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**PAPERS 1-3**
Acknowledgements

The present study is part of an overarching study at the Department of Geriatric Psychiatry, Diakonhjemmet Hospital, in which the authors aim to investigate the effects of electroconvulsive therapy on depression, cognition, and biomarkers. Inclusion of patients started September 1, 2009. From January 2012 my work was supported by the Norwegian ExtraFoundation for Health and Rehabilitation through the Norwegian Council for Mental Health. This challenging and rewarding work would not have been possible without financial support, and extensive collaboration with and support from colleagues and my family.

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SUMMARY

Electroconvulsive therapy (ECT) is recognized as an efficacious biological treatment of severe depression in the elderly. The treatment may lead to two opposing effects; 1) amnesia and other negative cognitive side effects, and 2) improved cognition in patients who respond to the treatment of the depression. Knowledge about cognitive side effects induced by ECT in depressed elderly patients is sparse.

In the present thesis my overall aim was to investigate the longitudinal cognitive course in a sample of nondemented depressed elderly inpatients that were treated with ECT. Our study included considerably more patients than previous studies of cognitive side effects of ECT in this age group. Only one previous study has assessed the memory of elderly patients at baseline, shortly after a session of ECT, and at an additional later follow-up. No previous study of the elderly has investigated whether patients with cognitive impairment at the baseline are more vulnerable to amnesia after ECT.

In paper I we characterized neuropsychological functioning at the baseline in depressed elderly patients. We found, as expected, that patients were more frequently cognitively impaired relative to healthy control (HC) subjects, and they performed significantly poorer in the domains of information processing speed and executive function. Even when controlling for differences in processing speed, patients showed more executive deficits than controls.

In paper II we investigated short term changes in the cognitive functioning of patients receiving ECT, by comparing with results from the HCs. In
contrast with previous studies, we investigated individual differences in addition to patterns at the group level. Overall, a comparison of group means showed longitudinal stability. Nevertheless, a substantial minority of elderly patients receiving ECT experienced mild neurocognitive impairments in the acute phase of treatment, especially on tests of anterograde memory, retrograde memory, and verbal fluency.

The research objective in paper III was to compare the cognitive course of a subgroup of patients with “cognitive impairment no dementia” at baseline (CIND) with a subgroup with “no cognitive impairment” (NCI). The results showed indications of transient cognitive side effects of ECT in the first week after ECT in a substantial minority of the patients, with no difference between subgroups. Patients with CIND showed more improvement in test scores over time than patients with NCI, especially on a test of information processing speed. At T3, half the CIND group had converted to NCI.

In conclusion, heterogeneity of cognitive function of patients with geriatric depression was corroborated across papers. Executive function was most frequently impaired at the baseline assessment. Cognitive impairment at the baseline may be permanent in some patients who remit from depression, but transient in others. Although the present findings require replication in larger follow-up samples, they may illuminate that even if group studies do not show indications of cognitive side effects of ECT in the elderly, a substantial minority have acute adverse effects. This study neither demonstrated long-term side effects of ECT, nor increased vulnerability of amnesia in patients with cognitive impairment who receive ECT.
LIST OF PAPERS

The present thesis is based upon the papers listed below.


**Abbreviations**

AA Anterograde Amnesia

ANOVA Analysis of Variance

BP Bipolar Disorder

BVMT-R Brief Visuospatial Memory Test – Revised

CAMI-SF Columbia Autobiographical Memory Interview – Short Form

CIND Cognitive Impairment No Dementia

CWIT Color Word Interference Test

D-KEFS Delis-Kaplan Executive Function System

DSM-IV Diagnostic and Statistical Manual of Mental Disorders 4th edition

ECT Electroconvulsive Therapy

HC Healthy Control

HDRS-17 Hamilton Depression Rating Scale (17 items)

HVLT-R Hopkins Verbal Learning Test – Revised

LLD Late-life Depression

MANOVA Multivariate Analysis of Variance

MCI Mild Cognitive Impairment

MDD Major Depressive Disorder
MDE Major Depressive Episode

MMSE Mini Mental State Examination

MINI Mini International Neuropsychiatric Interview- Plus

MQ Media Questionnaire

NCI No Cognitive Impairment

RA Retrograde Amnesia

RCI Reliable Change Index

RCT Randomized Controlled Trial

REK Regional Committee for Medical Research Ethics

SCID Structured Clinical Interview for DSM-IV

T1 Time 1 (baseline)

T2 Time 2 (first follow-up)

T3 Time 3 (second follow-up)

TMT Trail Making Test

WMH White Matter Hyperintensities
1. INTRODUCTION

Major depression ranks among the most prevalent mental illnesses, and most investigators agree that 10% of the population will meet diagnostic criteria for major depressive disorder during their lifetime (Cipriani, Barbui, Butler, Hatcher, & Geddes, 2011). Depression is the most frequent psychiatric illness of older people, and older, grieving, physically ill, and demented people are at especially high risk (Thomas & O'Brien, 2006). In addition to decreased quality of life in older adults, depression involves a considerable caregiver, and public health burden. Untreated major depression in the elderly can last for years and is associated with difficulties with social and physical functioning, worsening of chronic medical problems, and increased morbidity and mortality from suicide and other causes (Unutzer, 2007).

Depression is the main indication for electroconvulsive therapy (ECT) in contemporary practice in most western countries (Leiknes, Jarosh-von Schweder, & Hoie, 2012). Compared with psychopharmacological treatment, ECT is considered to be more effective in treating severe depression (Cipriani, et al., 2011). Older patients with major depression are more likely to be treated with ECT than younger patients in the USA, the UK (Dombrovski & Mulsant, 2007), and in Norway (Moksnes, Vatnaland, Eri, & Torvik, 2006). The main reason is that elderly patients often have co-morbid physical illness that renders them less likely to tolerate adequate antidepressant
medication dosages, and thus they are less likely to benefit from them (Dombrovski & Mulsant, 2007). Age-related vulnerability to the complications of severe depression, such as dehydration, malnutrition, and weight loss, mandate speedy recovery, also leading to increased referral for ECT (Tharyan, 2007). ECT in the depressed elderly is generally considered a therapeutic intervention if the patient is psychotic, speedy recovery is mandatory, or when pharmacological treatments have proven ineffective.

However, ECT is a controversial treatment method. Strong critics infer from cognitive side effects that ECT causes brain damage (Read & Bentall, 2010). In the field of psychiatry, ECT is generally considered to be a safe and effective treatment for depression with side effects that generally are transient (Sackeim, 2005). Although ECT can alleviate depression, this treatment inflicts epileptic seizures, which might potentially be toxic for the brain. While most evidence points toward modern ECT not causing brain damage, there are still some findings that raise questions about safety (Reisner, 2003). Patients complain about disturbing and lasting loss of autobiographical memories, as well as loss of impersonal information, such as knowledge of public events, after ECT (Rose, Fleischmann, Wykes, Leese, & Bindman, 2003; Squire, Slater, & Miller, 1981). Prospective follow-up studies of groups indicate that self-reported memory improves shortly after ECT relative to the baseline, and that this improvement continues to the next follow-up. Nevertheless, subjective reports of memory loss in retrospective questionnaire and
interview studies often extends over a longer period than is shown by objective neuropsychological tests (Fraser, O'Carroll, & Ebmeier, 2008).

Research using objective neuropsychological tests corroborate that ECT may cause functional decline in the form of anterograde and retrograde amnesia (AA and RA) (Semkovska, Keane, Babalola, & McLoughlin, 2011). While AA is probably resolved within weeks after ECT, there is disagreement among studies regarding the severity and persistence of RA (Meeter, 2003; Sackeim, et al., 2007). Cognitive side effects may interfere with functioning in daily life, communication with others, identity, and self-confidence (Vamos, 2008). Amnesia, even if experienced in a limited time period, may be frightening, and lead to later questions about whether memory functions have ever recovered after ECT (Squire & Slater, 1983).

As many elderly patients receive ECT, and previous research is sparse, more research on cognitive side effects in this age group is needed. Previous studies of elderly patients receiving ECT have investigated the longitudinal development of the group mean, but have not evaluated the frequency of clinically relevant decline in individuals. The potential role of baseline cognitive impairment for cognitive side effects in the elderly has only been studied with short rating scales of dementia.

The current study aimed to investigate the cognitive function of elderly depressed patients before and at follow-ups in the week
after ECT, and at an additional 3 months. Increased knowledge of adverse cognitive effects of ECT in the elderly may have important clinical implications, as well as relevance for theoretical models of course, and side effects in the cognitive domain for patients treated with ECT.

Before describing the project, a further description of relevant concepts and perspectives for our study will be presented.

1.1. Major depressive episode

A major depressive episode (MDE) as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association, 2000) denotes a moderate or severe depression. Initial onset of depression usually corresponds with psychosocial stressors (e.g. death of a spouse), which interact with individual vulnerabilities. Depression presents with low mood, and markedly diminished interest or pleasure in activities. There may in addition be biological changes, e.g. in sleep, appetite, and activity level, and psychological changes that may include low self-esteem, irrational feelings of guilt, recurrent thoughts of death, suicidal ideation, and diminished ability to concentrate and to make decisions. The extent and intensity of symptoms depends on the severity.

Patients with major depressive disorder (MDD) or bipolar disorder (BP) are among those who may experience one or more
MDEs. BPs are characterized by one or more episodes of mania (BP I) or hypomania (BP II) in addition to MDEs. Bipolar II is a less malignant form of the disorder than Bipolar I. MDE per the DSM-IV is considered to be a homogenous disorder that changes in terms of severity. In the DSM-IV, melancholic depression and psychotic depression are considered to be the most severe, but not qualitatively different subtypes (Quinn, Harris, & Kemp, 2012). The melancholic subtype of depression is characterized by anhedonia, weight loss, insomnia with early-morning awakening, guilt, and psychomotor agitation or retardation. The understanding that MDE is a homogenous disorder is criticized by professionals who state that the presence of subtypes such as psychotic depression and melancholia suggest much heterogeneity, possibly indicating biologically distinct subgroups (Gournellis, Oulis, & Howard, 2014; Parker, 2005). There are very few differences between definitions of MDD, and minor differences between definitions of BP in the DSM-IV and in the DSM-V (American Psychiatric Association, 2013; Angst, 2013).

Mood disorders have traditionally been regarded biologically as neurochemical disorders, and early research centered upon monoaminergic theories with particular focus first on norepinephrine and later serotonin. A number of other neurochemical differences between normal and depressed people are identified. New evidence suggest that reduced neurogenesis and glial changes in hippocampus play a key role in mood disorders (Gervasoni, et al., 2005; Nordanskog, et al., 2010). Studies of animals and humans raise the
possibility that increased cell proliferation and increased neuronal number may be a mechanism by which antidepressant treatment overcomes the stress-induced atrophy and loss of hippocampal neurons (Gervasoni, et al., 2005). Chemical substances like the protein brain-derived neurotrophic factor might be stimulated by the antidepressant treatment. Animal research has even provided evidence for a cell proliferative effect of ECT in the hippocampus. A Swedish study found ECT significantly to increase the hippocampus volume in humans from baseline in the week before ECT to the week after ECT series (Nordanskog, et al., 2010).

1.2 Late-life depression and late-life bipolar disorder

Perceived distinct characteristics of depression in the elderly have led to the evolution of the concept of late-life depression (LLD).According to O'Hara, Coman, and Butters (2006), late-life depression is still an evolving concept, which refers to the presence of a significant clinical depression (not necessarily meeting the DSM-IV criteria for MDE), in individuals over 60 years of age, and is typically defined independently of age of onset. Geriatric depression more frequently manifests as physical symptoms, hypochondria, and memory complaints, and appears to be more recurrent and more chronic than depression in younger patients (O'Hara, et al., 2006). Melancholia and psychosis are more frequent in older persons than in younger adults (Blazer, 2003; Brodaty, et al., 2005). There is a well-
established association between cerebrovascular pathology and development of depression in the elderly (Steffens & Potter, 2008).

