorders are anxiety disorders, substance abuse disorders and impulse control disorders (Kessler et al., 2003).

For the individual, major depression is a serious condition generally associated with high risk of psychosocial impairment (Angst, 1999, Judd et al., 2000), reduced quality of life (Isacson et al., 2005) and increased mortality and risk of suicide (Blair-West et al., 1999, Cuijpers and Smit, 2002). In many respects major depression should be regarded as a chronic and life-threatening disorder (Angst, 1999, Cuijpers and Smit,

2002). Major depression has extensive medical, social and economic effects and costs for society. The impaired work capacity of depressed people leads to a loss of productivity that has been suggested to exceed the costs of effective treatment of major depression (Wang et al., 2004).

All levels of depressive symptomatology can be found in the population. The symptoms range from none to mild, to subtreshold levels of major depression, to major depression, and it has been shown that many patients with subtreshold major depression receive treatment in the community (Angst and Merikangas, 1997). Diagnosis of MDD is based on anamnestic information and observation of clinical characteristics, not on evidence of underlying neurobiological pathology. MDD is also known as major depression, clinical depression or unipolar major depression (including only depressed mood and not the opposite pole of hypomania/mania as in bipolar disorders). MDD includes both single episode and recurrent episodes of unipolar major depression. The core symptoms of MDD are those involving disturbances of mood and affect. According to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders for Axis-I Disorders (DSM-IV) the diagnosis of a major depressive episode involves the presence of five or more of these listed symptoms for a period of at least two weeks: depressed mood, markedly diminished interest or pleasure, feelings of worthlessness or guilt, diminished ability to think or concentrate, recurrent thoughts of death or suicide, or various somatic symptoms such as weight loss/gain or decreased/increased appetite, insomnia/hypersomnia, psychomotor agitation/retardation and fatigue or loss of energy (American Psychiatric Association, 1994). Either depressed mood or diminished interest should at least be present. To qualify for recurrent MDD the patients must have had a minimum of two depression episodes with an interval of at least two consecutive months where the criteria of a

MDD is not fulfilled. MDD can be treated either with psychotherapy, pharmacotherapy

or preferably both (Kaplan et al., 1994, Bauer et al., 2002a, Bauer et al., 2002b). The

characteristic symptoms in schizophrenia are delusions, hallucinations, incoherent

speech, blunted/flat/inappropriate affect, catatonic behaviour and negative symptoms

(American Psychiatric Association, 1994). In order to diagnose schizophrenia

according to the DSM-IV, six criteria must be met. Today, schizophrenia is mainly

treated with newer antipsychotic medication in the western world (Marder, 2000).

Neuropsychological research has for more than three decades resulted in a view of

neurocognitive dysfunction as a core feature in both MDD and schizophrenia;

especially in schizophrenia (Austin et al., 2001, Green, 1998). Dysfunction may have

negative consequences for the patients' general functioning and ability to cope

occupationally (Austin et al., 2001, McCall and Dunn, 2003). Still, there are several

unanswered questions with regard to the association between MDD and neurocognitive

functions, in particular regarding recurrent MDD and EF.

Recurrent episodes

The majority of patients suffering from MDD will experience recurrent episodes of depression. It is therefore important to achieve greater insight into the association between recurrent MDD and neurocognitive function. MDD is a remitting though recurring disease. The likelihood of recurrence is higher than 50 % and the occurrence of a first episode of depression, especially if the episode is long, increases the risk of future episodes (Angst, 1999). Long-term estimates of recurrence have been as high as 85 % for patients with an episode of major depression and 58 % for patients who remained well for 5 years (Mueller et al., 1999). These risk factors for recurrence have been suggested: female sex, a lengthy index episode, several prior depression episodes and that the person has never been married (Mueller et al., 1999). Other predictors of recurrent episodes are psychosocial factors, loss events, previous hospitalisation and late-onset depression (Angst, 1999). The symptoms or subtypes have been shown to be highly variable from episode to episode in recurrent MDD (Oquendo et al., 2004). It has been reported that recurrently depressed patients often receive antidepressant treatment below levels shown effective in maintenance therapy; a prolonged treatment with effective levels of antidepressant treatment has been recommended to prevent or postpone recurrence of episodes (Mueller et al., 1999, Young, 2001). An increased understanding of how recurrent MDD and neurocognitive functions are related may improve preventive and therapeutic interventions for this subgroup of patients.

Neurocognitive function in unipolar major depression

Cognition, neuropsychology and mental disorders

Cognition can be defined as "the information-handling aspect of behaviour" (Lezak, 1995). While cognitive psychology focuses on the human information processes associated with normal function, neuropsychology is engaged in the behavioural expressions of brain dysfunction in both neurological and non-neurological disorders (Lezak, 1995, Lundh et al., 1996, Stuss and Levine, 2002). In patients with psychiatric symptoms, neuropsychological testing can be used in order to reveal possible underlying brain damage or neurological disorder causing the symptoms, or it can measure type and degree of neurocognitive dysfunction in patients with a known mental disorder (Howieson and Lezak, 1992).

The discipline of neuropsychology can be divided into clinical neuropsychology and experimental neuropsychology. Clinical neuropsychology engages in the clinical application of knowledge of brain-behaviour associations for diagnostic, treatment and rehabilitation purposes (Lezak, 1995). An important part of the evaluation is the neuropsychological testing that often includes both pencil and paper tests as well as computerised tests. The neuropsychological assessment of adults relies on comparisons between the patient's present level of functioning and the known or estimated level of premorbid functioning as well as on a comparison of inter-subjective results across a wide range of neuropsychological tests (Lezak, 1995). In clinical research, significance testing is most often used to detect differences between groups of subjects (Lezak, 1995, Zakzanis et al., 1999).

Historically, the localisation of brain functions has been central in neuropsychology (Stuss and Levine, 2002). Neuropsychological assessment is more a description of behaviour and a measure of functioning, and neuroimaging techniques are commonly used to identify functional brain abnormalities associated with major depression and schizophrenia. More recent neuroimaging studies often include an assessment of neuropsychological function (Austin et al., 2001, Elliott, 2002). So, it can be argued that localisation of neurocognitive functions has been actualised in recent clinical research linking behavioural data and neuroimaging evidence.

Neurocognitive function in unipolar major depression

To the experienced clinician, it is well known that depressed patients often complain of difficulties concentrating and remembering. A diminished ability to concentrate is also included as a key symptom in the diagnostic classification of a major depressive episode in the DSM-IV and is an integral component of some depression scales, i.e. the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979).

It is now widely accepted that major depression is associated with deficits in a range of neurocognitive domains (Austin et al., 2001, Elliott, 2002, Veiel, 1997). During the last two decades, studies have investigated neurocognitive deficits of different clinical subgroups of patients with major depression and impairment has been reported in attention (Landrø et al., 2001b, Mialet et al., 1996, Porter et al., 2003, Zakzanis et al., 1999), memory (Austin et al., 2001, Landrø et al., 1997, Veiel, 1997, Zakzanis et al., 1999), psychomotor functions (Degl'Innocenti et al., 1998, Mialet et al., 1996, Zakzanis et al., 1999) and EF (Austin et al., 2001, Degl'Innocenti et al., 1998, Fossati et al., 1999, Grant et al., 2001, Porter et al., 2003), and intellectual abilities have been

reported to be spared (Austin et al., 2001). There is still no general consensus of a specific neurocognitive profile for either unipolar major depression or schizophrenia, although several studies have compared the neuropsychological patterns of the two diagnostic groups (Egeland et al., 2003, Fossati et al., 1999, Goldberg et al., 1993, Merriam et al., 1999). While deficits are seen in several neurocognitive domains in unipolar major depression, executive deficits associated with frontal lobe dysfunction seem to be particularly prominent (Austin et al., 2001, Elliott, 1998, Veiel, 1997).

Regarding the severity of the dysfunction in depressed patients, some studies have indicated that major depressed patients perform at the same level as controls on neurocognitive tests (Grant et al., 2001), whereas others have compared their level of performance to that of patients with traumatic brain-damage (Veiel, 1997). Nevertheless, differences are most often reported to be within the range of from minus one half to minus one standard deviation (Lampe et al., 2004, Landrø et al., 2001b). Neuropsychological studies find performance in patients with major depression or schizophrenia below that of healthy controls, with schizophrenic patients consistently performing at lower levels than patients with major depression (Goldberg et al., 1993, Merriam et al., 1999). There also seems to be an inter-individual variation in severity of neurocognitive impairment in both major depression and schizophrenia, with some patients performing in the impaired and some in the non-impaired range (Palmer et al., 1997, Veiel, 1997). The question concerning how many unipolar major depressed patients are neurocognitively healthy is rarely discussed.

Executive functions in unipolar major depression

There is a general understanding of the presence and importance of superior control functions, but still there are numerous terms for these functions such as "executive

functions", "executive processing", "dysexecutive control", "frontal functions", "supervisory functions", "central executive" and many more (Landrø et al., 2001a, Logan, 2000, Stuss and Alexander, 2000). In the present thesis these higher order functions will be referred to as EF because this term is probably more often used in the literature. Some authors have viewed EF as a unitary function, but mostly several subfunctions or components have been described within the concept of EF (Lezak, 1995, Stuss and Alexander, 2000). There are several definitions of EF. In clinical studies, the concept is not often defined, but is rather described as results on tests thought to measure aspects of EF (Degl'Innocenti et al., 1998, Fossati et al., 1999, Grant et al., 2001, Merriam et al., 1999). Tests used to assess EF have either been shown to be impaired by frontal lesions or to exemplify a theoretical account of EF, or both (Pennington and Ozonoff, 1996). Lower performance on tests of EF can result from damage in the frontal lobes and damage in other brain areas (Stuss and Alexander, 2000).

In the present thesis EF is defined as higher order cognitive functions involved in complex, self-serving, intentional behaviour that control, integrate, organise, inhibit or maintain other cognitive functions, i.e. attention, memory and language functions (Bryan and Luszcz, 2000, Lezak, 1995, Pennington and Ozonoff, 1996, Pohjasvaara et al 2002). Further, the concept of EF has been defined and operationalised as a set of different components. Pennington and Ozonoff have described these components as abilities of set-shifting, planning, inhibition, working memory and fluency (Pennington and Ozonoff, 1996). The components of EF have been operationalised by using neuropsychological tests that are recognized as being able to measure these subfunctions. Some of these tests are used in studies of depressed samples.

Impaired EF can disrupt the ability to perform complex daily life skills, and may influence the personal, social, occupational or educational lives of patients with damage to the frontal lobes (Griegsby et al., 1998, Manchester et al., 2004, McGurk and Mueser, 2003).

In general, most previous studies investigating EF in MDD have included samples of patients with either first episode of depression or a mixture of single and recurrent episodes of major depression. There is a lack of neurocognitive studies investigating EF in homogeneous samples of recurrent MDD patients to obtain high statistical power. Deficits in EF have been found in patients with MDD on a group level (Austin et al., 2001, Degl'Innocenti et al., 1998, Fossati et al., 1999, Grant et al., 2000, Merriam et al., 1999). It remains a question whether there is a significant group difference between patients with recurrent depression and healthy controls on measures of EF. In addition, there is a lack of information regarding the pattern and severity of executive dysfunctions in these patients.

Even if a group difference is found, it is uncertain if all patients with recurrent MDD show EF deficits or if this is found in a sub-group only. In patients with schizophrenia, the level of performance varies across patients, with a substantial proportion of them performing as neuropsychologically normal as their healthy peers (Palmer et al., 1998). In general, there is a lack of studies that identify patients with MDD who are neuropsychologically normal, and in particular studies that identify and characterize patients without impaired EF. A recent report from a study of patients with unipolar depression indicated that EF impairment predicted non-response to fluoxetine, and it was suggested that EF assessment in depressed patients could "play a particular role in the pre-treatment identification of subjects likely to respond to specific medications"

(Dunkin et al., 2000). It is also possible that normal performance on EF can be a positive prognostic factor in patients with major depression as suggested for patients with schizophrenia (Palmer et al.,1998). Thus, it is important to identify the frequency and characteristics of patients with recurrent MDD without EF impairment.

Mental disorders as categorical or dimensional conditions

Different diagnostic categories or subtypes have been investigated to search for specific neurocognitive profiles as exemplified in the above section. Still, there is no general understanding of a specific profile for unipolar major depression or schizophrenia (or for any other mental disorder). Often quantitative performance differences between diagnostic groups have been reported, which reflects not only different levels of neurocognitive dysfunction but perhaps also different Levels of General Psychopathology (LGP). Therefore, it is interesting to explore whether executive dysfunctioning is associated with diagnostic category or with LGP. If executive dysfunctioning is more strongly related to LGP than to diagnosis, this can be taken as support for the continuum hypothesis in psychiatry.

The categorical approach is perhaps the most common in psychiatry, but psychiatric syndromes may be more dimensional than categorical by nature. First, there is a range of psychiatric symptoms in the population, and the same symptoms can be found in different syndromes (overlap). Many people have a mixture of symptoms indicative of the co-existence of several syndromes at the same time (co-morbidity). All levels of psychiatric symptoms are found in the population from none to high. There is also great variability in symptomatology and severity from patient to patient with the same

disorder. Additionally, over time there seems to be a shift between psychiatric diagnoses.

The discussion of whether mental disorders are categorical or dimensional conditions is old, but has been actualised by the ongoing work with the fifth version of DSM and an increasing focus on the short comings of the categorical approach for both clinical practice and research (Cuthbert, 2005, Krueger et al., 2005, Kupfer, 2005, Lunbeck, 1999, Widiger and Samuel, 2005). In clinical research, an ideal has been to include diagnostic homogenous groups of patients, patients that all have the same mental disorder or subtype of the disorder, and preferably none or few confusing co-morbid disorders. In clinical practise, clinicians must decide who is sufficiently ill to justify treatment and communicate with other clinicians. It is therefore necessary for them to use categorical concepts of mental disorders. Some of the problems connected with these categorical classification systems are: 1) the systems are consensus-based and not evidence-based, 2) the systems have extensive co-morbidity and overlap problems attached to them, 3) the systems produce an increasing number of mental disorders due to diagnostic splitting and 4) the systems have a problem with "sub threshold cases" (Lunbeck, 1999, Widiger and Samuel, 2005). Improved classification systems based on new findings from research in genetics, basic neurology and pathophysiology have been suggested (Hyman, 2002, Sher, 2000). On this basis, clinical research should probably include groups of patients with broader ranges of psychiatric symptomatology.

Recently, there has been a growing interest in the dimensional approach in psychiatry (Cuthbert, 2005). A psychiatric continuum ranging from bipolar disorders to schizophrenia, based on findings from genetic, biochemical and pharmacological

studies, has been depicted (Möller, 2003). New perspectives on mental disorders as
dimensions have also been proposed, and it is possible that the DSM-V will have
dimensional elements included (Cuthbert, 2005). Lately, studies designed to "integrate
spectrum and dimensional approaches in addition to categorical ones" have been
requested (Kupfer and Frank, 2003).

To the best of our knowledge, there is a lack of neuropsychological studies of patients
with mental disorders that explore the continuum hypothesis/dimensional approach.
Using this model, it can be argued that MDD and schizophrenia represent different
levels of psychopathology along the same continuum. There is also empirical evidence
that supports this view. Firstly, it has been shown that patients originally diagnosed
with MDD were later re-diagnosed with bipolar disorder and sometimes schizophrenia
(Chen et al., 1998). Secondly, there is no general understanding of a specific
neurocognitive profile for MDD or for schizophrenia, though mostly quantitative but
also qualitative differences between the groups have been suggested (Egeland et al.,
2003, Fossati et al., 1999, Franke et al., 1999, Goldberg et al., 1993, Merriam et al.,
1999). Thirdly, EF impairment is reported in both MDD and schizophrenia, with the
latter patient group consistently performing at lower levels (Austin et al., 2001,
Degl'Innocenti et al., 1998, Fossati et al., 1999, Grant et al., 2000, Merriam et al.,
1999). It is therefore still a question if and how LGP is associated with level of EF.

The neurobiology of unipolar major depression

Different neurochemical systems may interfere in unipolar major depression, and
abnormalities have been found within the serotonergic, dopaminergic and
noradrenergic systems. Two main neurobiological systems or circuitries have been

proposed for the pathogenesis of unipolar major depression as well as for EF, namely the frontal-subcortical systems and the Hypothalamic-Pituitary-Adrenal (HPA-) axis. Several psychopharmacological agents affecting these systems can be used to effectively treat unipolar major depression.

Frontal-subcortical systems

The depressive symptoms have been associated with dysfunction of the prefrontal cortex and frontal-subcortical circuitries, but so has impairment of EF (Elliott, 1998, Goodwin, 1997, Mayberg, 2000, Mega and Cummings, 1994, Royall, 1999). Results from functional brain imaging studies have confirmed decreased blood flow and glucose metabolism in the resting state in prefrontal cortex and the subcortical structures striatum, pallidum and thalamus (Drevets et al., 1992, George et al., 1994, Mayberg, 2000, Videbech, 2000). From a clinical point of view, lesions in any of these structures can give similar behavioural consequences. Cognitive activation studies are less conclusive, but indicate that depression is associated with an activation level in frontal and prefrontal regions that is different from what is found in normal controls (Kennedy et al., 1997). Recurrent unipolar major depression has recently been associated with volume loss of the same structures as mentioned above, and repeated episodes of hypercortisolism has been suggested as one possible aetiological mechanism (Sheline, 2000). In schizophrenic patients, a reduced frontal activation (hypofrontality) is often reported in functional neuroimaging studies, a finding that is also often reported in patients with major depression (Mayberg, 2003, Weinberger and Berman, 1996).

The cortisol hypothesis

Recurrent unipolar major depression is associated with elevated levels of cortisol, a stress hormone that may cause neuron loss (O'Brien, 1997, Sapolsky, 2000, Sheline,

2000). Whether neurocognitive deficits in general and specifically EF deficits found in depressed patients with recurrent episodes are associated with hypercortisolemia, is still unknown.

Under normal conditions the HPA-axis carries out an appropriate acute response to stress. There is an endocrine cascade-reaction starting with the hypothalamus, continuing to the pituitary, and ending with the secretion of cortisol from the adrenal gland. Negative feedback loops then operate at each of these levels to bring forth normal homeostasis. Major depression can be viewed as a condition that puts the body in a state of chronic stress, and this causes alterations in the HPA-axis with elevated levels of cortisol as a result (Kaplan et al., 1994, Sheline, 2000).

Hypercortisolemia is not found in all patients with depression (De Kloet, 2003). Chronically and acutely elevated levels of cortisol have been associated with memory dysfunctions in major depressed patients (De Quervain et al., 2003, Sauro et al., 2003). However, it is unclear whether level of cortisol is also associated with level of EF. If such an association can be found, it may help explain why some depressed patients are EF impaired whilst others are not. Results from both animal and human studies have shown that prolonged high levels of cortisol are neurotoxic (Wolkowitz et al., 2001). Studies on humans have found evidence of hippocampal volume loss in long-term corticosteroid therapy patients (Sherwood Brown et al., 2004). And it has been shown that hippocampal volume loss in women with recurrent depression was predicted by duration of depression (Sheline et al., 1999). In summary, it is uncertain if and how level of EF performance is correlated with level of cortisol.

Aims of the study

The main aim of the study was to investigate the association between recurrent MDD and EF. One objective was to explore whether recurrent MDD patients perform below healthy controls on components of EF (Paper I). Another aim was to examine whether all patients with recurrent MDD show EF impairment (Paper II). From the angle of investigating the predictive value of LGP (including patients with schizophrenia) and diagnosis on EF, the continuum hypothesis was explored (Paper III). Finally, the cortisol hypothesis was tested by looking at level of saliva cortisol and whether it is correlated with level of neurocognitive function, especially EF in recurrent MDD (Paper IV).

Methods and material

Research design

The present thesis is a clinical cross-sectional study performed on two groups of patients (recurrent MDD versus schizophrenia) and a healthy control group.