The clinical presentation of BP in late life compared to BP in younger persons, manifest itself more frequently by melancholic depressive features, a predominantly depressive polarity, and age at illness onset > 40 years (Nivoli, et al., 2014). Late-onset depression (Herrmann, Goodwin, & Ebmeier, 2007) and late-onset BP (Arciniegas, 2006) are terms that may be defined by first depression at > 60 years of age.

However, since neither LLD nor late-life BP is a formal diagnostic entity, researchers define them differently. For instance, according to O'Hara, et al. (2006), Blazer (2003), and Korsnes and Ulstein (2014), the concept of late-life depression does not exclude depressed patients with previous episodes of hypomania or mania. The use of the term in this thesis is in accordance with this view. Others present late-life BP more as a separate disorder compared to late-life depression (for instance Depp and Jeste, 2004).

1.3 Mild cognitive impairment

The concepts of “mild cognitive impairment” (MCI) and “cognitive impairment no dementia” (CIND) are commonly used in research, but are not formal diagnostic entities. They intend to identify the intermediate level of cognitive impairment that is a risk factor for
dementia, and thus sometimes a transitional phase from normal ageing to dementia (Schoenberg & Duff, 2011). The concept of CIND is a heterogeneous classification that includes non-demented elderly people who exhibit poor (not necessarily declined) performance on a cognitive measure on a specific point in time (Tuokko & Frerichs, 2000). CIND can be caused for instance by an early stage of dementing disease, focal abnormalities, lifelong developmental disabilities, and psychiatric illnesses (Tuokko, et al., 2003). An additional criterion for MCI is subjective complaints of appearance of cognitive impairment from the patient or an informant. Subtypes of MCI are the amnestic, non-amnestic single domain, and multi-domain (Schoenberg & Duff, 2011). MCI may be due to several causes including systemic disorders, medications, and psychiatric disorders. However, in contrast with research on CIND, such conditions are usually excluded when the research aim is to estimate the likelihood of progression of MCI to AD or other dementias (Petersen, et al., 2014).

1.4 Electroconvulsive therapy

1.4.1 The early history of ECT

ECT originated in the 1930s primarily as a treatment for schizophrenia, at a point of time when no efficacious treatment options for severe mental disease were known. Schizophrenia was
conceptualized as a brain disease, and various biological treatments were tried. ECT emerged as a new form of convulsive therapy, rather than a completely new treatment. The Hungarian neuropsychiatrist László Meduna first used chemically induced convulsive therapy in 1934 (Shorter & Healy, 2007). Epidemiological and histopathological studies had given rise to his hypothesis of an antagonism between epilepsy and schizophrenia. Thus, epileptic seizures were expected to improve the condition of schizophrenic patients. The Italian neurologist Ugo Cerletti wished to develop an effective convulsive therapy with fewer side effects than previous ones. He hypothesized that electricity might be more suitable than chemical substances to induce electric shocks, and tried to develop a safe procedure by first experimenting with electrically induced seizures in dogs. Cerletti and Bini first gave ECT to a patient in Rome in April 1938 (Shorter & Healy, 2007). The patient was schizophrenic, had eleven electroshock treatments and was discharged from the hospital in good condition and well-oriented (Endler, 1988). In line with the contemporary paternalistic mindset, the first ECT was initiated without consent. Anesthesia, muscle relaxants, and artificial ventilation under ECT were not commonly used until the 1950s. A frequent complication before ECT was modernized was bone fractures (especially vertebral fractures) which occurred in 5–9% of the cases (Kragh, 2009). The use of sine wave current and no artificial ventilation under ECT led to more severe amnesia than modern treatment.
1.4.2 ECT in Scandinavia

In Norway ECT was applied at the University Psychiatric Clinic in Oslo in 1942 (Psykiatrisk klinikk, Vinderen, 1951). In Sweden and Denmark, ECT was in regular use in university clinics in the late 1940s (Benbow & Bolwig, 2009). Among the early, well-known, and highly influential Scandinavian groups of ECT researchers are the groups headed by Jan-Otto Ottosson in Gothenburg and Tom G. Bolwig in Copenhagen (Benbow & Bolwig, 2009; Shorter & Healy, 2007). According to Benbow and Bolwig (2009), ECT is given in all the Scandinavian countries, but traditionally more so in Denmark and Sweden. Between roughly 1960 and 1980, ECT disappeared from the awareness of many clinicians in many western countries. In the 1960s, ECT met competition from groups that favored new psychotropic drugs (antipsychotics and antidepressants), or specific psychotherapeutic interventions. The increasingly critical light on ECT from the 1960-70s was concurrent with anti-psychiatric trends, and among critics of ECT are also opponents of psychopharmacological treatment (Hirshbein & Saravananda, 2008). The use in Norway increased from the 90s (Moksnes, et al., 2006), as in many other western countries (Sienaert, 2011). Bergsholm (1995) authored the first doctoral thesis in Norway about ECT. It described issues related to ECT and narcosis, physiology, radiological anatomy, electrode placement, and endocrinology.
1.4.3 Modern ECT

Moksnes et al. (2006) describe modern ECT as characterized by 1) an electrical brief pulse stimulus given via two electrodes, which is placed either on the right side of the head (unilateral ECT) or on both sides (bilateral ECT). 2) The entire procedure takes 10–15 minutes from the time the patient falls asleep to awakening. 3) In addition to the anesthetist and the doctor, a nurse is present during the entire session. And 4) During treatment electric activity of the brain and the heart, heart rate, and oxygen saturation are monitored, and blood pressure is measured before and after treatment. Modern ECT is implemented in Norway, and in many western countries, but is far from implemented worldwide (Leiknes, et al., 2012).

More than 75 years after the first treatment, ECT remains a controversial method of psychiatric treatment (Read & Bentall, 2010). In popular movies, ECT has been negatively portrayed as a controlling, even punitive, treatment for patients with psychiatric disorders, for instance in the award winning classic film One Flew over the Cuckoo's Nest (Forman, 1975). The present opinions of ECT are often polarized. While some perceive ECT as a reductionist and technological intervention possibly causing permanent brain injury (Read & Bentall, 2010), others think that ECT is a safe and effective treatment initiated by a genuine desire to provide health care to people with mental disorders (Hirshbein & Saravananda, 2008), or even that ECT is the “penicillin of psychiatry” (Shorter & Healy, 2007).
Prospective studies do not indicate that modern ECT causes structural damage to the brain (Bolwig, 2014; Devanand, Dwork, Hutchinson, Bolwig, & Sackeim, 1994). In epileptics the effect of repeated brief seizures on the brain appears to be limited, but due to many confounding variables it is difficult to estimate (Vingerhoets, 2006). Researchers have been looking for factors that may explain the therapeutic effect since ECT was introduced in the late 1930s. The mechanisms are probably multi-factorial. Normalization of neuroendocrine dysfunction, and increased hippocampal neurogenesis and synaptogenesis are among important current theories (Bolwig, 2011).

Naturalistic studies have found that 50% or more of remitted patients have a relapse of depression within 6 to 12 months of discontinuing acute ECT, so psychological and biological continuation treatment is indicated (Sienaert, 2011). Continuation ECT (for instance one ECT per month for half a year) is at least equally effective in avoiding relapse as continued psychopharmacological treatment (Smith, et al., 2010).

1.5 Cognition in depression in late life

1.5.1 Relevant domains

Anterograde memory, executive function, and information processing speed are among the most relevant domains to assess in
elderly with an MDE. In studies of cognitive side effects of ECT, measures of RA should be added. The inclusion of diverse sub processes implicates that the tests are more or less “impure” as measures of specific constructs (Phillips, 1997). Inevitably, nearly every measure in clinical neuropsychology literature involves multiple component operations (Dickinson, Ramsey, & Gold, 2007). Nevertheless, it is useful to categorize neuropsychological tests according to assessment of specific resources and constructs.

Information processing speed: This concept simply refers to the speed with which different cognitive operations could be executed, and is often measured by using simple tasks that most people could perform perfectly if there were no time limits (Salthouse, 2000). Normal aging and depression both slow information processing speed, and a combination of aging and depression amplifies these cognitive effects (Korsnes & Ulstein, 2014).

Executive function: The concept of executive function may be considered an umbrella term for a range of higher-order cognitive functions, and includes abilities of goal formation, planning, carrying out goal-directed plans, and effective performance (Miyake, et al., 2000). The abilities to attend to relevant aspects of our environment and to inhibit distraction by incidental environmental stimuli are also important executive functions (Schoenberg, et al., 2012). A critical measurement problem is that tasks that tap on executive processes must tap on practically all cognitive systems in addition to the
executive. Generally, executive tasks are less pure measures than non-executive ones (Burgess, 1997). Thus, a deficit on an executive measure is not by itself sufficient to infer the presence of a differential executive deficit, unless it is shown that the executive deficit is in excess of the averaged performance deficit across a range of other cognitive tasks that are not considered to impose heavy executive demands (Henry & Crawford, 2005). Performance on certain so-called executive tasks appears to be influenced considerably by processing speed in elderly depressed patients (Butters, et al., 2004).

Learning and memory: AA is impairment in the formation of new memories, due to deficits in the process of storage. RA is the loss of memories that were stored before the time of permanent or temporary damage of the brain (Meeter, 2003). Measures of RA are not included in a standard neuropsychological assessment, but might be investigated if RA is suspected. It is important to include measures of RA in studies of cognitive side effects of ECT. A key characteristic of RA is that in contrast to declined remote memory, it does not occur in healthy persons (Meeter, 2003).

1.5.2 Neuropsychological impairments

Comorbidity between depression in the elderly and mild cognitive impairment or dementia is frequent. Based on studies mostly of outpatients, about 20–50% of elderly individuals with depression are
estimated to have cognitive impairment (Koenig, Bhalla, & Butters, 2014). The rate in hospitalized patients is probably higher, because inpatients are generally more severely depressed (Basso, Miller, Estevis, & Combs, 2013). Because of the high rate of comorbidity between depression and mild dementia, severe cognitive impairment can be undiscovered in suffering patients until symptoms of dementia are pronounced (Bekkelund, Kujala, & Rosenvinge, 2001). Elderly patients who suffer from dementia (without any clinical information suggesting dementia) are occasionally admitted for the first time to a psychiatric hospital with depression.

Studies of major depression in elderly people have shown divergent findings, and impairment of executive functions, psychomotor speed, attention and inhibition, memory, expressive language, and visuospatial abilities have been reported (O'Hara, et al., 2006). The most consistent deficits occur in the areas of processing speed and executive functions, and these appear to increase with the severity of depression symptoms, particularly apathy / melancholia (Steffens & Potter, 2008). According to Lockwood, Alexopoulos, and van Gorp (2002), geriatric depressed subjects have, relative to their depressed younger counterparts and to healthy controls, disproportionately poor scores on neuropsychological tasks associated with frontal lobe integrity. The stability over time of these deficits requires further investigation (Lockwood, et al., 2002).
A broad range of patient characteristics may negatively affect neuropsychological performance in elderly depressed patients, including later onset of depression, medical comorbidity, and alcohol abuse. The presence of depression with psychosis in adults may negatively impact neuropsychological domains such as executive function, verbal and visual memory, and psychomotor skills to a greater extent relative to depression without psychotic features (McClintock, Husain, Greer, & Cullum, 2010). There are very few studies of cognitive function in psychotic elderly patients, and more research is needed (Gournellis, et al., 2014). It is claimed that elderly patients with BP depression have worse overall cognitive function than patients with MDD (Depp & Jeste, 2004; Gildengers, et al., 2012), but studies comparing these diagnostic groups in the elderly are extremely sparse. According to Basso, et al. (2013), BP depression and MDD likely yield equivalent neurocognitive impairment in adults. Any possible negative difference is probably larger between MMD and BP I, than between MMD and BP II (Kessler, et al., 2013; Xu, et al., 2012).