Subjects

The subjects included in the present study were recruited from and examined at five different psychiatric hospitals/clinics in Oslo and Bergen, Norway. The inclusion criteria were: 1) a primary DSM-IV diagnosis of unipolar major depressive episode, recurrent type or schizophrenia, not secondary to an organic or substance abuse disorder, and a minimum score of 18 on both the Hamilton Depression Rating Scale and the Montgomery-Åsberg Depression Rating Scale for the depressed patients, 2) age between 20 and 50, 3) written informed consent to participate in the study, 4) Norwegian language and 5) normal vision and hearing. The exclusion criteria were: 1) a history of head trauma, neurological disorder or developmental dysfunction, 2) present alcohol or substance abuse, 3) other medical conditions likely to affect neurocognitive functions and 4) recent Electro Convulsive Therapy (ECT).

Patient samples

Originally, N=50 patients with unipolar major depressive episode, recurrent type (recurrent MDD) according to DSM-IV were included in the BOP. All patients had suffered from a minimum of two life-time episodes of major depression, ranging from two to five episodes. At inclusion, five depressed patients had psychotic features. The depressed patients were moderately to severely depressed, scoring a minimum of 21 points on the MADRS (Montgomery and Åsberg, 1979), 10 items and 18 points on the

Hamilton Depression Rating Scale (HDRS), 17 items (Table 1) (Hamilton, 1960).

Forty-six patients were taking psychotropic medication, and of these 28 used Selective

Serotonin Re-uptake Inhibitors (SSRIs) and none used tricyclic antidepressant

medication. As additional medication, 11 patients were taking small doses of

neuroleptics (typical neuroleptics: 7, atypical: 3, both: 1). In the present thesis,

different sub-samples of the original BOP-sample of patients with recurrent MDD are

studied (Table 1). From the original BOP-sample of N=50 recurrent MDD patients,

five were excluded due to psychotic symptoms (Paper I), and two for missing data on

tests assessing EF (Papers II and III). In paper IV, only the N=26 patients who

delivered a saliva cortisol sample were studied. In Papers I, II and IV, the recurrent

MDD patients are compared with healthy controls, and in paper III to schizophrenic

patients.

Table 1: Demographic and clinical characteristics of the recurrent MDD samples

Characteristics	BOP-sample Mean (SD)	Paper I sample Mean (SD)	Papers II & III sample Mean (SD)	Paper IV sample Mean (SD)
Number	50	45	43	26
Age (years)	35.1 (8.7)	35.6 (8.4)	35.3 (8.4)	35.8 (8.9)
Gender (M:F)	21:29	18:27	16:27	8:18
Education (years)	13.9 (2.9)	13.7 (2.8)	13.8 (2.7)	13.4 (2.5)
HDRS total	22.4 (4.3)	22.4 (4.4)	22.5 (4.5)	21.4 (2.9)
MADRS total	28.5 (4.4)	28.8 (4.4)	28.8 (4.5)	27.7 (4.1)
BPRS-E total	43.5 (7.3)	43.0 (8.8)	43.2 (6.6)	42.1 (4.5)
GAF total	45.9 (8.4)	46.5 (8.8)	46.7 (8.8)	45.5 (8.0)

Abbreviations: HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg
Depression Rating Scale, BPRS-E = Brief Psychiatric Rating Scale-Expanded, GAF = Global
Assesment of Functioning Scale from SCID-I

In paper III, a group of patients with schizophrenia (N=53) according to DSM-IV was also included. The mean Positive And Negative Syndrome Scale (PANSS) score for this group was 75.5 (Key et al., 1987). From this original BOP-sample of schizophrenic patients, six were excluded due to missing data on either variables of intellectual abilities, EF or LGP, giving the total sum of N=47 schizophrenic patients in the present study (paper III). There was one patient with catatonic type, three with disorganised type, 37 patients with paranoid type, two with residual type and four with undifferentiated type. The majority of the schizophrenic patients were on second generation atypical antipsychotic medication.

Control group

The control group was recruited through advertisements in the local paper and the community and through personal networks. The control group was not significantly different from the original BOP-samples of depressed and schizophrenic patients regarding age, gender, education, handedness and intellectual abilities. Control subjects had no previous psychiatric difficulties. For further information about background data, please consult Papers I-IV.

Methods of measurement

Clinical evaluation and psychometric instruments

The clinical psychiatric evaluation was individually performed by five trained psychiatrists. The inter-rater reliability was estimated according to the procedure described in the paper by Egeland et al. (2003), and the average measure Intra-Class Correlations (ICC) were found to be over 0.80 for the rating scales used in this study.

The patients were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders, version 2.0 (SCID-I) (First et al., 1995). Severity of depression was estimated by the 17-item HDRS and the 10-item MADRS. Daily psychological, social and occupational functioning of the patients was assessed with the Global Assessment of Functioning scale (GAF) from SCID-I (First et al. 1995). LGP of the patients was measured by the Brief Psychiatric Rating Scale, Expanded version (BPRS-E) (Lukoff and Ventura, 1986). In addition, the PANSS was used on both depressed and schizophrenic patients. The General Psychopathology subscale (PANSS-G) of the PANSS instrument was, together with BPRS-E, used as composite scale of LGP (Paper III). BPRS-E is widely used in the evaluation of level of symptoms in different psychiatric patient groups and also in schizophrenia and mood disorders. The PANSS was mainly developed to assess symptom levels in schizophrenic patients but has also been previously included in studies of depressed patients (Galynker et al., 2000).

Neuropsychological assessment

The neuropsychological test battery was administered to the patients within three days after the clinical psychiatric evaluation. The neuropsychological test battery used in BOP included tests assessing several neurocognitive domains: attention, memory, psychomotor functions, EF and intellectual abilities. The neuropsychological tests were administered by a licensed clinical neuropsychologists, a graduate psychology student or by a medical doctor (Kirsten Irene Stordal) supervised by a neuropsychologists. Examiners attempted to obtain maximal performance. The subjects were tested individually. The time taken to complete the test battery was approximately 4 hours. Subjects were allowed breaks between the tests as needed. All subjects had at least one break with test administration typically divided into 1.5 to 2 hours sessions.

Operationalisation of executive functions

The neuropsychological tests used to assess EF in this thesis were selected according to the following criteria: 1) the tests had been used as EF tests in earlier studies of depressed patients and 2) the tests were described as measures of EF components, mainly as specified by Pennington and Ozonoff (Pennington and Ozonoff, 1996). The six tests included are as follows: Controlled Oral Word Association Test (COWAT) (Benton and Hamsher, 1989), Tower of London (ToL) (Krikorian et al., 1994, Shallice, 1982), Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977) and the Digits Span Backward (DB) subtest from WAIS-R (Wechsler, 1981), Stroop Colour and Word Test (Stroop) (Mitrushina et al., 1999, Stroop, 1935) and Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993). All tests were administrated and scored according to the test manuals.

Other neuropsychological tests

In addition, the California Verbal Learning Test (CVLT) (Delis et al., 1987) was used to assess memory function in paper IV, and the California Computerised Assessment Package (CalCAP) (Miller, 1993) together with Stroop were used to measure psychomotor function in Papers I and IV. The Victoria Symptom Validity Test (VSVT) was included to screen for non-optimal performance during testing and for detecting biased or random responding (Slick et al., 1997). Low performance can also be associated with motivation problems. Intellectual abilities were assessed with the Picture Completion (PC) and Similarities (SIM) subtests from Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981). For an overview of the neuropsychological tests and measures used and neurocognitive components assessed, see Table 2 on page 40.

Saliva cortisol

The depressed patients were asked for a saliva cortisol sample at 08.00 a.m. on the morning of the day that the neuropsychological testing took place. Measurement of saliva cortisol is generally recognised as a better measure of active cortisol in the body compared to serum cortisol (Vining et al., 1983). Subjects were instructed to give the sample before drinking, eating, smoking or brushing their teeth. Only a morning sample was collected in the present study. The samples were deep frozen until the moment of analysis. Thereafter, the samples were analysed by radioimmunoassay technique with a commercial kit (coat-a-count; Diagnostic Products Corporation, Los Angeles, CA, USA) that had an intra-assay variation coefficient between 1.2 and 5.3% and a detection limit of 0.2 mg/dl. Saliva cortisol has been found to be highly correlated with serum and plasma levels, is largely unbound and represents the free, biologically active fraction of cortisol (glucocorticoid hormone) (Vining and McGinley, 1986).

Table 2: The neuropsychological tests, measures of neurocognitive function and neurocognitive components assessed

Domains	Neuropsychological tests	Measures/Scores	Components
Executive functions	WCST	Failure to maintain set Categories completed Perseverative errors	Set-maintenance Set-shifting Set-shifting
	Stroop	Colour Word	Inhibition
	COWAT	Phonemic verbal fluency Categorical verbal fluency	Verbal fluency
	PASAT	3- and 2-sec. inter stimulus intervals	Working memory
	DB	Number correctly reorganised sequences	Working memory
	ToL	Number of trials completed	Planning
Intellectual abilities	SIM	Number of correct answers	Verbal abilities, Abstraction
	PC	Number of correct answers	Visual analysis, Concentration
Memory	CVLT	Acquisition Long Delay Free Recall Recognition Storage Retrieval	
Psychomotor functions	CalCAP	SiRT CRT SeqRT1 SeqRT2	Psychomotor speed
	Stroop	Word Colour	Psychomotor speed
Validity test	VSVT	5-sec. task	Motivation

Abbreviations: WCST= Wisconsin Card Sorting Test, Stroop= Stroop Colour and Word test, COWAT= Controlled Oral Word Association Test, PASAT= Paced Auditory Serial Addition Test, DB= Digit Span Backwards, ToL= Tower of London, SIM= Similarities from WAIS-R, PC= Picture Completion from WAIS-R, CVLT= California Verbal Learning Test, CalCAP= California Computerised Assessment Package, VSVT= Victoria Symptom Validity Test.

Statistical analyses

For Papers I-IV, SPSS for Windows 11.0 was used for statistical analyses. Significance levels of $p < 0.05$ or $p < 0.01$ and 1- tailed (where we did not expect the depressed subjects to perform better than the healthy controls) or 2- tailed levels are reported for each test measure. Results from the different neuropsychological tests used were not directly

comparable with one another, and in order to make comparisons necessary for evaluating cognitive impairment, the different test scores were converted into a scale with identical units. In this thesis, the normal distribution based on the mean and the standard deviation unit (SD) (Lezak, 1995) and standardized scores (z-scores) were used.