Several theories have been introduced to explain cognitive impairment in depressed patients. Motivation may be of some importance, but is probably not a main explanation (Landrø & Andersson, 2008). Two explanatory frameworks for cognitive impairment in depression are the effort hypothesis and the cognitive speed hypothesis. The effort hypothesis states that patients with mood disorders show impairment on tasks that demand cognitive effort as
opposed to automatic and over-learned material. The cognitive speed hypothesis states that reduced information processing speed is the basic explanatory factor of cognitive impairment in mood disorders. There is a differentiation between cognitive impairment, which can be explained by severity of symptoms (state-related), and cognitive impairment that is stable over time regardless of whether any symptoms of depression are present or not (trait-related). Among relevant state-dependent variables are intrusive thoughts, anxiety, psychomotor retardation, and tiredness. If state-dependent variables are important, then neuropsychological impairments are expected to be present in symptomatic phases and an association between cognitive impairment and increasing depression severity is expected.

1.5.3 Assessment of change over time

When measuring longitudinal change in cognition in a patient group that receives ECT, the study design is significantly strengthened if change can be assessed also in a non-ECT-treated comparison group. Without an appropriate control group in treatment studies, side effects can more easily be concealed by practice effects and effects of regression to the mean in lower-functioning individuals (Barr, 2002; Calamia, Markon, & Tranel, 2012). A weak point of most ECT studies in adults and all previous studies in older adults is the lack of a comparison group that did not receive ECT. For instance the review
An inclusion of a control group simplifies studies of individual differences in cognitive side effects by making test-retest data on all relevant tests from a suitable group available for comparison. Given the often-polarized debate concerning the extent and seriousness of cognitive side effects of ECT (Bergsholm, 2013; Fosse, 2011; Moksnes, 2012a, 2012b; Read & Bentall, 2010; Rose, et al., 2003), a research focus on individual differences in addition to mean group differences seems highly relevant.

Analysis of reliable decline can provide information about change in individuals that can supplement treatment research (Barr, 2002). Reliable change indices (RCIs) are used to estimate the probability that changes in test scores across test sessions are attributable to a clinically meaningful change in an individual's ability to perform a task, rather than to measurement error. There are several methods that are used in determining whether a reliable change has occurred over time (in the order of increasing sophistication); simple discrepancy scores, a standard deviation index, RCI without or with correction for practice effects, or formulas based on simple or multiple regression (Duff, 2012). Measures based on bivariate regression are recommended because they account for several potential sources of confound when investigating cognitive change; test-retest reliability, practice-effects, regression to the mean, and the impact of initial
performance, and in addition they are relatively easy to compute (Barr, 2002; Charter, 1996; Estevis, Basso, & Combs, 2012; Temkin, Heaton, Grant, & Dikmen, 1999). A 90% confidence interval is often used, implying an error margin of 5% in the direction of decline and 5% in the direction of improvement. Thus, even in a presumably healthy elderly sample of a reasonable size, 5% of individuals are expected to have RCIs on single tests in the declined range.

We were the first to use RCIs when investigating acute side effects of an initial series of ECT. Rami et al. (2004) used RCIs, without correcting for practice, in a study of continuation ECT. Previously, statistical methods for assessing reliable decline have been used in, among others, the following diagnostic groups; sports concussion, traumatic brain injury, epilepsies, multiple sclerosis, stroke, Parkinson’s disease, and mild cognitive impairment (Barr, 2002; Duff, 2012).

1.6 The effects of ECT on cognition

1.6.1 Cognitive side effects in adults

Memory impairment as a side effect was apparent even in the earliest days of ECT use, and RA was the most worrying because it could be persistent (Shorter & Healy, 2007). Memories from events occurring just prior to ECT are most vulnerable to amnesia (Söderlund, Percy, & Levine, 2012). RA may imply impaired
autobiographical memory (recollection of incidents and events that were experienced by the person in the past), and / or impaired semantic memory (knowledge of language, concepts, and facts). According to Michael D. Kopelman (2002), RA may be mild (duration: seconds, minutes, or hours), moderate (duration: last days, weeks, or up to two – three years), or extensive (duration: lasting for a period longer than 2-3 years). Generally are mild and moderate RAs described as side effects of ECT. Primarily the extensive RAs are described in the general neuropsychological literature, and cortical damage seems to be required (Kopelman, 2002).

Although many studies have investigated cognitive side effects of ECT, the studies are generally characterized by methodological weaknesses. Few studies have managed to use the methodological gold standard of a randomized controlled trial (RCT) where one of the groups did not receive ECT. A Norwegian study comparing bipolar patients randomized to ECT or psychopharmacological treatment is one of these few (Kessler, et al., 2014; Schoeyen, et al., 2014). According to the acknowledged National Institute for Health and Clinical Excellence in UK guideline on the treatment and management of depression in adults (NICE, 2010) and the UK ECT review group (2003), only four RCTs (the last published in 1985) compared patients receiving ECT with patients receiving psychopharmacological agents or sham ECT. The neuropsychological test batteries used were limited, and findings were inconclusive, although not giving indications of severe nor long-lasting cognitive side effects of ECT.
Systematic reviews and meta-analysis have analyzed data from observation studies of patients given ECT. Semkovska and McLoughlin (2010) conclude that not only reduced anterograde memory, but also decline on tests of verbal fluency, information processing speed, and executive function, are common in the first three days after an ECT session. However, they found cognitive side effects to be transient. They did not include tests of retrograde memory. Early studies found that amnesia for personal memories after ECT improved substantially, but only partly over time (Squire, et al., 1981). Time line interview data at three years post ECT indicated an RA of up to about six months and an AA of up to about two months after bitemporal ECT (Squire & Slater, 1983). Generally, sine wave ECT was administered at that time. Contemporary studies differ regarding whether findings support a temporariness of RA for autobiographical information (Lisanby, Maddox, Prudic, Devanand, & Sackeim, 2000; Sackeim, et al., 2007), and for information of public events (Lisanby, et al., 2000; Meeter, Murre, Janssen, Birkenhager, & van den Broek, 2011). A large naturalistic study showed that 12% of the patients still had RA for autobiographical information six months after the ECT (Sackeim, et al., 2007). Most of them had received ECT with bitemporal electrode placement.

The mechanisms of action for how ECT causes amnesia remain unknown, but several theories exist (McClintock, et al., 2014). According to Nobler and Sackeim (2008), hippocampus has a low seizure threshold, implicating that cognitive functions connected to
the hippocampus may be especially vulnerable to ECT. The hippocampus and medial temporal structures are essential for the gradual consolidation process of new memories. However, the storage and retrieval of old memories are most likely dependent upon a widespread network of neural connections. Although retrieval of memories is controlled by executive functions, the retrieval of memories of specific episodes involves re-experiencing the event and probably also involve the hippocampus (Moscovitch, et al., 2005). Several neurochemical mechanisms induced by ECT may cause cognitive side effects, but sparse knowledge illuminates them at present (Andrade & Bolwig, 2014). Rodent models have found that electrically induced seizures disrupted long-term potentiation, a mechanism for learning and memory (McClintock, et al., 2014).

Cognitive side effects of ECT affecting other functions than memory are less studied, and therefore more studies investigating for instance executive function are needed (Ingram, Saling, & Schweitzer, 2008). Little is also known about individual predictors of cognitive side effects of ECT in younger and elderly adults. Sobin et al. (1995) found that lower pretreatment global cognitive status was a significant predictor of RA in the week after a course of ECT and at a 2-month follow-up. The only potential cognitive side-effect of ECT that was studied was RA for personal information, which was assessed with a comprehensive interview with 281 inquiries about recent and remote personal memories. In this study, they assessed patients with a mean age of 54 years with the modified Mini Mental State Examination
MMSE (Stern, Sano, Pauson, & Mayeux, 1987), which is a measure of global cognitive status and an expanded version (range 0–57) of the original MMSE (range 0-30) (Folstein, Folstein, & McHugh, 1975). Valid data were available for 67 patients at baseline and short-time point, and for 44 patients at 2-month follow-up. MMSE is a multidomain screening tool that takes about 10 minutes to administer. The MMSE is modestly effective at ruling out dementia in specialist settings (Mitchell, 2009).

There probably is variation in vulnerability to the adverse cognitive effects of ECT, but little is known about this topic (McClintock et al., 2014; Sackeim et al., 2007). The potential clinical implication of such knowledge would be the possibility of exercising particular caution in treatment of patients belonging to a risk group. McClintock, et al. (2014) attempt to synthesize the multiple moderating and mediating factors that are thought to underlie the neurocognitive effects of ECT into a coherent model. Among essential demographic, neuropsychological, neuropsychiatric, and neurophysiological factors they list age, years of education, premorbid intellectual ability, neuropsychiatric symptoms, number of distinct neuropsychiatric episodes, length of illness, comorbidity, and neuroanatomical structural changes. Per today very little is known about the associations between these factors and cognitive side effects of ECT.
There is far more available knowledge about how technical factors, such as dose of electricity relative to seizure threshold, electrode position, and frequency of treatment can affect cognitive function (Charlson, et al., 2012; McClintock, et al., 2014). Many high-quality RCTs compare different techniques in ECT, e.g. electrode placements (Cipriani, et al., 2011). The cognitive profile of the three commonly used electrode placements, right unilateral, bitemporal, and bifrontal, does not seem to differ dramatically (Kellner, et al., 2010; Sienaert, 2011), although some researchers have found the bitemporal placement associated with more memory impairment (Sackeim, et al., 2007).

1.6.2 Cognitive side effects in older adults

Per today, possible side effects of ECT in the elderly have not been adequately examined because of methodological shortcomings, including lack of randomized evidence (Van der Wurff, Stek, Hoogendijk, & Beekman, 2003). However, the risk of interictal, often transient, confusion is known to be increased by age-associated neurological conditions such as Alzheimer’s dementia, Parkinson’s Disease, and cerebrovascular disease, although the MMSE is on average better at the end of ECT than before ECT (Gardner & O'Connor, 2008; Rao & Lyketsos, 2000).
Previous studies using a neuropsychological test battery in the elderly treated with ECT have reported large difficulties with the recruitment of patients even to observational studies. While they chose a time point for testing that was intended to maximize recruitment, O'Connor, Gardner, Eppingstall, and Tofler (2010) managed to include only 35% of eligible patients in a cognitive assessment after the first or second ECT and after the fifth or sixth ECT. Verwijk, et al. (2014) reported a low recruitment rate and high attrition between the first and the second follow-up as a main limitation. Owing to the overwhelming difficulties of recruiting and motivating elderly persons to participate in a clinical trial randomizing elderly depressed patients to ECT or psycho-pharmacological drugs, Stek, van der Wurff, Uitdehaag, Beekman, and Hoogendijk (2007) unfortunately had to terminate the study.

Two reviews summarize that previous research in the elderly is characterized by small and heterogenic samples, limited test batteries, and a lack of a comparison group (Gardner & O'Connor, 2008; Tielkes, Comijs, Verwijk, & Stek, 2008). There is only one prior study to ours assessing patients’ memory before ECT, a short time after ECT, and at one additional follow-up (Verwijk, et al., 2014). The study included 42 patients at baseline and the first follow-up, and 24 at the second follow-up six months after ECT. They concluded that there were no indications of cognitive side effects of ECT, and hypothesized that elderly may be less vulnerable to adverse cognitive effects of ECT than younger adults. Their findings were somewhat
unexpected, because elderly depressed patients are often supposed to
be more vulnerable of cognitive side effects of ECT than younger
adults, because of age-related changes of the brain.

Studies in this field often include both nondemented and
demented patients. For instance Verwijk, et al. (2014) neither
explicitly excluded patients with a clinical diagnosis of dementia nor
excluded patients by using a criterion from a rating scale of dementia
(for instance MMSE). The most widely used cut-off score for likely
dementia on the MMSE is ≤ 23 out of 30 (Engedal, 2000; Ramlall,
Chipps, Bhigjee, & Pillay, 2013). Potential participants in the study of
Verwijk, et al. (2014) had MMSE scores in the range from 6 – 30. The
patients who actually chose to participate had MMSE scores in the
range 15-30 at baseline. Although there is a need of knowledge about
cognitive side effects of ECT even in patients with a moderate or
severe cognitive impairment at baseline, neuropsychological tests are
likely too demanding for patients with moderate and severe cognitive
impairment. The functioning of these patients will probably be
consistent with a floor effect on traditional neuropsychological tests.
Floor effects on tests implicate that further decline is unlikely or
impossible (Duff, 2012; Strauss, Sherman, & Spreen, 2006). Thus the
possibility to detect cognitive side effects of ECT in the elderly with
standardized neuropsychological tests is likely hampered by floor
effects if patients with moderate and severe cognitive impairment are
not excluded.
Only two prior studies have included a measure of RA. Stoppe, Louza, Rosa, Gil, and Rigonatti (2006) asked 21 questions about autobiographical information, but only seven were really relevant as they dealt with recent life. The study of Verwijk, et al. (2014) used a self-designed questionnaire, with 18 unpublished questions about personal semantic memories and seven questions about public events.

To date, only two studies of cognitive course in elderly patients treated with ECT have compared subgroups defined according to cognitive function at baseline. Hausner, Damian, Sartorius, and Frolich (2011) measured short- and long-term effects of ECT on cognition using the MMSE. Forty-four elderly patients were included. The patients were divided into three groups based on clinical investigation and neuropsychological findings: MCI (n = 19), Alzheimer’s dementia (n = 12), and no cognitive impairment (NCI) (n = 13). They conclude that pre-ECT cognitive deficits were the best predictor of MMSE decline at 6 weeks after ECT, but cognitive deficits were transient. Stoudemire, et al. (1991) investigated the long-term cognitive course using the Mattis Dementia Rating Scale (Marson, Dymek, Duke, & Harrell, 1997) before and 6 months after the ECT course. Subjects who had scores below 130 at the baseline were considered cognitively impaired (n = 15). The study also included 11 patients with normal cognitive functioning. While the mean score of the impaired patients increased significantly from pretreatment to posttreatment (mean 107.4 to 123.4), there was no
increase in the mean score of the patients with normal cognitive functioning.

In those two studies, the comparisons of cognitive course were performed using the global sum scores of a brief rating scale. Despite being useful instruments, these scales lack sensitive measures of AA, especially in patients with NCI, are not adequate measures of RA, and cannot elucidate the course of specific cognitive functions during treatment.

Few studies of patients with geriatric depression have investigated the associations between brain structure and cognitive side effects of ECT, and each have either just rated the clinical impression or used only a single measure of cognitive function. Figiel, Coffey, Djang, Hoffman, and Doraiswamy (1990) found that brain magnetic resonance imaging (MRI) revealed several structural abnormalities, particularly basal ganglia and moderate to severe subcortical white-matter lesions, in the patients who developed reversible delirium, which was induced by ECT. Depressed elderly patients with WMH who receive bitemporal ECT are at increased risk of transient cognitive impairment (Oudega, et al., 2014). Lekwauwa, McQuoid, and Steffens (2006) examined hippocampal volume and acute memory outcomes in 15 patients following an index course of ECT. Smaller hippocampal volume was associated with poorer ECT-related memory outcomes.
1.6.3 Treatment-related improvement

Similar to other treatments for depression, ECT can result in improved cognitive function concurrent with improvement of the mood disorder (Sackeim, 2005). Thus, there is a complicated interaction between cognitive impairment due to depression, cognitive improvement as part of response to depression treatment, and cognitive impairment induced by ECT (Kosmidis & Papanicolaou, 2006). Bosboom and Deijen (2006) found that depression alleviation after ECT was associated with a short-term cognitive improvement that was greater in older patients (≥ 60). According to the review of Douglas and Porter (2009), improved psychomotor speed is most closely related to treatment response in late-life major depression. Barch et al. (2012) found that episodic memory and executive function demonstrated significant improvement among adults with late-life depression during treatment with sertraline.

Sparse research has illuminated if there are associations between subgroups of patients and cognitive improvement after ECT. It is possible that marked improvement is more often seen in psychotic patients (Bayless, et al., 2010; Wagner, McClintock, Rosenquist, McCall, & Kahn, 2011). Bayless, et al. (2010) presented evidence that 30% of younger adult patients with psychotic depression showed pre-ECT cognitive dysfunction in the week before ECT, versus 10% two-three weeks after. Patients with improvement in negative symptoms (poverty of speech, affective flattening, lack of drive, and anhedonia)
showed most improvement in cognitive function. However, such findings of marked improvement are also seen in nonpsychotic elderly patients with cognitive impairment at baseline (Butters, et al., 2000; Doraiswamy, et al., 2003; Pier, Briggs, Pasculli, & Kellner, 2012). Older age and higher vascular risk scores predict less change in executive function in non-psychotic patients (Barch, et al., 2012).

1.7 UNANSWERED QUESTIONS

There is considerable consensus that impairment of cognitive function is common in geriatric depression. Although deficits in information processing speed and executive function are most common, findings are not limited to these functions and are inconsistent regarding the degree and type of impairment. It is uncertain if impairment on executive tasks can be explained fully by processing speed (Butters, et al., 2004). Cognitive function in hospitalized patients and patients with psychotic symptoms are understudied.

At the time the current thesis was planned, no study in the elderly had investigated both short-term and long-term effects of ECT on anterograde and retrograde memory. Effects on information processing speed and executive function were also understudied. Patients with cognitive impairment at baseline were assumed to be
more vulnerable to amnesia after ECT, but no study on the elderly had addressed this assumption by using a neuropsychological test battery.

Conflicting results had been presented regarding how cognitive course in the elderly is affected by the biological treatment of depression, disregarding the specific type of treatment.

2. AIMS

The main objective of the present study was to assess the cognitive function of elderly persons with a major depressive episode who received ECT, by employing performance-based assessments of various cognitive skills (memory, executive function, and information processing speed). We aimed at a longitudinal study of cognitive course, investigating change in cognition both at the group level and at the individual level with regard to baseline status.

In paper I, the aim was to confirm the presence and magnitude of neuropsychological impairments in a sample of currently depressed hospitalized elderly patients by comparing the neurocognitive profile with healthy controls.

In paper II, the aim was to investigate acute, short-term cognitive side effects of ECT, by comparing the test results from a group of nondemented elderly depressed patients receiving ECT with results from a control group of healthy elderly.
In paper III, the aim was to compare the cognitive course of patients with CIND and NCI, to investigate whether CIND patients are more vulnerable to acute and lasting cognitive side effects of ECT than NCI patients. In addition, the aim was to compare acute and long-term effects of ECT.

3. METHODS

3.1. Design

Various designs were used in the study. Paper I was based on a cross-sectional design, while papers II and III were based on a longitudinal design. Tor Magne Bjølseth, MD, planned a randomized study comparing the effect of bifrontal and right unilateral electrode placement on depression from 2006. I was invited to collaborate in the further planning and implementation of a study of cognitive side effects of ECT in the elderly. From 2008, study work was intensified. Dr. Lars Tanum agreed to supervise Tor Magne Bjølseth in his work on a doctoral thesis. A test battery intended to measure important aspects of cognitive function, especially memory and executive function, and at the same time presumably not too demanding of the patients’ time or effort was composed. Inclusion of patients took place between September 1, 2009 and April 30, 2013.

The conception of the problems to be addressed in papers II and III evolved over time. Preliminary analyses indicated no significant
differences in demographics or neuropsychological test results between the two randomized groups. This result was consistent with recent findings of small differences in cognitive side effects between bifrontal and right unilateral electrode placement in adults (Kellner, et al., 2010; Sienaert, Vansteelandt, Demyttenaere, & Peuskens, 2010). Thus, we chose to analyze the patients as one ECT group. The study of cognitive side effects of ECT was not prospective, in contrast with the study conducted by Tor Magne Bjølseth. The clinical impression during collection of neuropsychological data of considerable heterogeneity among included patients stimulated a focus on change on an individual level in addition to on a group level. The hypotheses of the study of cognitive side effects have among other factors also been affected by newer research, and by a recent debate about ECT in Norway (Bergsholm, 2013; Fosse, 2011; Moksnes, 2012a). Two highly relevant reviews of cognitive side effects in elderly patients were published before we started including patients (Gardner & O’Connor, 2008; Tielkes, et al., 2008). No highly relevant studies with a sample of elderly patients were published from 2007 to the present (Semkovska & McLoughlin, 2010; Verwijk, et al., 2012), with one exception (Verwijk, et al., 2014).

The study of Tor Magne Bjølseth had mean depression score and frequencies of response and remission from depression as primary outcome measures. In my study, depression was a confounding factor. We agreed that I should not discuss the relation between test scores and rates of response and remission in papers II and III.
3.2 Procedure

3.2.1 Recruitment and assessment

Clinical participants were recruited consecutively as in-patients. Healthy control participants were recruited at Asker Senior Center in 2010. Patients who were soon to receive ECT were asked to join the study. The clinical assessment and determination of diagnoses was performed under supervision of an experienced psychiatrist (the head project manager) who held regular diagnostic consensus meetings.

3.2.2 Biological treatment

Drugs. Antidepressants were reduced or ended 3–10 days before starting ECT. Antiepileptic drugs or mood stabilizers were discontinued 1 week prior to ECT. Patients were allowed to use predefined dosages of specific drugs if needed for anxiety, insomnia, psychotic features or agitation. The procedures are presented in detail in paper II.

ECT. Patients were randomized to formula-based ECT with right unilateral (RUL) or bifrontal (BF) electrode placement. An approach that involves the use of a standard age-based dosing algorithm was used to determine the stimulus dosage in the first ECT (Abrams, 2002). Aged-based dosing is the method generally used in the clinics in Norway (Schweder, Wahlund, Bergsholm, & Linaker, 2011).
Adjustments of stimulus dosages were made at subsequent treatments to optimize therapeutic effects and reduce adverse cognitive effects.

A Thymatron system IV machine (Somatics, LLC, Lake Bluff, Illinois, USA) with a 0.5 ms pulse width was employed. ECT was given twice weekly. Supplementary information about the ECT method used is presented in paper II.

3.3 Participants

Elderly patients suffering from an MDE, and diagnosed as either MDD or BP, with or without psychosis, could be included. Because we wanted to include patients with moderate and severe depression, the corresponding cut-off of 17 or higher on the 17-item Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1960) was used (Zimmerman, Martinez, Young, Chelminski, & Dalrymple, 2013). Patients were excluded if they showed signs of dementia, an MMSE (Folstein, et al., 1975; Strobel & Engedal, 2008) score of less than 24, schizophrenia, schizoaffective disorder, neurodegenerative disorder, serious brain injury (e.g. head injury, moderate-size or large-size stroke), or early onset alcohol use disorder. Additional exclusion criteria were substance abuse in the last 3 weeks, somatic contraindications for ECT, or ECT during the last 6 months.

Figure 1 in the Appendix shows a flow chart of patients who were evaluated for inclusion. Sixty-two patients were included in
analyses of cognitive side effects of ECT in paper II and 54 in analyses in paper III. The majority of the 62 patients fulfilled the criteria for MDD (recurrent type: 68%; single episode: 23%). Because the analyses in paper I were undertaken before inclusion to the main study was finished, and a few additional exclusion criteria were added (mild brain injury e.g. small-size stroke, and any history of substance abuse), there are fewer included patients (n = 39). The control group consisted of 18 elderly persons with no history of psychiatric illness, of whom 17 were tested twice.