In Paper I, multivariate linear regression analyses were conducted to explore inter-group differences. The first regression model included a depression measure as predictor variable and each EF measure as dependent variable. In the next steps, demographic variables, psychoactive medication and psychomotor speed was adjusted for as possible confounding factors. Inter-group differences were also illustrated using z-scores, and a reliability analysis (alpha) was performed for all EF measures together and a composite score was made based on the mean of z-scores for these 10 EF measures.

In Paper II, z-scores were calculated for the set-maintenance, inhibition, verbal fluency and working memory measures to obtain a dimensional EF summary score. Since a Cronbach's coefficient alpha of 0.701 was found for the z-scores calculated from these four EF measures, the scores were summarised. EF unimpairment was defined from the distribution of EF scores in the control group and as performance above -1.0 SD. To be defined as impaired on working memory, both the PASAT and the DB scores had to be impaired. Choen's d was used as an effect-size measure (Rosnow, Rosenthal and Rubin 2000). To explore associations between demographic/clinical characteristics and EF impairment, linear and categorical analyses were performed using Pearsons' correlation and Student t-test/Pearson Chi-square test, respectively. A multivariate regression model was used to explore the interaction between

demographics/intellectual abilities and diagnosis (dichotomous variable indicating depression or non-depression) in the prediction of EF impairment. In this model the EF summary score was treated as a dependent variable (i.e. level of EF impairment = diagnosis + age + age x diagnosis). Demographic and intellectual abilities variables were used as independent variables.

In Paper III, a dimensional LGP measure was calculated by using the sum scores of both BPRS-E and PANSS-G because both measures together gave higher effect sizes than each one alone in the statistical analyses. For the depressed and schizophrenic patients together, N=90, z-scores were calculated for each of these measures. A Cronbach's coefficient alpha of .94 was found for the z-scores of BPRS-E and PANSS-G, and therefore these scores were summarised. As for the operationalisation of a dimensional EF measure, z-scores were calculated for set-maintenance, inhibition, verbal fluency and working memory measures for the depressed and schizophrenic patients together (N=90). A Cronbach's coefficient alpha of 0.61 was found for the z-scores calculated from the four EF measures, and likewise the results from these scores were summarised. Multiple linear regression models were performed and all were adjusted for age and gender.

In Paper IV, z-scores were calculated for the neurocognitive measures of the depressed patients based on the performance of the control group. Inter-group differences were explored by ANOVA analyses. Associations between clinical, biological, intellectual ability and cognitive measures were explored using Pearsons' correlation coefficient *r*. Partial correlations were performed in order to investigate possible confounding factors.

Ethical aspects

The study was approved by the Regional Committee for Medical Research Ethics. All participants provided written informed consent to participate in the study. There were no risks or suffering connected with participation. The patients received treatment for their existing condition, both psychotherapy and antidepressant medication/neuroleptics as well as additional medication. Due to suffering and suicide risk it would be highly unethical to ask patients to stop taking their antidepressant medication in order to participate in the study. The extensive neuropsychological test battery could for some patients, both depressed and schizophrenic be hard to endure, but they were encouraged to take as many breaks as they needed. For some patients it was necessary to finish the battery the following day. A few patients, especially in the schizophrenic group, did not manage to complete the whole battery and were registered with missing data for some of the tests or subtests. In order to reduce possible suffering, the patients were asked to deliver saliva cortisol samples instead of blood samples. The results from the neuropsychological evaluation where given to the psychiatrist/psychologist of the patients, so the information could be used for rehabilitation purposes.

Results

Summary of results from Papers I-IV

Paper I

In the part of the study reported in paper I, a set of neuropsychological tests was used to measure different components of EF to assess if patients with recurrent MDD performed below healthy controls and to study characteristics of the pattern and severity of this EF dysfunction. The group of patients with recurrent MDD (N=45) consistently performed below the healthy control group on the EF measures. Significant group differences were found for eight of the 10 EF measures assessed. These were measures of verbal fluency, inhibition, working memory and set-maintenance and set-shifting. There was no significant group difference for planning as measured by ToL. The group difference was still significant for all components except for set-shifting after adjusting for additional medication and psychomotor retardation. The severity of the executive dysfunction was within –1.0 SD from the control group mean for each of the 10 EF measures. For the composite EF z-score, severity was calculated to -0.22 SD.

Paper II

In paper II, the aim of paper I was extended by posing questions such as: Is impairment of EF a general finding in recurrent MDD? What are the characteristics of depressed patients with unimpaired EF? The depressed subjects (N=43) were assessed with the same neuropsychological tests as in paper I except for ToL, which was not used here. According to the definition of EF unimpairment as determined from the distribution of the control group, 56 % of the recurrent MDD patients were defined as EF unimpaired.

Altogether 16 % of the healthy controls were defined as EF impaired. An odds ratio of 4.2 (95 % C.I. from 1.6-10.9) indicated that the risk of EF impairment was about four times higher in recurrent MDD patients than in healthy controls. Another finding was that 90 % of the variance in EF could be explained by other factors than being depressed. The depressed patients without EF impairment were characterised by fewer depression episodes and higher intellectual abilities than patients with EF impairment, but the groups were not significantly different on measures of symptomatology, general psychopathology and global functioning.

Paper III

In this part of the study, employing data including patients with recurrent MDD and schizophrenia (N=90), it was examined whether the variance in EF is related to psychiatric diagnosis or to LGP. The EF tests used were similar to those used in Paper II. LGP explained more of the variance (14.4 %) in EF than did diagnosis (9.7 %). Correspondingly, the standardised regression coefficients (betas) were stronger in LGP than in diagnosis. LGP predicted only about 25 % of the effect of diagnosis on EF. In other words, most of the effect of diagnosis on EF could not be attributed to LGP. Diagnosis explained about 15 % of the effect of LGP on EF. Thus, most of the effect of LGP on EF could not be attributed to diagnosis. It was shown that approximately 5 % of the variance in EF could be explained by diagnosis, when LGP was already included in the model. It was also shown that approximately 10 % of the variance in EF could be explained by LGP, when diagnosis was already included in the model. To sum up, LGP has a stronger independent effect on EF and explains more additional variance in EF in addition to diagnosis than vice versa.

Paper IV

In the final part of the study reported in Paper IV, a neurobiological correlate (saliva cortisol) was included. It was asked if EF was correlated with saliva cortisol in patients with recurrent MDD (N=26) and how. As measures of EF, failure to maintain set from WCST and Stroop colour-word subtask were included. Also, psychomotor speed (CalCAP and Stroop) and memory measures (CVLT) were included in this study. It was found that level of saliva cortisol was significantly and inversely correlated with EF and retrieval from CVLT. Another finding was that depressive symptomatology (measured by HDRS and MADRS) was significantly and inversely correlated with psychomotor speed. In other words, an elevated level of saliva cortisol was associated with EF dysfunction as well as with a post-encoding memory deficit, but not with psychomotor retardation in recurrent MDD.

Discussion and conclusion

Synopsis of results

The study shows that a group of moderately to severely depressed patients with recurrent MDD has mild dysfunction across EF components compared with a healthy control group. The following EF components are statistically significantly affected in recurrent MDD: verbal fluency, inhibition, set-maintenance and working memory. Set-shifting and planning seem to be spared. Despite that patients with recurrent MDD on a group basis perform below healthy controls on several components of EF, more than half of the patients can be classified as EF unimpaired when the definition of unimpairment is based on the performance of the control group. The unimpaired subgroup is characterised by fewer depression episodes and higher intellectual abilities than the impaired subgroup, but the subgroups are not significantly different regarding symptomatology, general psychopathology and global functioning. Further, LGP explains more of the variance in EF than does diagnosis (recurrent MDD or schizophrenia), though diagnosis independently explains some of the variance. Finally, level of saliva cortisol is inversely correlated with performance on measures of EF in recurrent MDD.

Results in view of previous findings

The association between recurrent unipolar major depression and executive functions

A significant group difference between patients and healthy controls

The study confirms earlier findings that patients with MDD on a group basis show EF impairment when in the symptomatic phase, but also confirms depressed patients' complaints of neurocognitive problems as well as psychiatrists' or psychologists' observations of such in depressed patients. In general, there is a lack of neurocognitive studies, which restrict samples to MDD patients with recurrent episodes. Therefore, results from the present study are compared with findings from earlier studies of 1) currently depressed patients with MDD, including patients with a mixture of recurrent and first episode(s) of depression, and 2) recurrent MDD patients with no or mild current depressive symptomatology.

In the present study, a statistically significant group difference was found for measures of EF between patients with moderate to severe, recurrent MDD and healthy controls. This finding is in line with most previous studies (Degl'Innocenti et al., 1998, Grant et al., 2001, Landrø et al., 2001b, Porter et al., 2003). Porter et al. (2003) found a group difference on EF measures between unmedicated patients with MDD and controls. Two recent papers have investigated EF in samples of patients with recurrent episodes, and both have confirmed that patients with recurrent MDD perform below healthy controls on measures of EF, even when in the euthymic phase (Lampe et al., 2004, Paelecke-Habermann et al., 2005). Paelecke-Habermann and colleagues (2005) found that MDD patients in the euthymic phase with three or more depression episodes showed a lower performance on measures of EF compared to patients with one to two

episodes. In the present study, a group difference was also found between patients with recurrent MDD and schizophrenia for EF measures, a finding in line with most previous studies (Fossati et al., 1999, Goldberg et al., 1993, Merriam et al., 1999, Rund et al., 2006), but not all (Franke et al., 1993). The result that executive dysfunctions co-occur with recurrent MDD (but also with schizophrenia) therefore seems to be a strong finding.

A mild dysfunction across components of executive functions

Another finding in the present study was that the executive dysfunctions were mild in recurrent MDD when evaluating group differences in effect sizes. This finding may have clinical implications. Statistically significant dysfunctions were found for verbal fluency, inhibition, set-maintenance and working memory. There were no significant group differences between patients and controls for set-shifting after controlling for psychomotor speed and additional psychotropic medication. Planning abilities, as measured by a version of ToL, were also spared. However, the non-significant finding for planning is possibly due to good a ceiling effect. The version of the ToL test used was too easy for both patients and controls resulting in good test performance in both groups. Previously, preserved planning abilities in out-patients, mainly first episode MDD patients, have been reported (Porter et al., 2003), although deficits have been shown in other studies (DeBattista, 2005). Verbal fluency dysfunction has consistently been reported in studies of MDD, even in unmedicated patients (Degl'Innocenti et al., 1998, Fossati et al., 1999, Landrø et al., 2001b, Porter et al., 2003, Veiel, 1997), yet contradictory findings also have been reported (Grant et al., 2001). Regarding the presence of a dysfunction in inhibition, some studies support this finding (Lampe et al., 2004, Paelecke-Habermann et al., 2005), while others do not (Degl'Innocenti et al., 1998). Two meta-analyses have also confirmed inhibition problems in MDD (Veiel,

1997, Zakzanis et al., 1999). Zakzanis et al. (1999) suggested that this could be caused by reduced psychomotor speed. In the present study, reduced psychomotor speed was controlled for in the statistical analysis, but still an inhibition dysfunction was present in recurrent MDD. The results of the present study are in contrast to most previous findings for set-maintenance and set-shifting as well. In a review by Austin and colleagues (2001) a selective set-shifting deficit was suggested for patients with MDD, though the results of the present study can not support this. As for set-maintenance, Grant and co-workers (2001) also reported a low performance on failure to maintain set from WCST. This is of interest because most often this parameter is not affected in patients with MDD (Degl'Innocenti et al., 1998, Merriam et al., 1999). Regarding working memory, dysfunction of this EF component has been reported in other studies of MDD (Landrø et al., 2001b, Paelecke-Habermann et al., 2005, Porter et al., 2003). A recent review has highlighted deficits in working memory as central in MDD (DeBattista, 2005).

These differences in results across studies of MDD regarding which EF components are affected or spared may be due to methodological problems. One problem is differences in operationalisation of EF. Another problem is including a homogeneous sample of MDD patients. The heterogeneity of unipolar major depression (psychotic vs. non-psychotic, recurrent vs. first-episode) (Lampe et al., 2004, Porter et al., 2003, Schatzberg et al., 2000), the medication status (with or without psychotropic medication) (Lampe et al., 2004, Porter et al., 2003) and the status of depressed patients (hospitalised or out-patients) (Degl'Innocenti et al., 1998, Elliott, 1998, Grant et al., 2001) may contribute to the lack of reliable findings regarding EF deficits. Differences in age and severity of depression of MDD samples are other factors that have been suggested to explain inconsistency in findings (Austin, 2001, Elliott, 1998).

The present study confirms that mild EF dysfunctions are associated with recurrent MDD. The performance of the depressed patients on measures of verbal fluency, inhibition, set-maintenance and working memory was within 1.0 SD of the sample mean below the controls. For the EF summary score, the group difference between depressed patients and controls was calculated to 0.22 SD of the sample mean in favour of the controls. There are previous studies that have also used the z-score format in severity calculations of neurocognitive deficits in MDD (Lampe et al., 2004, Landrø et al., 2001b, Reischies and Neu, 2000). Investigating euthymic or mildly depressed female recurrent MDD patients, Lampe et al. (2004) found a slightly more severe result on a composite EF score (based on measures from Stroop and WCST) with these patients performing 0.65 SD of the sample mean below the control group. It is possible that this group difference would have been larger if the patient group had been moderately to severely depressed like our sample. Landrø and colleagues (2001b) found even more severe effect sizes for both working memory and verbal fluency, but still within approximately 1.25 SD of the sample mean in favour of controls in a group of mainly female recurrent MDD patients. Reischies and Neu (2000) found effect sizes in MDD patients that ranged within 0.5 to 1.0 SD from the sample mean below the control group for measures of verbal fluency, memory and psychomotor speed. Based on the reported effect sizes between EF and depression, it seems reasonable to conclude that the severity of the dysfunction is mild in recurrent MDD on a group basis.

Do all patients with recurrent unipolar major depression have executive dysfunctions?

Many recurrently depressed patients have unimpaired executive functions

Though recurrent MDD patients on a group basis consistently show executive dysfunctions, the present study showed that more than 50 % have unimpaired EF when unimpairment was defined as performance above -1.0 SD of the sample mean of the control group on more than one component of EF. The unimpaired subgroup of recurrent depressed patients was characterised by higher intellectual abilities and fewer depression episodes. In comparison, 16 % of the controls were classified as EF impaired when impairment was defined as performance equal to or below -1.0 SD in the control group on more than one component of EF. A similar study of schizophrenic patients and neuropsychological functioning found that nearly one third was classified as neuropsychologically normal, whereas 15 % of the controls were impaired on neurocognitive functions (Palmer et al., 1997). Our study only assessed one neurocognitive domain, EF. In the study by Palmer et al. (1997) several neurocognitive domains were investigated but the prevalence of impairment in the healthy control group in this study was comparable to the prevalence found in the present study. It is also reasonable that EF impairment is present in a subgroup of healthy controls. The results confirm findings from other studies of the existence of groups of unipolar major depressed patients with normal or nearly normal EF (Grant et al., 2001, Purcell et al., 1997).

In the present study, 44 % of patients with recurrent MDD were defined as EF impaired. The choice of cut-off for impairment of neurocognitive functions varies across studies; as does the EF variables studied. Thus, it is difficult to directly compare

this result to the results from other studies. A study using the 5th percentile as cut-off, found that about 37 % of a group of major depressed patients, some with recurrent depression, performed below a matched control group on a measure of verbal fluency (Reischies and Neu, 2000). In a meta-analysis, 11 % of the MDD samples scored 2 SD or below the control group mean on measures of verbal fluency (COWAT), whereas 50.2% scored equal to or below the cut-off on measures of mental flexibility and control (Trail Making Test part B and Stroop colour-word subtest) (Veiel, 1997). In a recent study by Rund et al. (2006), investigating the schizophrenic and recurrent MDD patients from BOP, 25 % of depressed patients scored more than 1.5 SD below the mean of the control group on measures of working memory and psychomotor speed. In sum, there is a large heterogeneity within MDD patients regarding EF with some patients performing in the normal range and some in the impaired range.

The EF unimpaired subgroup had suffered from fewer depression episodes than the impaired subgroup. The finding gives support to the model of recurrent MDD involving repeated episodes of hypercortisolism causing structural changes affecting fronto-subcortical systems (Sheline et al., 1999, Sheline et al., 2000). Therefore, it is possible that patients with recurrent MDD but with fewer episodes will have less EF impairment compared with patients who have experienced more depression episodes. Another finding was that EF unimpairment was associated with higher intellectual abilities as measured by PC and SIM from WAIS-R. Is it possible that we measure IQ rather than EF? This raises the question about how EF are related to IQ, and specifically how the different components of EF relates to IQ. Recently, it was shown that both WAIS-R and Wechsler Intelligence Scale for Children-Reviced IQ measures are differentially correlated with different EF components (inhibition, set-shifting and set-maintenance, updating working memory, verbal fluency), though mostly low and

non-significant correlations were found (Ardila et al., 2000, Friedman et al., 2006). An interesting result of the present study is that 35 % recurrent MDD patients showed no EF impairment at all. These patients have a recurring brain dysfunction, and yet show no dysfunction in EF. One possible explanation for this finding is that these patients may have had above average EF before the start of the MDD. Due to problems with the low sensitivity and ecologic validity associated with the tests, it is possible that some patients within the unimpaired group still may have real-life executive dysfunctions (Manchester et al., 2004). Thus, it appears that there are true but small differences between EF normal and EF impaired recurrent MDD patients.

The present study may perhaps be criticised for the choice of EF tests and unimpairment definitions. Currently, there is no general understanding of how this should be done and there are many examples of other definitions and operationalisations; differences are even found within the BOP (Degl'Innocenti et al., 1998, Egeland et al., 2003, Fossati et al., 1999, Grant et al., 2001, Landrø et al., 2001, Merriam et al., 1999, Palmer et al., 1997, Rund et al., 2006). Further research will be needed to determine whether the differences in EF represent differences in either clinical subtypes of MDD, degrees of illness or premorbid level of functioning. Still, the identification of MDD subgroups with regards to present or absent EF impairment will be important because the two groups may have different treatment needs (DeBattista, 2005, Dunkin et al. 2000, Mohlman, 2005, Palmer et al., 1997, Rund et al., 2006).

Are executive dysfunctions associated with diagnosis or level of psychopathology?

Exploring the continuum hypothesis of psychiatric disorders

Despite that EF deficits consistently have been reported in MDD patients including the present results, it can be argued that the association between recurrent MDD and EF is rather weak. Two results from the study support this: The finding that 90 % of the variance in EF was explained by other factors than depression, and the result that more than 50 % of the depressed patients were EF unimpaired (Paper II). Findings reported elsewhere as depicted in the introduction section may lead to speculation if general factors other than the depression itself can not explain the variance in EF.

In the present study it was found that LGP as measured by BPRS-E and PANSS-G explained more of the variance in EF than the diagnosis of MDD (or schizophrenia). Diagnosis also explained some, though less, of the variance. Rephrasing the result, the study shows that a variable (general psychopathology) common across mental disorders (though imperfectly illustrated by only two diagnoses) explains more of EF than the specific diagnostic categories do (MDD versus schizophrenia). It can therefore be assumed that the shared symptomatology of mental disorders is more important for the understanding of neurocognitive functioning (as illustrated by EF) than their differences represented by conventional categorical diagnoses. This finding is in line with the continuum hypothesis of psychiatry, and also supports clinical intuition that mental disorders probably are dimensional rather than categorical conditions. That a dimensional approach explains more of EF than a categorical approach is interesting because this research field has mostly been engaged in investigating specific diagnostic groups and subgroups of psychiatric patients on measures of neurocognitive function.

In sum, there seems to be more similarities than differences between MDD and schizophrenia regarding EF.