3.4 Measures

3.4.1 Clinical assessment

Trained psychiatrists or the author carried out clinical assessment. Diagnosis was based on the DSM-IV criteria, available medical records, information from family members and treating clinicians, and the MINI International Neuropsychiatric Interview-Plus (MINI) (Mordal, Gundersen, & Bramness, 2010; Sheehan, et al., 1998), which also was used when screening for psychiatric comorbidity. Two psychiatrists confirmed and agreed upon the diagnoses of the treatment group participants. The MINI is a relatively short, structured diagnostic interview. It covers 18 Axis I disorders and has shown good inter-rater reliability (Sheehan, et al., 1998). Because many Axis I disorders demand certain obligatory criteria, the MINI has skipping
rules if such criteria are not met. The rating of each criterion on the MINI is absent or present, and the number of positive criteria is summarized as disorder present or absent. The interviewers were formally trained in using the MINI.

A psychiatrist gathered the remaining clinical data; determined age at onset, other disease parameters, and somatic morbidity from the clinical interview and the medical charts. Global cognitive functioning was assessed with a revised version of the MMSE (Strobel & Engedal, 2008). Scoring of the Cumulative Illness Rating Scale for Geriatric Patients (Miller, et al., 1992) was performed (except for the psychiatric item) to document physical disorder morbidities. A psychiatrist examined depression severity using the semi-structured interview HDRS-17 at inclusion (Hamilton, 1960; Williams, 1988).

A trained test assistant, Marianne Larsen (a nurse), and the author also administered the HDRS-17 at T1 and at follow-ups concurrent with the neurocognitive assessment of the patients. Our interrater reliability was tested and found satisfactory, with Intra Class Coefficient = 0.90 for HRSD-17. At T1, the mean HDRS-17 score in the patient group was 23.8 (SD = 3.9), and at T2 it was 9.8 (SD = 6.3). Zimmerman et al. (2013) recommend the interpretation of HDRS-17 scores as follows: 0–7 no depression, 8–16 mild depression, 17–23 moderate depression, and ≥ 24 severe depression.
3.4.2 Neuropsychological assessment

Either the present author or a test assistant conducted the neuropsychological testing and depression rating. I trained and supervised the test assistants in the project, to ensure common administration. Patients were tested at T1, within a week after ECT (T2), and at a 3-month control (T3). Controls were tested twice with an approximate eight-week interval. In addition, the retrograde memory of the 17 HCs who were tested twice was also tested by a telephone interview at T3. The two-and-a-half-hour test battery was administered with as many breaks as the participant felt he or she needed. Tests administered in the study were two screening measures of RA, and subtests from standard test batteries validated for Norwegian use assessing anterograde memory, information processing speed, and executive function.

*General cognitive functioning:* The Vocabulary Test from the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2007) measures lexical knowledge and is highly correlated with general cognitive ability (Lezak, Howieson, Bigler, & Tranel, 2012). It was administered at baseline.

*Anterograde memory:* Learning and memory for verbal material were measured using the official Norwegian research versions of the Hopkins Verbal Learning Test – revised (HVLT-R) (Brandt & Benedict, 2001). A list of 12 words is presented orally to
the patient. Results for total recall over three trials, free delayed recall after 20-25 minutes, and forced-choice recognition were recorded.

Learning and memory for non-verbal material was measured using the Brief Visuospatial Memory Test – revised (BVMT-R) (Benedict, 1997). A plate with six simple geometric designs is presented for 10 s, after which time the patient is asked to draw as many of the designs as possible, in the same locations as they appear on the display. The procedure is administered thrice in succession. After 25 min, the patient is asked to reproduce the designs again, and then a recognition task is administered. Results for total recall for three trials, free delayed recall after 20-25 minutes, and recognition were recorded.

*Information processing speed* was assessed by the Trail Making Test (TMT) part A (Reitan & Wolfson, 1993), and the Delis Kaplan Executive Function System (D-KEFS) Color Word Interference Test (CWIT; Delis, Kaplan, and Kramer, 2005), parts 1 and 2. TMT A is a paper-and-pencil test, on which the participant is asked to draw a line in the right order between circles with numbers from 1 to 25. On the CWIT1, the participant names 50 small color squares (red, blue, green) as quickly as possible, and on CWIT2, the participant reads words that denote the same colors printed in black ink. Time to complete the tasks was noted.

*Executive function:* The D-KEFS Tower Test (Delis, et al., 2005) was used as a measure of problem-solving and planning.
abilities. The participant was asked to move five disks across three pegs to build a specific tower in the fewest movements possible. Total score was noted. In addition, effectiveness was calculated for analyses in article 1 (moves used on tasks solved / minimum moves needed to solve these tasks).

On the TMT part B (Reitan & Wolfson, 1993), a paper-and-pencil test, the participant is asked to connect circles switching between numbers and letters as quickly as possible by drawing a line in the right order. Total time was noted.

The CWIT, part 3 (time) was used to measure cognitive inhibition of an overlearned response; the patient was asked to name the ink color in which color words are printed. The CWIT, part 4, measuring inhibition and flexibility was administered initially, but excluded from our analyses (basis described in paper I). Time to complete the CWIT 3 was used in all the analyses; in addition total number of errors was used in paper 1.

Measures of verbal fluency may be listed as measures of executive function (Lezak, et al., 2012; Strauss, et al., 2006), or alternatively as measures of language function (Butters, et al., 2004; Shao, Janse, Visser, & Meyer, 2014). Verbal fluency was assessed with the Letter Fluency Test from the D-KEFS battery (Delis, et al., 2005); in three 60 s trials, the participant was asked to say words that begin with a specified letter (F, A, S). On the Animal Naming Test,
the participant is asked to say as many words in 60 s that belong to the category of animals.

**Retrograde memory:** In collaboration with colleagues, the author constructed a Media Questionnaire (MQ). The purpose was to create an instrument for examination of retrograde memory for factual knowledge for use in the current study. Upon review of five years of "Hvem Hva Hvor", covering public facts presented in the media from 2004 – 2008 (Kristiansen, 2003, 2004, 2005, 2006, 2007) the author chose 43 questions. A pilot study was undertaken before a list of 20 questions considered suitable for older persons was prepared.

An adapted version of the Columbia Autobiographical Memory Interview – Short Form (CAMI-SF; McElhiney, Moody, & Sackeim, 2001) was administered. The questions primarily tap memory for recent semantic autobiographical information, for instance addresses, duration of a trip, and name of a doctor. The CAMI-SF was developed for use in adults, and some questions are less relevant for elderly people. We received the permission from McElhiney and Sackeim to adapt it for use in our study. In contrast with the original CAMI-SF we did not ask about the last job, because the patient might have been retired for many years. Because numerous patients probably are alone on the New Year Eve, we asked about the last Christmas instead. We removed the question about the last birthday, because most patients were assumed to be with family both at Christmas and at the last birthday.
The test–retest reliabilities of measures of RA are expected to be high in healthy controls (Meeter, 2003). As described in paper II, the test–retest reliability of the modified CAMI-SF for the control group was unacceptable ($\rho = .48$). We removed three items that threatened the validity of the CAMI-SF as a measure of RA, because these items could not be answered consistently at T2 by at least 80% of controls. An example of an excluded question is “What presents did you receive last Christmas?” In addition we removed two items that many healthy controls could not answer at T1. The maximum score for the modified version was 30. The test–retest correlation for the 17 control subjects was improved, but still questionable ($\rho = .60$, $p = .011$). Memory change scores were computed for the modified CAMI-SF and the MQ (total score at retest minus total score at T1). Unusually low scores were interpreted as indications of RA.

*General considerations regarding cognitive testing:* The memory measures were prioritized if it was difficult to motivate the patient to complete all tests. We used raw scores on tests for analyses in articles I and II. Missing neuropsychological test scores were not imputed, except when using multivariate analysis of variance (MANOVA) in papers I and III. Patients were given maximum scores on the TMT, and the CWIT if these tasks were not completed within their respective time limits. We created composite scores in paper I, by defining tests within domains of function. We then chose to classify verbal fluency tests as a language domain. Verbal fluency tests have been reported as rather insensitive measures of executive
function, generally (Phillips, 1997), in depressed patients (Henry & Crawford, 2005), and in the elderly (Rodriguez-Aranda & Sundet, 2006).

In addition to using raw scores, we also used scores standardized by the results for the control group in paper I. In paper III we used published norms, which are from the general population and standardized by age. Comprehensively demographically adjusted norms were available for some of the included tests (Heaton, Miller, Taylor, & Grant, 2004). Scores under the 7th percentile at T1 were rather common in the patient group on the CWIT3, the CWIT4, the TMT A and B, and the BVMT-R. Low T1 scores decrease the probability of detecting decline (side effects). For paper III we chose to include the 6 standardized test measures that were the least restricted by floor effects, and that discriminated best between patients with and without cognitive impairment. In addition we included the screening measures of RA.

3.5 Ethical considerations

The included patients were admitted to the department for treatment of depression, and were patients who had a mood disorder for which ECT generally is recommended. ECT can be given to consenting patients without somatic contraindications to ECT, after informing them of benefits and risks (Schweder, Wahlund, et al., 2011). This
The study was conducted in compliance with institutional standards for human research and in accordance with the Helsinki Declaration. The study is approved by the Regional Committee for Medical Research Ethics (REK), which included an approval for the use of ECT in both moderate and severe depression and as a first-line medical treatment in selected cases. During the inclusion period, the REK also approved of the division of the study in three partly separate sections; one that focused on the effect of bifrontal and right unilateral ECT on depression, one that focused on cognitive side effects of the treatment, and one that focused on biomarkers. After a complete description of the study, including the possibility to withdraw from the study at any time, written informed consent concerning participation in the study was obtained from patients and controls.

The pressure to participate in the study is a factor vulnerable patients might have experienced and is one among ethical problems to be addressed concerning the study of cognitive side effects of ECT. On the other hand, they were informed that not taking part in the study should not affect treatment negatively. Results were used to benefit the individual patients, for instance if T1 results gave suspicion of cognitive impairment, then test results at T2 and T3 were examined especially closely. In addition, patients were offered information about the cognitive test results, and results were shared with their therapists. Actually, neuropsychological testing during the treatment period has been proposed as a measure to limit side effects of ECT, because the treatment could even be tailored to side effects that might show up
during treatment (Porter, Douglas, & Knight, 2008). Another factor is that patients might have felt overwhelmed by the amount of assessment. Neuropsychological testing might for some be experienced as stressful, especially at baseline. Considerations were taken to create a supportive testing atmosphere. To ensure minimal patient frustration with the process, we were flexible about when to interview / test, offered frequent breaks in the assessment, and often dispersed the sessions over several days.

Considerations were taken to create a supportive testing atmosphere even for HCs, because tests might be experienced as more demanding than they were prepared for. Controls were offered information about the cognitive test results. They received a gift voucher with a moderate fee for compensation (€ = 32) each time they met for assessment.

3.6 Statistical analyses

Analyses were conducted using the Statistical Package for the Social Sciences (SPSS Statistics for Windows, Version 20.0; IBM, Armonk, NY). Means and standard deviations or median and range were reported for continuous variables, and numbers of participants and percentages were reported for categorical variables. Differences in demographic characteristics were investigated using the Student’s $t$-test on continuous variables. Dichotomous variables were subjected to
chi-squared analyses. Statistical significance was determined using a threshold of \( p \leq .05 \). Change over time for groups in standardized neurocognitive tests was analyzed with repeated-measures analyses of variance (ANOVA). The test scores were the dependent measures, time the within-subjects factor, and group the between-subjects factor. In papers I and III, MANOVA was used first to confirm the presence of group differences while concurrently reduce the risk of type I errors. Before using MANOVA, missing scores were replaced with the average score for the group. We followed-up significant findings in the MANOVAs using single-test analysis of variance.

Non-parametric tests, the Independent-Samples Mann–Whitney \( U \) test, and the Kruskal-Wallis test, were used to compare groups when variables were clearly non-normally distributed, for instance on the CAMI-SF. Effect sizes were reported as partial eta squared. Bonferroni corrections were performed by adjusting the required \( p \) value by the number of tests. Spearman or Pearson correlations were used to assess associations between variables.

To explore reliable change in individuals in papers II and III, we developed regression-based RCIs (standardized \( z \) scores) based on the results of the control subjects. The standard deviation of the discrepancies between predicted scores and actual scores was computed and confidence intervals around the mean of these discrepancies were calculated. A 90\% confidence interval for reliable change was used to indicate declined scores. Thus, an \( RCI \leq -1.645 \).
would be considered a clinically meaningful “reliable decline” (Duff, 2012). In paper II, the number of declined test scores was added, resulting in an impairment score (range: 0–11) for each participant.

A thorough description of the statistical analyses used in the studies is presented in the three papers.

4. SUMMARY OF PAPERS

Table 1 in the appendix presents an overview of the papers I-III and includes details about the number of included participants, the period of inclusion, the time of testing related to ECT, the neuropsychological measures that were included, and the exclusion criteria that were used.

Paper I

Background: Our aim was to determine the characteristics of neuropsychological functioning in nondemented elderly patients suffering from an MDE.

Method: A neuropsychological battery was administered to a group of hospitalized patients and healthy control subjects at T1. Thirty-nine patients without dementia, 60 years or older meeting DSM-IV criteria for an MDE (unipolar or bipolar depression), and 18 non-depressed control subjects were included. Neurocognitive scores were calculated for the domains of information processing speed, verbal memory,
visuospatial memory, executive function, and language. Number of impairments (performance below the 10th percentile of the control group per domain) for each participant was calculated.

Results: Nearly half of the patients had a clinically significant cognitive impairment in at least one neurocognitive domain. Relative to HC subjects, patients performed significantly poorer in the domains of executive function and information processing speed. Executive abilities were most frequently impaired in the patient group (39%). Even when controlling for differences in processing speed, patients showed more executive deficits than controls.

Conclusion: Reduced executive function appears to be the core neurocognitive deficit in elderly patients with a major depression.

Paper II

Background: Our aim was to compare short-term changes in the cognitive functioning of patients receiving ECT with healthy elderly who were tested twice, and to evaluate change both on the group and the individual level.

Method: We investigated changes in the cognitive functioning of nondemented elderly depressed patients receiving ECT (n = 62) compared with healthy elderly (n = 17). Neuropsychological tests for
patients were administered at T1 and T2. For standardized tests, we computed RCIs using simple regression methods.

Results: At the group level, only letter fluency performance was found to be significantly reduced in the ECT group compared with the controls, whereas both groups demonstrated stable or improved performance on all other measures. At the individual level, however, 11% of patients showed RA for public facts post-ECT. Forty percent of the patients showed a significant decline on a summary measure based on RCIs. Decline on a test of delayed verbal anterograde memory was most common.

Conclusion: Our findings indicate that there are mild neurocognitive impairments in the acute phase for a substantial minority of elderly patients receiving ECT. The difference in findings between the comparison of groups and the analyses at the individual level were substantial.

Paper III

Background: Elderly depressed patients with CIND are reported being more vulnerable to the cognitive side effects of ECT compared with patients with NCI. The few studies that have concluded thus may be criticized for only using rating scales of dementia. The present study aimed to investigate this claim by using standard neuropsychological tests before and after twice-weekly, individually tailored ECT.
Method: Patients were assessed at the baseline (T1), within 1 week after ECT (T2), and followed-up 3 months later (T3). The sample included 54 patients with NCI (n = 36) and CIND (n = 18). Tests of anterograde memory, information-processing speed, executive function, and retrograde memory were administered. We computed reliable change indices (RCIs) using simple regression methods.

Results: Short-term side effects were detected at T2 in a large minority of patients, with no significant differences between NCI and CIND patients. Considerable improvement in global cognitive function from T1 to T3 was observed in 44% of the CIND patients. At the group level, both information-processing speed and average test performance improved significantly in CIND vs NCI patients.

Conclusions: Elderly depressed patients with CIND at baseline were not more vulnerable to amnesia after ECT than patients with NCI. Long-term cognitive side effects of ECT were not detected.

5. DISCUSSION

5.1. Main findings

5.1.1 Cognitive function in geriatric depression

In the first study, we found as expected that non-demented patients with geriatric depression overall were more cognitively impaired than HCs. The differences were reaching the level of nominal significance in six of the single 15 measures (TMT A, TMT B, Tower Test, CWIT1, CWIT 3 time, and CWIT 3 errors). Nearly
half of the patients had a clinically significant cognitive impairment in at least one neurocognitive domain. These findings also corroborate that although many elderly patients who suffer from an MDE have cognitive impairments, many have normal cognitive function (McClintock, et al., 2010).

Our findings are consistent with several others reporting main differences between elderly patients with an MDE and HCs on tests of information processing speed and executive function (Butters, et al., 2004; Herrmann, et al., 2007; Sheline, et al., 2006). Contrary to the findings reported by Butters, et al. (2004), but in line with others (Nebes, et al., 2000; Sexton, et al., 2012), we found that deficits in the executive function could not be fully explained by a general information processing speed deficit. In line with Butters, et al. (2004) we defined verbal fluency tests within the domain of language and not within the domain of executive function. Thus, this choice regarding the definition of the fluency tests cannot explain the difference in the main deficit findings between their study and ours.

Some inconsistencies between findings of a specific study of cognitive function in geriatric depression and aspects of previous research findings are rather the rule than the exception (O'Hara, et al., 2006). In accordance with Butters, et al. (2004), but in contrast to O'Brien, Lloyd, McKeith, Gholkar, and Ferrier (2004), we did not find significant differences between groups on tests of verbal fluency at baseline. We did not find any significant difference between the
groups in anterograde memory either, in contrast with reports by some studies (Butters, et al., 2004; Lockwood, Alexopoulos, Kakuma, & Van Gorp, 2000).

Divergent findings among studies in the field may be caused by multiple factors. Geriatric depression is highly comorbid with other somatic and psychiatric disorders, and the main explanation of divergent findings may be the heterogeneity of this patient group. Differences between studies regarding composition of the test batteries and definitions of composite neurocognitive measures may be of some importance. Differences in depression severity of study groups may also contribute to explaining disparity among findings. In addition, the concepts of LLD and geriatric depression are not unambiguously defined. Thus, the conceptual boundaries of geriatric depression are fuzzy, resulting in variable inclusion and exclusion criteria among studies.

In line with some studies, and in contrast with others, we included psychotic patients. These patients are less characterized than the remainder of patients with geriatric depression. They are found to perform worse on the Wisconsin Card Sorting Test and the TMT B (Gournellis, et al., 2014), which are regarded as sensitive to executive dysfunction. We found that psychotic patients were significantly more impaired than nonpsychotic patients on three out of twelve standardized tests at T1; the HVLT-R total learning, the Tower Test, and the Animal Naming Test (paper II). Thus, in our study, patients
with psychotic symptoms did have somewhat weaker cognitive function at baseline overall, but not unambiguously weaker results in one specific cognitive domain. Most of the patients in our study were characterized by melancholia, as is common in elderly hospitalized patients with an MDE. Patients with melancholic features are reported to show impairment on measures of mental flexibility, set-shifting and information processing speed, implicating frontal-striatal dysfunction (Basso, et al., 2013; Steffens & Potter, 2008). Issues to be addressed regarding diagnoses will even be elaborated upon in the methodological discussion.

Several general hypotheses have been put forward to explain cognitive impairment in depressed adults. I will briefly present some of them, and evaluate whether our findings support these hypotheses on the nature of cognitive impairment in depressed elderly patients. Slow processing speed is characteristic of geriatric depression, and might be state-dependent if it is fully explained by deficiencies in mental effort and attention only when mood symptoms are prominent (Korten, et al., 2014). However, alternatively it is possible that the decrement in information processing speed and executive functions are stable traits arising from brain changes associated with geriatric depression (Alexopoulos, et al., 2000; Nebes, et al., 2000). The psychomotor speed hypothesis of cognitive impairment in depression receives support at T1, but paper I shows that psychomotor speed cannot fully explain impairments in executive function. Paper III indicates that decrement in processing speed is not a stable trait in all
patients with geriatric depression. Overall, the effort hypothesis was not supported in our study, because there were no significant differences between patients and HCs at baseline on several tests that demand effort, for instance the HVLT-R and the Letter Fluency Test.

As is the rule in longitudinal treatment studies of depression, there was variation in depression severity at baseline, and all the patients did not remit from depression during the treatment period. However, the mean depression score in the patient group decreased markedly over time. Thus, we were given an opportunity to analyse the relation between depression severity and neuropsychological test results. In contemporary literature on geriatric depression, the commonality of permanence of cognitive impairment despite improvement in depression is described (Bhalla, et al., 2009; Bhalla, et al., 2006; Butters, et al., 2008; Koenig, et al., 2014). Such results indicate that neuropsychological impairments under depression may be primarily trait-dependent. However, in some individuals, indications of severe cognitive impairment at baseline are not present after a course of ECT, if remission was achieved (Pier, Briggs, Pasculli, & Kellner, 2012; Wagner, McClintock, Rosenquist, McCall, & Kahn, 2011). In paper III we showed that the CIND group generally improved more than the NCI group, and that a minority of CIND patients experienced the most marked improvement.

Our findings in papers I - III confirm that the relation between depression severity and cognitive function in the depressed elderly is
complex. In paper I, we found that correlations between cognitive measures and depression scores showed small to medium effects. Further, in paper II we investigated correlations between the change in HDRS-17 score from T1 to T2 assessment and the standardized change in individual neuropsychological test scores (RCIs) from T1 to T2. As expected, there were mostly negative correlations, but they were small and not statistically significant. However, the heterogeneity of cognitive course from T1 to T2 might be a confounding factor for the analysis of association. The same analysis for the 19 patients who demonstrated no reliable declined scores from T1 to T2 did not show statistically significant correlations either, except for the CWIT 3, which was negative and large. Overall, these results from paper I and II were consistent with trait-dependent cognitive impairment.

Paper III demonstrated that 8/18 CIND patients changed status to NCI at T3, implicating that their cognitive impairment at baseline was state-related. Although the HDRS-17 scores of these individuals did not differ significantly from the remaining 10 CIND patients at T3, the potential for marked improvement of cognitive function in a subgroup of CIND patients undergoing treatment for depression was demonstrated. Overall, the results from paper I – III are consistent with mainly state-dependent cognitive impairment in some patients with geriatric depression, and impairment related mostly to trait in others (Barch, et al., 2012). Such findings might be expected, because geriatric depression is heterogenic and highly comorbid with somatic
diseases that affect the brain. For instance cerebral small-vessel disease might explain the persistent impairment of information processing speed and executive function in some of the patients (Prins, et al., 2005). Other patients with geriatric depression may have a healthier brain for their age, and marked improvement may be seen in cognitive function after remission of the depression.

5.1.2 Cognitive side effects of ECT

Overall, our results at the group level were in accordance with the recent study of Verwijk, et al. (2014) of an elderly sample. They did not find indications of short-term or long-term cognitive side effects of ECT, including on a measure of retrograde memory. However, the basis for their conclusions could be questioned. For instance, as opposed to our study, they did not investigate decline in individuals, and did not include a comparison group. Then it is neither possible to account for the heterogeneity of cognitive courses of participants, nor for potential practice effects on traditional neuropsychological tests. The validity of their measure of RA cannot be evaluated on the basis of their paper, as it is very briefly described.

At the group level, we found decline only in the patient group on the Letter Fluency Test in the week after ECT. A decline on this test has been found by several previous ECT-studies in adults (Semkovska & McLoughlin, 2010). The Letter Fluency Test is a
sensitive measure of brain dysfunction, but not very specific. Impairments of information processing speed, language, and/or executive skills might potentially reduce verbal fluency. Our control group showed an evident practice effect on this test. A transient reliable decline of moderate effect size in information processing speed and executive function (specifically on the TMT A, the TMT B, and the Tower Test) showed up in a minority (15-22%) of the patients (paper II, table 4). The data do not support a specific interpretation of the finding of reduced letter fluency in patients compared to HCs. Most importantly, this decline was transient.