The present study put restrictions on both symptomatology and severity of illness. In the planning phase of the study we though that it would be a strength of the study to include homogeneous patient groups, but as the work progressed and we became increasingly engaged in the dimensional approach to mental disorders this actually proved problematic. Ideally, patient groups with intermediate diagnoses (i.e. psychotic depression, schizoaffective disorder, and bipolar disorder as well as other mental disorders) and all severity levels could have been included. In addition, healthy controls could also have been included. On the other hand, because the included patient groups were homogenous and thus, limiting the variance, it could be argued that the results are even stronger. Also, there is the possibility that the findings could have been caused by a statistical phenomenon. It is generally more difficult to achieve statistically significant correlations between categorical variables (which reduce variance) and a dimensional out-come measure (EF) than with dimensional variables. In light of this, the finding that EF is more associated with LGP than with diagnosis needs to be replicated in future studies.

The results of this study are in line with previous neuropsychological studies claiming that there are quantitative differences between MDD and schizophrenia regarding neurocognitive function in general and specifically EF (Goldberg et al., 1993, Fossati et al., 1999, Franke et al., 1993). But the findings are also in line with studies finding qualitative differences between the two diagnostic groups (Goldberg et al., 1993, Rund et al., 2006). In a recent study by Rund and co-workers (2006), the recurrent MDD patients and schizophrenic patients were qualitatively different regarding

neurocognitive profiles. By using diagnostic classifications we may be prevented from understanding aspects of psychiatric disorders that are relevant to EF. This finding partly favours the continuum hypothesis in psychiatry and partly the conventional diagnostic classification.

Thus, EF deficits are not specific for MDD since such deficits are present in schizophrenia as well as other mental disorders (Stein et al., 2002, van den Heuvel et al., 2005). In a review by Schillerstrom et al. (2005) it was shown that EF impairment has also been found in diverse medical diseases such as vascular disease, hypertension, respiratory and cardiac illnesses, HIV, diabetes, renal failure and neoplastic illness after controlling for comorbid psychiatric illness.

The present study showed that level of psychopathology explained EF more than diagnosis. Another more creative extrapolation from this finding is that the level of pathology explains EF. Perhaps EF impairment reflects a more universal effect of being severely ill. In Maslow's hierarchy of needs (Maslow, 1954) the premise is that unless an individual's basic needs have been met, higher levels in the pyramid such as self-realisation are of no relevance because survival is the most basic human component. Drawing a parallel to this idea, we can imagine that as long as the body is ill and needs to heal, higher order intellectual processes may become a luxury that the body cannot afford.

The present study supports the inclusion of dimensional approaches in coming diagnostic classification systems. Future research of EF in mental disorders should perhaps include dimensional measures to increase the variance in psychiatric

symptomatology and to avoid problems with co-morbidity, diagnostic overlap and overemphasising effects of diagnosis.

The association between executive functions and saliva cortisol in recurrent unipolar major depression

In the present study two results provide indirect support to the cortisol hypothesis and the assumption that repeated depression episodes with elevated levels of cortisol can cause progressive brain damage in frontal-subcortical systems. The results are also in favour of the assumption that executive dysfunctions in recurrent MDD are linked to the same postulated progressive brain damage. Firstly, an association between higher saliva cortisol levels and lower EF was found in the recurrent MDD patients (Paper IV). Secondly, the recurrent MDD subgroup with EF impairment had experienced a higher number of depression episodes than the subgroup with normal EF (Paper II). Thus, recurrent MDD seems to be associated with elevated cortisol, which again may be associated with executive dysfunctions. It also seems that the more depression episodes (with a probable elevated level of cortisol) a patient has suffered the higher the possibility of EF impairment.

It can be argued that the association between saliva cortisol and EF probably is stronger than shown in the present study. The finding of an inverse association between saliva cortisol and EF in this study is weaker than it actually is because only one morning saliva cortisol sample was collected. This is a limitation of the present study that can lower validity. Today, due to present knowledge of irregular diurnal patterns of cortisol secretion in MDD, the collection of several saliva samples are recommended, but one sample was not uncommon at the time that we included our

depressed patients (Odber et al., 1998, Peeters et al., 2004). In the correlation analyses in paper IV multiple comparisons were made with the possibility of Type I errors.

Despite these limitations, the results of the present study may be indicative of that executive dysfunctions in recurrent MDD can be attributed to cortisol hypersecretion. As reported elsewhere, hypercortisolemia is well documented in MDD but found only in about half of the patients (De Kloet, 2003). Both chronically elevated cortisol level and increases due to stress or experimental injections have been associated with memory deficits (De Quervain et al., 2003, Sauro et al., 2003, Young et al., 2001). A recent study reported that higher cortisol levels were associated with higher numbers of depression episodes in unipolar major depression (Sher et al., 2004). Together, this evidence may be one explanation for why only half of the recurrent MDD patients were EF impaired.

Possible functional consequences of mild executive dysfunctions

Though mild, it is possible that dysfunctions in several EF components will have functional and clinical consequences for patients with recurrent MDD. The literature on the association between depression-related executive dysfunctioning and functional disability is sparse. It is known that functioning deteriorates by actual depressive symptomatology (Spijker et al., 2004), and it can be speculated about to what extent co-occurring executive dysfunctions will further reduce functioning. In a study of elderly people, EF determined functional status for both self-reported and observed activities of daily living (Grigsby et al., 1998). In geriatric non-demented patients with current or a history of MDD, executive dysfunctions were associated with reduced ability to shop, prepare meals, take medicine (compliance) and manage money (Kiosses and Alexopoulos, 2005). In patients with frontal lobe damage, executive

dysfunctions may compromise independent living and disrupt the patients' personal and social lives and their abilities to work or attend school (Manchester et al., 2004). The severity of executive dysfunctions is probably higher in the patient groups mentioned above compared to our patient sample, but the functional effects might be similar, though of a milder type. Conversely, it can be assumed that normalisation of executive dysfunctions will improve general functioning.

Recently, studies have referred to clinical and treatment issues concerning executive dysfunctions in patients with MDD. Regarding outcome, EF has been suggested to be a predictor of treatment outcome in both adult and elderly MDD patients (Dunkin et al., 2000, Mohlman, 2005). Dunkin et al. (2000) found that executive dysfunctions in MDD predicted lack of response to pharmacotherapy (fluoxetine). MDD is associated with an increased risk of suicide, and recently deficits in EF were associated with suicidal ideation (Marzuk et al., 2005). Very few studies have investigated beneficial effects of psychopharmacological treatment on executive dysfunctions in MDD. However, some agents have been suggested, i.e. SSRIs (sertraline), noradrenergic agents, dopamine enhancing agents, modafinil and antiglucocorticoids (Constant et al., 2005, DeBattista, 2005). In addition to psychopharmacological treatment, a specific type of psychotherapy may be effective. It has been shown that in elderly MDD patients with executive dysfunctions, psychotherapy (problem-solving therapy) was more effective on reducing both depressive symptomatology, functional disability and executive dysfunctions than supportive therapy, though normal levels for EF were not attained (Alexopoulos et al., 2003). Also, exercise has been shown to improve executive dysfunctions in adults with MDD (Kubesch et al., 2003). For rehabilitation, tailored EF compensatory techniques have been suggested for MDD patients (Kiosses and Alexopoulos, 2005). It has also been suggested that EF are neurocognitive

functions that must be taken into account to ensure occupational success in patients with severe mental disorders, including MDD (McGurk and Mueser, 2003).

Traditional executive tests have been criticised for not being "direct evidence for the existence or nature of basic operations of frontal systems" and for having low relevance for everyday life (Alexander and Stuss, 2006, Manchester et al., 2004). At present, there seems to be two main trends evolving with regards to the development of tests of EF. The first aims at developing tests with increased construct validity; these are intended to measure the actual brain functions involved in EF (Alexander and Stuss, 2006). The second aims at increasing the ecological validity by making executive tests that reflect real world functioning (Manchester et al., 2004). Comparative information on how patients function neurocognitively as well as behavioural observations of how patients perform when carrying out a structured task in a real-life setting have been suggested for EF evaluations of patients (Alexander and Stuss, 2006, Manchester et al., 2004). In summary, executive dysfunctions may be an extra burden to the functional disabilities associated with recurrent MDD. It is important to identify such neurocognitive deficits in MDD for optimal treatment, counselling and rehabilitation.

Speculations regarding the pathogenesis of executive dysfunctions in unipolar major depression

Due to the design of the present study it is only possible to speculate about where in the brain executive dysfunctions are situated. The results from this study show that patients with recurrent MDD have deficits in verbal fluency, inhibition, set-maintenance and working memory. Results from functional neuroimaging studies investigating activation patterns in MDD patients while patients are performing

neuropsychological tasks assessing these EF components have shown the following: verbal fluency is associated with the dorsolateral prefrontal cortex, inhibition is associated with the anterior cingulate and dorsolateral prefrontal cortex and working memory is associated with lateral prefrontal cortex and anterior cingulate (Frith et al., 1991, Rose et al., 2005, Wagner et al., 2006). No functional neuroimaging studies have, to the best of my knowledge, reported activation patterns related to deficits of failure to maintain set from WCST in MDD, but a meta-analysis concluded that the WCST could be viewed as an attention-demanding executive task due to fronto-parietal activation patterns (Buchsbaum et al., 2005). In a functional Magnetic Resonance Imaging (fMRI) study investigating 12 of the recurrent MDD patients included in the present study on a variant of the PASAT task, brain activation was shown in the frontal lobes (right inferior and middle frontal gyrus) (Hugdahl et al., 2004). In addition, reduced psychomotor speed was observed in the recurrent depressed patients of the present study, a finding that has been associated with the striatum (Degl'Innocenti et al., 1998). Functional neuroimaging studies investigating recurrent MDD patients have shown a reduced hippocampal volume (Sheline et al., 1999, Neumeister et al., 2005). Thus, the EF pattern of recurrent MDD is compatible with dysfunctions of frontal-subcortical circuitries that also have been associated with depressive symptomatology. The "hypofrontality" hypothesis of unipolar major depression is still strong, but now there is evidence from functional neuroimaging studies that have shown increased frontal activation associated with depression (for a review see Surguladze et al., 2003).