The RCIs represented a valuable addition relative to the use of the standard neuropsychological scores by controlling practice effects and measurement error, and allowing investigation of frequency of individual decline. In paper II, we found a highly significant difference between patients and HCs when we analysed the sum of declined scores over 11 test measures in individual cases; effect sizes for the individual tests were smaller when we compared the numbers in each group that demonstrated reliable decline. Thus, in line with Heaton, et al. (2001), we found that a neuropsychological prediction model, which was applied together with multiple measures, was the most sensitive to negative changes in neurological status.

Our findings of transient cognitive side effects of ECT confirm previous findings in adults (Ingram, et al., 2008; Semkovska & McLoughlin, 2010). We found that AA for verbal information was a
common decline at T2, in line with previous findings in adults (Semkovska & McLoughlin, 2010). We found reliable decline at T2 in up to one quarter of the patients even on tests of information processing speed and executive function (table 4, paper II), however there was no statistically significantly difference between patients and controls on each individual measure. A few other studies have found slowed information processing even at a group level at time points closer to the last ECT compared with our study (Semkovska, et al., 2011; Tsourtos, Spong, & Stough, 2007).

In contrast with several previous studies in adults (Kessler, et al., 2014; Lisanby, et al., 2000; Meeter, et al., 2011), our comparison between patients and controls at the group level did not indicate RA for either autobiographical information or for media questions even in the first week after ECT. The two previous studies in the elderly, which included a measure of RA, did not find significant decline in the patient group over time either (Stoppe, et al., 2006; Verwijk, et al., 2014).

We defined RA by inconsistency between T1 and follow-up answers on the modified CAMI-SF and the MQ, as is customary in ECT research. Because considerable inconsistency over time on the CAMI-SF is normal even for HCs and patients who are not treated with ECT (Semkovska, Noone, Carton, & McLoughlin, 2012), the definition of a cut-off for RA is uncertain. Inclusion of a comparison group renders possible both the account for normal decline on
measures like the CAMI-SF and the MQ, and the evaluation of RA in individuals, despite no significant differences between group means. The MQ was suggestive that seven out of 61 patients had higher inconsistency at T2 than any of the HCs (paper II), and this was interpreted as indications of RA.

In contrast with Sobin, et al. (1995), we did not find that CIND patients were more vulnerable to RA than NCI patients (paper III). RA for public facts was not indicated in either of the groups at T3. In contrast with theories of more vulnerability even of AA in CIND patients (Sackeim, 2005), we found no significant difference at T2 or T3 between CIND and NCI patients.

5.2 Methodological discussion

5.2.1 Study population

5.2.1.1 Diagnoses and representativity

All the patients were subject to psychiatric examination supported by the MINI, which has high acceptance and validity (Mordal, et al., 2010). Psychiatrists or a psychologist with many years of experience with psychiatric assessment conducted the interviews. Although the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 2002) is more thorough than the MINI (Sheehan, et al., 1998), we chose the MINI because the SCID
frequently takes 2½–3 hours to administer to an elderly patient (Blazer, 2004).

A high fraction of the eligible patients accepted to participate in the study, so the representativity among patients who are referred to our department and correspond to the criteria is probably high. The attrition was low compared to previous studies, as only 8/62 patients did not participate at the last follow-up. The general representativity compared with elderly patients receiving ECT is uncertain. Our patient population was comparable to previous study populations with regard to education, gender, estimated IQ, and medical morbidity. However, ECT is also used in elderly depressed patients with a moderate or severe cognitive impairment at baseline, and these patients were excluded by our study. The use of ECT is unevenly distributed among health regions in Norway (Schweder, Lydersen, Wahlund, Bergsholm, & Linaker, 2011). Laws and guidelines for the practice of ECT vary between countries. In some European countries, such as Italia, Ireland, and Latvia, there might be a far higher threshold for referring patients to ECT (Gazdag, Takács, Ungvari, & Sienaert, 2012). Differences in criteria for referral to ECT, availability of ECT, and attitudes regarding ECT within and among countries probably result in variability among studied research samples. Even if patients from some other regions of Norway and from some other western countries generally might be more severely depressed before they are referred to ECT, our findings are of considerable clinical interest. Paradoxically, illuminating results from standard
neuropsychological tests presuppose that the included patients are testable, which may not be the case with extremely depressed elderly patients. A prerequisite for the discovery of cognitive adverse effects is valid baseline results that are not at the floor level.

Our inclusion and exclusion criteria in papers II and III correspond well with common criteria in ECT research. For instance both unipolar and bipolar patients, with or without psychosis, are generally included in studies of cognitive side effects of ECT in adults. Many patients with psychotic depression receive ECT (Abrams, 2002; Swartz, 2009). In paper I, our inclusion and exclusion criteria regarding age, dementia diagnosis, neurological and neurodegenerative disease, and severity of depression correspond well with previous studies. As is very common in the research on LLD, operationalization of criteria may differ among studies. A few differences between the study of Sheline, et al. (2006) and our study can serve as an illustration. We defined MMSE score < 24 and previous stroke as exclusion criteria, while Sheline, et al. (2006) defined MMSE score < 21, and stroke in the last three months as exclusion criteria. In contrast with our choice of life-time substance abuse as an exclusion criterion in paper I, neither abuse of alcohol nor other substances are explicit exclusion criteria in several comparable studies (Butters, et al., 2004; Sheline, et al., 2006).
A characteristic of studies in the field of geriatric depression is that results often are presented as descriptive of elderly patients with an MDE in general, even if studies focused on subgroups. Some of the studies of LLD patients include only outpatients (Butters, et al., 2004), but few include only hospitalized patients. Inpatient status is associated with severity of depression and is among factors that contribute to cognitive impairment (Basso, et al., 2013). Although 20-45% of hospitalized patients with geriatric depression are psychotic (Blazer, 2003), these patients are often excluded from studies of LLD. In line with some studies (for instance Lockwood, et al., 2000) we did not exclude patients with psychotic symptoms. Since the incidence of psychotic symptoms is rather high in hospitalized patients, a sample that includes psychotic patients is more representative.

In contrast with many studies of cognitive impairment in patients with late-life depression we did not exclude bipolar patients. However, the inclusion of patients with a bipolar II diagnosis probably did not influence results in paper I significantly, as the difference in cognitive function between MDD and BP II is small (Basso, et al., 2013). In paper II, we found no significant group differences at T1 in neuropsychological test results between patients who presented with bipolar II disorder and those who did not.
5.2.1.2 Possible confounding factors

Dementia, MMSE score of less than 24, neurodegenerative disorder, serious brain injury, substance abuse in the last 3 weeks, or ECT during the last 6 months were specified as a priori exclusion criteria in the study of cognitive side effects of ECT to control for potential confounders known to influence cognition. However, all potential confounding factors cannot be controlled in an observational study. When demographical and clinical variables known to influence cognition differed between groups, these potential confounders were statistically controlled for when possible.

A potential confounder in comparisons between depressed patients and HCs is psychotropic medication (Korten, et al., 2014; Tannenbaum, Paquette, Hilmer, Holroyd-Leduc, & Carnahan, 2012). The patients in our study were allowed to use predefined dosages of drugs if needed for anxiety, insomnia, psychotic features or agitation. However, according to Basso, et al. (2013), medication status generally has no compelling effects on neurocognitive function in MDD. Use of psychotropic medication is a factor that is impossible to control when studying a group of inpatients with mainly long-standing symptoms of a depressive episode.

Because we excluded patients if consumption of alcohol in the three weeks before ECT was excessive, improved cognition in the treatment course because of a lower intake of alcohol was an unlikely confounding factor in our study (Powell, 2013). The specific type of
ECT treatment given can be a confounding factor. Side effects vary with technical factors, for instance if ECT is given twice or thrice weekly (Charlson, et al., 2012), thus results from one study do not necessarily apply fully to all forms of ECT.

An age difference of approximately 3 years between patients and HCs may be a confounder in our study. The imbalance at T1 was addressed by using age as a covariate in group comparisons. The difference was not statistically significant at the < 0.05 level ($p = 0.087$), but we are among those who choose a larger $p$ value just to be safe. Analyses were considered possibly to benefit from covariate adjustment because age is a strong predictor of cognitive test results, and thus related to the outcome (Assmann, Pocock, Enos, & Kasten, 2000). In paper I, we found moderate associations ($r \geq 0.30$) between five test measures and age for the patient group.

Perhaps contrary to common expectations, short-term practice effects are probably not significantly related to age in samples with a restricted age range (e.g. $\geq 65$ years) (Duff, Callister, Dennett, & Tometich, 2012; Krenk, Rasmussen, Siersma, & Kehlet, 2012). Thus, although the mean age difference between patients and HCs was 3.4 years ($t_{77} = -1.97, p = 0.053$) in paper II, we did not expect different practice effects to be related to age in the two groups. Hence, we chose to use a conventional cut-off at $p \leq 0.050$ as a criterion for evaluating the use of covariate adjustment.
Although participants in both groups were excluded if they were thought to be in the process of developing dementia, in paper II, patients scored statistically lower on the MMSE compared with controls. The mean difference was 1.1 points. We used the MMSE as a covariate in follow-up analyses to control for the effect of mild cognitive impairment. Our findings remained unchanged.

Previous research shows divergent findings regarding the association between depression and cognitive impairment. Several studies of cognitive side effects of ECT in the elderly found that cognitive measurements were not significantly influenced by severity of depression or change in depression severity (O'Connor, et al., 2010; Stoppe, et al., 2006; Verwijk, et al., 2014). However, as illustrated by paper III and previous studies, considerable cognitive improvement can occur in a minority of elderly patients who receive ECT. This is an important finding in itself, because both demonstration of improvement and side effects illuminate the cognitive course of patients treated with ECT. With a few exceptions (Bhalla, et al., 2006; Stoudemire, Hill, Morris, & Dalton, 1995; Stoudemire, et al., 1991) the frequency of persistence of status as cognitive impaired from baseline to end of treatment is seldom described in the literature. However, although cognitive improvement is an important and positive clinical outcome, it is also a source of puzzlement in studies of cognitive side effects of ECT in the elderly. If results are exclusively analyzed at a group level, side effects might be concealed if they appear only in a minority of patients, especially if another
subgroup experienced marked improvement. Thus, it is indicated to analyze results at an individual level as well. Because stable or improved test results over time generally are expected in patients receiving efficacious biological treatment for an MDE, a demonstration of reliable decline in patients compared to healthy elderly likely indicates a side effect of ECT. A comparison between CIND and NCI patients which does not account for potential differences in effect of treatment might also be biased, given a significant difference of effect between these subgroups. However, there were no significant differences in course of depression scores for the CIND and NCI groups in our study.

In papers II and III, we could not control for many potential confounding variables such as an RCT comparing patients who receive ECT with patients who receive antidepressants might have done. However, recruiting patients to such studies is very difficult in adults (Kessler, et al., 2014; Schoeyen, et al., 2014), and almost impossible in the elderly (Stek, et al., 2007). Additionally, only a comparison with an almost equally efficacious treatment of depression would have controlled fully for improvement of the mood disorder. Because elderly patients with melancholia and particularly with psychotic depression generally respond rather poorly to antidepressants, but well to ECT (Blazer, 2003), differences in antidepressant efficacy might have shown up even if using an RCT design comparing ECT with another active treatment.
To deal with the potential confound of different treatment efficacy between groups, analyses may be confined for instance to the comparison of patients who remitted from the treatment. Butters, et al. (2000) compared the cognitive course of remitted CIND and NCI patients after treatment with an antidepressant: 10 with CIND and 35 with NCI. Such an approach has merits, but easily results in a small number of participants in the groups to be compared. This way dealing with change of depression score as a confounder is very uncommon in ECT research. An exception is Smith, et al. (2010) who in a study of cognitive effects of continuation ECT versus psychopharmacological drugs for a six-month period after the initial course of ECT, limited the patient group to remitters. This approach was not feasible in our comparison between NCI and CIND patients. Our sample was small, and although many patients responded to the treatment, only a fraction remitted (defined conventionally as HDRS-17 < 7). As described in paper II, at T2, the mean HDRS-17 score in the patient group was 9.8 (SD = 6.3) (range: 0–26). Primarily, we wanted to study the full sample.

5.2.2 Measurement

We found indication of a higher floor at T1 on four of the standardized test measures; the CWIT 3 (time), the BVMT-R, the TMT A, and the TMT B, operationally defined by many patients having scores ≤ 1.5 SD under the normed-based mean. Perceived
difficulty of tests is in addition reflected by the amount of missing data per test. For instance, in paper 1, the TMT B was too difficult for 8/39 patients who gave up before the task was completed. It was impossible to measure a decline on the TMT B in these patients. Difficulties on the TMT B are found by previous studies of cognitive function in geriatric depression (King, Cox, Lyness, & Caine, 1995). Even if some of the tests that we used showed evidence of floor effects in a subgroup of the patients, the majority of test measures did not. The included tests in article 3 were specifically chosen because they were the least hampered by floor effects. At baseline, scores ≤ 1.5 SD under the norm-based age-adjusted mean were present in from 12 to 26% of patients on the six included test measures.

The measurement of RA is challenging in ECT studies. According to Meeter (2003), studies of criterion validity have not been made. It is uncertain whether the tests of RA have sufficient sensitivity and specificity. The Autobiographical Memory Interview (AMI) (Kopelman, Wilson, & Baddeley, 1989) might be an exception. However, the AMI is validated as a measure of moderate and severe amnesia and might not be sensitive to milder forms of RA (Kopelman, 2002). Until recently, reliability and validity of measures of RA used in ECT research have not been scrutinized in the literature (Sackeim, 2014; Semkovska & McLoughlin, 2013, 2014; Semkovska, et al., 2012, Söderlund et al., 2012). Our findings of a large decrease in retrieval consistency on the modified CAMI-SF for healthy volunteers
are consistent with the findings of Semkovska, et al. (2012). Commonly accepted kinds of measures of RA were used in our study.

5.3 Implications

5.3.1 Implications for measurement

The probability that elderly patients will first accept assessment with traditional neuropsychological tests and second that the usefulness of any test results will not be hampered by severe floor effects is high only in patients with NCI or mild cognitive impairment (Morris & Brookes, 2013). If cognitive side effects of ECT in patients with moderate and severe cognitive impairment at baseline are investigated, then tests designed for use in moderate and severe dementia is preferable (Butters, et al., 2000; Stoudemire, et al., 1991). Such tests will be rather insensitive of change in individuals with normal cognitive function.

The tests with a high floor were among the speed dependent tasks. This might imply that some of the speed-dependent tasks that are supposed to measure higher order cognitive functions (the CWIT 3, the BVMT-R, and the TMT B) have reduced validity in studies of cognitive side effects of ECT in the depressed elderly. The speed with which individuals process information can be related to their performance on tasks that lack obvious speeded components, because the individual may not be able to complete, in the time available, all of
the processing necessary for satisfactory performance (Dickinson, et al., 2007; Kail & Salthouse, 1994). According to Tam and Schmitter-Edgecombe (2013), processing speed deficits should be considered when interpreting BVMT-R performance. Although the BVMT-R has considerable assets such as six parallel versions, this test might not be optimally suitable for assessing decline in visual memory in elderly depressed patients treated with ECT, as the stimulus material is only presented for 10 s at a time.

According to Söderlund, et al. (2012) and Semkovska and McLoughlin (2014), it is possible that the real memory impairment after ECT has so far been underestimated due to failure to specifically measure episodic autobiographical memory, as compared to semantic autobiographical memory. Per today this is a hypothesis, and no published studies can support or disprove it. Autobiographical memory has both episodic and semantic aspects (Semkovska & McLoughlin, 2013, 2014). The most commonly used instrument in contemporary ECT research for assessment of RA, the CAMI-SF (McElhiney, Moody, & Sackeim, 2001) primarily examines autobiographical semantic memory (Semkovska & McLoughlin, 2014). However, the distinction between autobiographical memory and semantic memory is not clear-cut, and tests of RA are not very “pure” (Kopelman, 2002). We consider the part III of the AMI (about recent events), the MQ, the original and our modified CAMI-SF as screening measures of RA, although they are not commonly described as such in the literature.
5.3.2 Clinical implications

Patients with geriatric depression ought to be screened routinely for cognitive impairment upon admission at a department of geriatric psychiatry. Results from more detailed neuropsychological assessment can aid differential diagnoses, and identify areas of cognitive impairment that impact on treatment and prognosis. For instance therapeutic communication might be tailored to the patients’ level of cognitive function. Identification of executive function deficits can be of use, as it indicates a higher likelihood of functional impairment and a higher need of frequent and more supporting follow-up psychosocial treatment after discharge from the hospital. Longitudinal neuropsychological assessment can effectively track the extent to which cognitive deficits are reversible, stable or progressive. Realistic expectations and tailored treatment can hopefully make relapse of depression after remission less likely.

Patients receiving twice-weekly formula-based ECT and their next of kin can be informed that less than half of the patients experience short-term mild to moderate cognitive side effects. Simultaneously, they should be encouraged to inform the doctor if cognitive side effects are experienced. In the first weeks after ECT, the patient can be advised to take care writing down appointments in the calendar, because they may more easily forget things. The patient and the next of kin can be recommended to anticipate the transiency of the side effects. Then anticipatory anxiety can be reduced. The
interpretation that side effects may be evident, but temporary, can reduce fear and strengthen the hope for a good future.

Likely, some individuals are more vulnerable to the transient side effects than others. Since the cause of susceptibility is unknown, the risk of cognitive side effects can probably best be minimized primarily if the patients are observed and questioned with regard to declined memory in the treatment period and the psychiatrist who is responsible for the ECT treatment adjusts accordingly (Porter, et al., 2008).

5.4 Limitations and implications for further research

The primary strength is that we have gathered a well-characterized and, compared to previous studies, large, study material from neuropsychological testing at baseline and at two follow-ups on a group of patients that is very challenging to include in research (O'Connor, et al., 2010; Stek, et al., 2007; Verwijk, et al., 2014). Strengths of our study have been illuminated by the thesis, including the preceding discussion, which has compared our study with others.

Limitations can be evaluated both compared with previous studies of the problems to be addressed and compared to general standards of research quality. Compared with the sparse previous studies with many methodological weaknesses, the strengths of our study are obvious. Even so, there are limitations. For instance, the
control group should ideally have been larger and with no mean age difference compared with the patients. It might have been advantageous if we had compared the patient group with both a healthy control group and a control group of depressed patients who did not receive ECT. We did not have the opportunity to assess the control group three times. Studies have shown that the positive effects of practice are most evident between the first and second administration of a cognitive test (Collie, Maruff, Darby, & McStephen, 2003). Further, since response and remission after ECT treatment was the primary outcome of the study of Tor Magne Bjølseth, we had agreed not to relate neuropsychological results to these important variables. Limitations are elaborated on in the papers.

Further studies of neuropsychological functioning in LLD patients are needed to characterize more specifically what kinds of executive impairments patients have. Additional studies of remitted LLD patients are needed to separate episode-related and persistent impairments. Cognitive function in subgroups of depressed patients should be investigated further, e.g. psychotic patients (Gournellis, et al., 2014). The cognitive function of inpatients and melancholic patients also is understudied. There is still a need for methodologically sound studies of reasonably large samples of elderly depressed patients receiving ECT, preferably including a control group.

More studies of cognitive side effects of ECT in the elderly are needed. Ideally, more knowledge about side effects in specific diagnostic (sub)groups should have been available (McClintock, et al.,
2014). Knowledge of individual risk factors of cognitive side effects of ECT would render possible a more tailored treatment. We need comprehensive studies to research RA as a potential side effect of ECT in geriatric depression, and request the refinement of measures of RA in the future.

6. CONCLUSION

Patients with geriatric depression are more frequently cognitively impaired than healthy controls, and poor performance in the domains of information processing speed and executive function is common. We found that even when controlling for differences in processing speed, patients showed more executive deficits than controls. The comparison between patients receiving ECT and HCs showed a longitudinal stability on the group level. Nevertheless, a substantial minority of elderly patients receiving ECT acquired mild neurocognitive impairments in the acute phase of treatment. These impairments were transient, and equally frequent in patients with CIND and NCI at baseline. Patients with CIND showed markedly more improvement in test scores over time than patients with NCI. The CIND subgroup was also heterogenic, as half the group changed status from CIND at T1 to NCI at T3, while the other half showed little or no cognitive improvement.
In conclusion, heterogeneity of cognitive function and longitudinal course of patients with geriatric depression who are treated with ECT were shown across the follow-up period. The benefit of investigating individual differences and subgroups as well as comparing groups was also demonstrated.
7. REFERENCES

(number of references: 187 )


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Parkinson’s Disease undergoing deep brain stimulation (DBS) surgery. The Clinical Neuropsychologist, 26, 255-270.


Appendix

Table 1 Characteristics of the three included papers

<table>
<thead>
<tr>
<th>Nr.</th>
<th>N</th>
<th>Inclusion Time</th>
<th>Tests</th>
<th>Exclusion Criteria</th>
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<tr>
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<td>39</td>
<td>09.01.09 &amp; 12.22.12</td>
<td>T1</td>
<td>Standard for the study</td>
</tr>
<tr>
<td></td>
<td>+ 18</td>
<td>–</td>
<td></td>
<td></td>
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<tr>
<td>II</td>
<td>62</td>
<td>09.01.09 &amp; 04.30.13</td>
<td>T1 &amp; T2</td>
<td>Standard for the study</td>
</tr>
<tr>
<td></td>
<td>+ 17</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>54</td>
<td>09.01.09 &amp; 04.30.13</td>
<td>T1, T2 &amp; T3</td>
<td>Standard for the study</td>
</tr>
<tr>
<td></td>
<td>+ 17</td>
<td>–</td>
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</tr>
</tbody>
</table>

\[ a \] Patients and controls

\[ b \] Two screening measures of remote memory for autobiographical and public facts were administered at T1, T2, and T3 (the MQ and the CAMI-SF). In addition, the standardized neuropsychological tests included in this study were the HVLT-R, the BVMT-R, the TMT, the CWIT (1,2,3), the Tower test, the Letter Fluency Test, and the Animal Naming Test.

\[ c \] Either standard for the study or extended with two additional criteria (paper I): 1) mild brain injury (e.g., small-size stroke), and 2) any history of substance abuse.

\[ d \] HCs were only assessed by the MQ and the modified CAMI-SF at this time point.
Fig. 1. Patient flow

Patients assessed for eligibility (n=97)

Excluded (n=18)
  - Withdrew consent during screening (n=2)
  - Did not meet inclusion criteria (n=2)
  - Met exclusion criteria (n=14)

Included (n=79)

Dropped out (n=7)
  - Physical complaints (n=2)
  - Afraid of treatment (n=1)
  - Confusion (n=1)
  - ECT not working, perceived by patient (n=3)

No post-baseline assessment (n=6)
  - Withdrew consent (n=4)
  - Diagnosis altered (n=1)
  - Violation of protocol (n=1)

≤ 4 ECT (n=4)

Modified sample with ≥ 5 ECT (n=62)
  Neuropsychologically tested at baseline and within one week after ECT

Lost to follow-up (n=8)
  - Somatic morbidity (n=2)
  - Refused to come (n=6)

Analyzed after 3 months (n=54)