General methodological issues

Medication effects on executive functions

An overview of antidepressants and additional medication used by the participating subjects at the time of neuropsychological testing is given in the methods section and in Papers I-IV. In the present study we did not have adequate control over medication effects, and this is a limitation of the study. Despite that investigation of medication effects on EF was not a scope of the present study, it is important to keep in mind that medication effects are a possible confounding factor. In an un-medicated sample of recurrent MDD patients, the performance on tests of EF may have been lower. In the literature, findings are inconclusive with respect to the effects of antidepressant medication on neurocognitive functions in general (Amado-Boccara et al., 1995). However, modern antidepressant medication, SSRIs and monoamine oxidase inhibitors, are known to have less negative or even positive effects on neurocognitive functions compared with older tricyclic antidepressant medication, which due to anticholinergic and antihistaminergic properties have sedative effects affecting psychomotor speed (Amado-Boccara et al., 1995, Elliott, 1998). In the present study, all patients were taking newer types of antidepressants (mainly SSRIs). However, previous studies assessing EF in medication free MDD patients, have also detected significant associations between depression and lower performance on measures of EF (Grant et al., 2001, Porter et al., 2003). Although we could not rule out the effects of medication in the present study, additional medication (benzodiazepines and/or antipsychotic medication) was adjusted for in the statistical analyses of Papers I and IV, and this did not change the main results of these papers. Long-time use of benzodiazepines seems to be associated with impairment in neurocognitive functions (Golombok et al., 1988). As for antipsychotics, either used as additional medication in

recurrent MDD or as main medication in schizophrenia, Mohamed et al. (1999) found
no significant differences in neurocognitive performance in medicated or un-medicated
patients with schizophrenia. Others have shown that atypical antipsychotics may even
have beneficial effects on neurocognitive functions (Purdon, 2001). It is therefore
unlikely that the EF dysfunction in recurrent MDD can be strongly related to
medication use, although we cannot rule out medication as a possible confounding
factor.

Measurement of psychiatric symptomatology

In the present study only conventional diagnostic and psychometric instruments were
used. Patients were diagnosed by the SCID-I at inclusion by trained psychiatrists.
Though imperfect, the diagnostic criteria in the DSM-IV are consensus-based and
under revision. The level of depressive symptomatology, general psychopathology and
global functioning was measured by "gold standards", i.e. frequently used, and well
validated continuous scales (HDRS, MADRS, PANSS, BPRS and GAF). For research
purposes, these conventional instruments make it relatively easy to compare samples of
depressed patients across neurocognitive studies.

Measurement of neurocognitive functions and particularly executive functions

Neuropsychological assessment has been concerned with delineating isolated
components of cognitive functioning using standardised tests administered under
laboratory conditions. There is a rich selection of standardised single tests available
that can be used to assess EF or the separate components. The neuropsychological test
battery constructed for the BOP-study was based on theory, tradition and prior
experience with the tests. It mainly included often used and well validated tests
assessing different cognitive domains such as attention, memory function,
psychomotor function and EF. There were two exceptions. They were experimental

neuropsychological tests called the Backward Masking and Dichotic Listening, but these were not included in the papers of this thesis. In the present thesis, the tests acknowledged to assess EF, which by definition are demanding and complex tasks, were selected because they had been used as EF tests in previous studies of depressed patients and because the tests had been described as measures of components of EF (Pennington and Ozonoff, 1991). The neuropsychological testing was performed by trained test-technicians under standardised "laboratory" conditions. In this thesis, neuropsychological operationalisation was based on either theoretical foundations (i.e. Pennington and Ozonoff, 1991) and/or estimates of internal reliability within dimensions. The view that different tests or test measures are indicators of different aspects of cognitive functions can be problematic because there is substantial overlapping across test measures and cognitive domains (Lezak, 1995, Zakzanis et al., 1999). In addition, many neuropsychological tests are multi-factorial, especially if the tests are "complex" (Stuss and Alexander, 2000). Another aspect is the sensitivity and specificity of EF tests as tests that are sensitive may not be specific and vice versa. The EF tests used in the present thesis are generally recognized as sensitive to frontal lobe damage, although evidence exists that these tests sometimes can be insensitive to even large lesions of the frontal lobes (Manchester et al., 2004). It is also important to keep in mind that the relationship between EF (a psychological construct) and the functional anatomy of the frontal lobes, and probably also other brain regions, is not completely understood (Stuss and Alexander, 2000). Neuropsychological research supplemented with functional and structural neuroimaging techniques can therefore be useful in extrapolating deficits of EF deficits to the functional anatomy of the brain. Since neuropsychological tests vary from study to study, uni-factorial tests are rare, and the operationalisation of EF is difficult. This makes it more difficult to compare the performance of depressed samples across neuropsychological studies.

Reliability considerations and underestimation of strength

The higher the reliability of measures in a study, the easier it will be to demonstrate real group differences and associations. On the contrary, lower reliability will reduce the effect size or strength of associations, but will never give false positive findings. In the present thesis, the reliability varies. Regarding the diagnostic instrument, rating scales and neuropsychological tests these were most often "gold standard" instruments and therefore the potential reliability is assumed to be high. The five raters that determined diagnoses and severity of illness were trained psychiatrists that were informed that the inter-rater reliability were to be calculated for the scaled instruments. Five cases were selected, and the inter-rater reliability was calculated for HDRS, MADRS, PANSS, BPRS and GAF. Average measure ICC was over 0.80 for all rating scales. For the diagnoses, consensus was reached for selected cases during clinical discussion and no diagnostic disagreement was found. For other measures included in the study, i.e. the saliva cortisol measure, duration of illness and number of depression episodes and some demographic variables, the reliability may have been lower. Regarding the administration of the neuropsychological tests, there were altogether three test technicians. The tests were administered under standardised conditions according to the test manuals, and test protocols were used that contained the information/text that was read aloud to the subjects during testing. But unfortunately, no ICC was calculated for the test technicians, and though this is not often done within this research field, this could be considered a limitation with the present study. Due to the fact that several tests are computerised, it is not always a useful procedure. A substantial variance was found for the depression, EF and saliva cortisol measures (Papers I-IV). But when the measurement of interest is highly variable, large samples are needed to get reliable results (Altman, 1991). In the analyses of data, it was mainly summary scores that were calculated, although single measures were also used. To

produce composite scores or summary scores of EF, single measures were reliability tested and summarised when high internal consistency was found. As a consequence of reliability being moderate to high, the risk of underestimating the strength of associations is rather low.

Power considerations and Type II errors

The size of the sample is important to obtain statistically significant results. The significance level, the sample size, the strength of the association, and the power constitute a closed system in that three of the parameters can determine the fourth (Altman, 1991). In the planning phase of BOP, the total number of patients and controls that had to be included to secure sufficient power was calculated from neuropsychological data from earlier studies on older depressed patients. Since younger, better functioning depressed patients were included in the study, and due to missing data, this resulted in a loss in power. In the present study the sample size is small or marginal in statistical terms, although it could be argued that it is relatively large as compared to studies within the same research tradition. An implication of a marginal power for Papers I-IV is reduced possibility of finding significant results and accordingly an increased risk of false negative results (Type II error) (Altman, 1991). One way of combating low power is to reduce the total number of single test measures by calculating summary scores. Therefore, in Paper III composite scores were calculated for both psychopathology and EF. Summary scores for EF were also calculated in Papers I and II. This will increase the reliability and the strength of the association as well as the statistical power.

When performance of a clinical group on a particular neuropsychological test or measure is found to be significantly different from that of a non-clinical group, this

finding is often used to support the view that the test or measure is able to differentiate between the groups. However, it is important to keep in mind that statistical significance only reflects the likelihood or probability of a particular finding being observed by chance. It neither reflects the size of differences between groups, nor if every individual of the clinical group is affected or only some, nor does it indicate if the test or measure can discriminate participants with sufficient accuracy for clinical use. In Paper IV, multiple comparisons were performed between the clinical, neuropsychological and saliva cortisol variables and several statistically significant results on the 0.05 level were reported. Performing multiple comparisons increases the risk of false positive results (Type I error) (Altman, 1991). Multiple comparisons were also performed in Papers I and II. To avoid the risk of false positive findings, post hoc adjustment, i.e. by the Bonferroni method could have been performed. The Bonferroni method is recognised as a conservative method, and applying this adjustment on our results would most certainly have led to mostly non-significant findings. On the other hand, this conservatism also increases the risk of losing true associations between variables. In conclusion, the increase in reliability achieved by computing summary scores should be regarded as favourable compared to using multiple test measures because the hypothesis is tested only once. However, in Paper I where one of the aims was to investigate the profile of EF in recurrently depressed individuals, multiple single test measures had to be used. Analyses on single test measures can therefore be useful provided that the statistical power is sufficiently high. In addition to significance, it is also important to evaluate confidence intervals. For the present thesis, confidence intervals could have been reported more often.

Generalisation of findings

To decide whether the findings can be applied to the population of interest, namely people with unipolar major depression, it must be determined as to whether the sample is representative of this population in the first place. The multi-centre design of the study gave access to mainly hospitalised patients or patients with a history of hospitalisation. Some of the patients at the point of inclusion were recruited from out-patient clinics. A minority (and mainly in the depressed group) of the out-patients had not been hospitalised earlier.

The sample of patients with recurrent MDD that was included in the present study is representative for this population, and the results can therefore be generalised to this group of patients. For the depressed group only recurrently depressed patients were included, yet this is the most prevalent type of the disorder in the population (Angst, 1999, Mueller, 1999). By doing so, we anticipated that the recurrently depressed sample would be more cognitively impaired compared to first-time depressed samples or a mix of the two, but in fact they were comparably neurocognitively impaired to other studies. Of course, directly comparing our results to that of other studies is not entirely safe as the studies may be different regarding design, sample, measures, etc., but still we allowed our selves to do this. The patients were moderately to severely depressed according to the depression scales, and therefore more severely depressed than samples in some studies, but not others (Degl'Innocenti et al., 1998, Landrø et al., 1997, Purcell et al., 1997). The decision of not including patients with milder depression restricts findings to more severe forms of depression. Patients with psychotic features or bipolar disorder were excluded together with those who satisfied other exclusion criteria set for all subjects. Thus, the depressed patient group represents an intermediate group regarding level of psychopathology load. In conclusion, the

findings of the present study can be generalised to unipolar major depressed patients but probably to a lesser degree to milder, older or first-time or never hospitalised depressed patient groups.

The control group subjects were recruited through newspaper and community advertisements, but also from personal networks. Among 50 control subjects it is possible that some had milder psychiatric symptomatology and non-severe organic brain damage that can influence the performance on neuropsychological tests. The controls were not administered the psychiatric psychometric instruments, and this is a limitation of the study. In addition, the majority of subjects within the control group were working. This is not representative to the general population. This also implies that their cognitive functioning was better than a control group that contained a larger proportion of unemployed or long term sick-leave subjects, which increases group differences.

It can be argued that both the depressed and the schizophrenic groups are homogeneous groups (which was also an explicit aim of the BOP); while these limited groups increase the power of the study they also limit the generalisation of findings. In conclusion, the inclusion criteria of the study probably restricts generalisation more than the exclusion criteria.

Research design

It is important that the research design suites the objectives of the study. Sometimes it is obvious what the best design is, but more often there are several reasonable ways of designing a study (Altman, 1991). The cross-sectional design was chosen in the present study. This is a commonly used design because it is inexpensive and easy to conduct.

In the present study, the first aim was to investigate between-group differences regarding EF. Perhaps the better research design for this aim (Paper I) was in fact the cross-sectional design we used, although in hindsight increased power is desirable. A longitudinal design would have been an alternative for the second aim (Paper II) where it is questioned if all depressed patients are impaired in EF. For the third aim, the cross-sectional design was appropriate in the search for other explanations than diagnosis of the variance in EF (Paper III). Optimally though, for this aim the depressed and schizophrenic patient samples included should have been more heterogeneous in regards to severity of illness. Additional patients with psychotic depression, bipolar disorder, schizoaffective disorder and healthy control subjects should also have been included so that the sample reflected many symptoms belonging to the psychiatric continuum. For the fourth aim, the cross-sectional design was appropriate for studying associations between saliva cortisol level and level of neurocognitive function (Paper IV). Another option would have been to use a longitudinal design allowing inferences to be made on the causality of the associations, although longitudinal designs also have shortcomings. To sum up, the cross-sectional design was optimal for the specific aims of this thesis, but for other objectives such as causality or "trait or state" issues, longitudinal designs would have been the preferred research design.

Biases and possible confounding factors

Selection and volunteer biases

Selection biases may have been present for all papers included in this thesis. Depressed and schizophrenic patients complaining about cognitive problems may systematically have been referred more often to the study by their psychiatrist or psychologist than patients without such complaints. If so, inflation in effect sizes for differences between

depressed patients and healthy controls may have occurred in the present study. Another potential bias that goes in the opposite direction is that when recruiting volunteer subjects to participate in a research project there is the possibility that only optimally functioning subjects choose to participate. The patients who were referred, but chose not to participate were possibly more cognitively impaired and more severely ill from their depression or schizophrenia, and this would have reduced effect sizes. For the schizophrenic patients there was also a bias towards better cognitively functioning paranoid schizophrenic patients, which in Paper III may have led to underestimation of effect sizes for the association between level of psychopathology and level of EF. The patient samples were based on individuals, who volunteered to participate and were not consecutively admitted, a preferred method because this would have reduced the possibility of selection bias at this stage of the study. Demographic data and health-related data were not collected for the patients who did not volunteer. As for the control subjects, these were mainly working and were therefore probably healthier, more sociable and more neurocognitively well than the depressed patients. Most likely, this selection bias would have led to an inflation of effect sizes for differences between depressed patients and healthy controls. In conclusion, because biases go in opposite directions the strength of the associations found are probably neither inflated nor underestimated.

Possible confounding factors

In Papers I and II there were no statistically significant group differences between the depressed group and the control group for age, gender, education or intellectual abilities. In Paper III, there was no group difference for level of education. However, there is the possibility that also many other factors or third variables can confound the association between depression and EF, i.e. psychotropic medication and other

substances, psychomotor speed, intellectual abilities, general functioning, sleep, motivation, occupational status, etc. (Kiosses and Alexopoulos, 2005, Lezak, 1995, Mortensen et al., 2005, Porter et al., 2003). These confounding factors may exist independent of the disorder or may be part of the disease. In Paper I, an effort was made to adjust for additional medication and psychomotor speed as possible third variables and this adjustment reduced the effect sizes for the association between depression and EF by one-third to one-fourth, respectively. In Paper III, age and gender was adjusted for in the multiple linear regression models, but not the level of intellectual abilities. In Paper IV, the level of intellectual abilities was especially controlled for in partial correlations, and this adjustment did not change the fact that a statistically significant correlation was found between elevated saliva cortisol and executive dysfunction. In schizophrenic patients the mean IQ level is usually below that of depressed patients and controls who all have normal IQ. This third variable is an important confounding factor between mental disorders and neurocognitive function (Lezak, 1995, Mortensen et al., 2005). A test assessing motivational aspects was included in the present study, the VSVT, and the results showed normal motivation in the depressed group as compared to controls. The matching of the study groups is no guarantee for having controlled for all variables that may affect the result. There may be other variables that can explain the results and also residual confounding from the variables already mentioned. This was not performed in the present papers. No pair-wise matching or randomisation was performed in the present study. In conclusion, there may be possible confounding effects that partially explain some of the findings from the present study.

Strengths of the study

As discussed above, the clinical samples were well characterised and homogeneous. The SCID-I was used. In addition, the neuropsychological test battery was broader and the depressed and schizophrenic samples were relatively well-sized compared to other neuropsychological studies on depressed and schizophrenic patients.

Conclusions

The contributions of the papers in this thesis may be summarised as follows:
The present study confirms earlier findings as well as patients' subjective complaints and clinicians' observations that patients with unipolar major depression perform below healthy controls on most measures of higher order cognitive functions, EF. This is also true for patients that have suffered from two or more recurrent episodes of depression. Several components of EF such as verbal fluency, inhibition, set-maintenance and working memory were affected in the recurrently depressed group compared to controls, whereas set-shifting was spared. On a group basis, the executive dysfunction was mild in patients with recurrent MDD.

Despite a significant group difference between patients and healthy controls, many recurrent MDD patients had unimpaired EF. The subgroup of patients without executive dysfunctions was characterised by fewer episodes of depression and higher intellectual abilities than patients with EF impairment. It therefore seems that increasing numbers of depression episodes are associated with executive dysfunctioning whereas higher intellectual abilities are associated with normal EF.

The present thesis also showed that more than 90% of the variance in EF was explained by other factors than being depressed. In the search for other explaining

factors, it was found that LGP explained more of the variance in EF than diagnosis did. But diagnosis also had a separate contribution to the variance in EF. The study thus partly provides empirical support for the continuum hypothesis in psychiatry, namely that different mental disorders can be viewed as different levels of psychopathology. A consequence of this model is that dimensional approaches may be applied to mental disorders and neurocognitive function in future research as opposed to continuing the search for unique neurocognitive profiles for narrower diagnostic groups.

The level of EF was found to be inversely associated with the level of saliva cortisol in a smaller sub-sample of patients with recurrent unipolar major depression. Therefore, the present study both directly and indirectly supports the cortisol hypothesis.

Clinical implications of findings

It may be difficult to directly transfer the evidence from a laboratory setting in the present study to every day situations. Nevertheless, it can be speculated that the findings from the present study may have implications for the clinical investigation, management and rehabilitation of patients with recurrent unipolar major depression. Clinicians may choose to include a neuropsychological assessment in the clinical investigation in order to identify patients with executive dysfunctions and other neuropsychological dysfunctions because these patients may have special treatment and rehabilitation needs. Evidence elsewhere suggests targeted, psychopharmacological and psychotherapeutical treatments for patients with unipolar major depression who experience co-occurring executive dysfunctions (Alexopoulos et al., 2003, DeBattista, 2005). There are a few indications that executive dysfunctions should be a focus in the rehabilitation of unipolar major depressed patients in order to improve general functioning and get them back to work (Grigsby et al., 1998, Kiosses

and Alexopoulos, 2005, Manchester et al., 2004, McGurk and Mueser, 2003, Spijker et al., 2004). It is possible that patients with recurrent major depression who have executive dysfunctions, and because of that have problems solving complex tasks, will need a longer sick-leave period than patients without executive dysfunctions.

In a more global perspective, the main challenge will still be to diagnose and treat patients with unipolar major depression to reduce disability and suffering. For patients with recurrent unipolar major depression it is important to effectively treat the acute depression episode as well as avoid future episodes. In the future, simple screening instruments should be available for physicians in order to detect executive dysfunctioning and other neurocognitive dysfunctions in patients with unipolar major depression. Also, antidepressant medication should be developed that target executive dysfunctioning in patients with unipolar major depression. It will also be important to avoid using antidepressants with negative side-effects on neurocognitive functioning. It can also be argued that there is a need for a consensus and standardisation within the field of neuropsychology regarding the operationalisation of EF as parallel to the psychiatric consensus-based diagnostic systems.

Suggestions for future research

The present thesis has shown a need for future studies within this and overlapping research fields that:

1) aim to clarify the concept of EF and the relationship to the functional frontal lobe

2) investigate the functional, treatment or rehabilitation consequences of an additional "diagnosis" of executive dysfunctions in patients with unipolar major depression

3) document effects of antidepressant medications or other agents that are targeted towards executive dysfunctioning in unipolar major depression

4) include dimensional approaches, in addition to categorical approaches, to both depressive/psychiatric symptomatology and executive/neurocognitive functioning

5) include possible biological correlates, i.e. cortisol

6) continue to explore the causality of executive dysfunctions in mental disorders including unipolar major depression

In order to perform these investigations, several methods and research designs should be combined. In the first review paper of neurocognitive deficits in depression, William Miller (1975) concluded: "There is rather widespread agreement regarding the clinical description of depression, and there is a considerable amount of research which demonstrates that depressives exhibit deficits relative to normals and neurotics on intelligence tests and laboratory tasks and in communication. What is most needed now are theories of depressive deficits and studies designed to test these theories." To a certain extent this statement is still valid today. Hopefully, future studies will focus on the non-uniqueness of neurocognitive deficits in mental disorders and explore the continuum way of thinking about mental illness and neurocognitive functions.

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