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Right unilateral and bifrontal electroconvulsive therapy in the treatment of depression with special reference to neurophysiological and clinical aspects

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ACADEMIC DISSERTATION

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To Leena, Niina and Tytti

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ABBREVIATIONS

ABF	anterior brifrontal
AD	antidepressant
AM	age method
APA	American Psychiatric Association
BF	bifrontal
BL	bilateral
BT	bitemporal
BZD	benzodiazepine
CNS	central nervous system
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTM	dose titration method
ECG	electrocardiography
ECS	electroconvulsive shock (refers to animal experiments to investigate the mechanism of action of ECT)
ECT	electroconvulsive therapy
ECT-T-U	electroconvulsive-treatment-unit
EEG	electroencephalography, -gram
EMG	electromyography
ENT (TNE)	estimated number of treatments
FHD	fixed high dose
fT	femto Tesla
HAM	half age method
HDRS	Hamilton depression rating scale
ICD	International Classification of Diseases
ITT	intention to treat
MADRS	Montgomery and Åsberg Rating scale
LF	left frontal
LF/O	left frontal to occipital ratio
LOCF	last observation carried forward
mC	millicoulomb
MEG	magnetoencephalography
MMSE	Minimental State Examination
MRI	magnetic resonance imaging
RDC	research diagnostic criteria
RF	right frontal
RF/O	right frontal to occipital ratio
RUL	right unilateral
SQUID	superconducting quantum interference device
SSRI	selective serotine reuptake inhibitor
ST	seizure threshold
TCA	tricyclic antidepressant
TMS	transmagnetic stimulation

LIST OF ORIGINAL PUBLICATIONS

The Thesis is based on four publications, and one submitted manuscript (Study II). The studies are referred to in the text by their Roman numerals.

I Heikman P, Salmelin R, Mäkelä J, Hari R, Katila H, and Kuoppasalmi K. Relation between the frontal 3-7 Hz MEG activity and the efficacy of ECT in major depression. *J ECT* 2001;17:136-40.

II Heikman P, Tuunainen A, Sailas E, and Kuoppasalmi K. Seizures induced by low-dose right unilateral and bifrontal electroconvulsive stimuli. Submitted.

III Heikman P, Tuunainen A, and Kuoppasalmi K. Value of the initial stimulus dose in right unilateral and bifrontal electroconvulsive therapy. *Psychol Med* 1999;29:1417-1423.

IV Heikman P, Kalska H, Katila H, Sarna S, Tuunainen A, and Kuoppasalmi K. Right unilateral and bifrontal electroconvulsive therapy in the treatment of depression: a preliminary study. *J ECT* 2002;18:26-30.

V Heikman P, Katila H, Sarna S, Wahlbeck K, and Kuoppasalmi K. Differential response to right unilateral ECT in depressed patients: impact of comorbidity and severity of illness. *BMC psychiatry* 2002;2:2 [ISRCTN 39974945].

1. ABSTRACT

Background: Both neurophysiological effects and the clinical outcome of electroconvulsive therapy (ECT) are dependent on stimulus dose and placement of the stimulus. The stimulus gan be directed over both temples of the head (BT), over the right side of the head (RUL) or over the frontal (BF) areas of the head. To find more specific solutions concerning the interactions between the technical factors of ECT and the neurophysiological effects and clinical outcome is perhaps the most important challenge for present ECT research. The efficacy of ECT in major depression has been linked to the accentuation of post-convulsive frontal EEG slow-wave activity (delta range**)** induced by different combinations of stimulus placements and stimulus doses. Although the significance of seizure duration as such seems at present to play a minor role in the mechanism of action for ECT, an inverse relationship between seizure duration and the minimal dose that elicits an adequate seizure, i.e. the seizure threshold (ST), has been replicated using RUL and BT stimulus placements. That inverse relationship can indicate the estimated ST level reflects at least partly those neural processes that determine seizure duration. In clinical practice, the stimulus dose for ECT can base on the dose titration method (DTM) on which the estimated ST level is based or on methods of a predetermined dose, e.g., the age-method (AM), the half age method (HAM) or the fixed high dose method (FHDM). The age-based methods assume a clear relationship between the age of the patients and the ST level. There is an on-going debate concerning which of these methods should be used. In addition, optimal stimulus doses in each of the stimulus placement has been a focus of recent ECT research. Unfortunately, most of the recent efficacy studies on ECT have excluded many groups of patients treated with ECT in clinical practice. The generality of those studies is therefore clearly limited.

Purpose and Methods: All study patients were hospitalized because of depression. The first aim was to investigate any ECT-induced changes, both RUL and BF, in frontal slow-wave activity (in the 0.5-3 Hz, delta range, and the 3-7 Hz, theta range) and their relation to clinical outcome using a whole-scalp magnetoencephalography (MEG). This method had not been previously used for this purpose. Second, this study examined the relationship between seizure duration and ST level as estimated by DTM in RUL ECT and made preliminary observations for BF ECT. Third, we compared the relationship between DTM, and AM and HAM separately for RUL and BF ECT and the relationship between DTM and FHDM also for RUL ECT. FHDM has not been used in the clinical practice of BF ECT. This study aimed to give guidelines for ECT dosing in the clinical practice of RUL and BF ECT. Fourth, this study compared the short-term clinical outcomes between high-dose RUL ECT, moderate-dose RUL ECT and low-dose BF ECT. Fifth, the study compared the outcome of RUL ECT for patients with pure major depressive episodes, and depressive patients with a variety of comorbid conditions or with low severity of the major depressive episodes. The latter group of patients has been excluded in most of the recent efficacy studies.

Results: The theta range of the MEG slow-wave activity increased in the right frontal and occipital regions during the course of ECT treatment. After four treatments, the increase of the theta MEG activity in the left frontal cortex correlated with the efficacy of the ECT treatment. Moreover, the change of the ratio of left and right frontal MEG theta activity to the occipital theta activity correlated positively with the therapeutic effect. The MEG study found no relationship between clinical outcome and delta activity. In RUL ECT, the Study II found an inverse relationship between seizure duration and initial ST level. This relationship was not found in BF ECT. The ECT dosing methods based on the predetermined dose would

have led to give patients with the lowest seizure thresholds in the RUL ECT group very high stimulus doses, up to 12 (AM) or 15 (FHDM) times the individual ST. In contrast, the RUL ECT patients with the highest ST levels would have received low stimulus doses down to 1.5 times (HAM method) the initial ST. In the BF ECT group the AM based dose would have been similarly dependent on the initial ST level. Patients treated with low-dose BF ECT needed more treatments than patients treated with high-dose RUL ECT treatment, i.e. twelve vs. seven treatments (Study IV). The heterogeneous depression group responded in a less efficient manner (8% vs. 63%) to RUL ECT, and more often had simultaneous worsening in the global cognitive functioning than the homogeneous depression group (Study V).

Conclusions: The findings suggest that an efficient ECT treatment regardless of electrode placement and stimulus intensity increases MEG theta activity in the frontal cortex. In BF ECT, the lack of an inverse relationship between seizure duration and initial ST level may indicate that the lowest level in the BF ECT schedule was overestimated. If this really is the case, the initial BF ST level would be essentially lower than the previous study conducted has estimated. The use of the DTM is recommended in RUL and BF ECT treatments, because it is the only method which allows for the individual selection of ECT stimulus doses relative to the ST. High-dose RUL ECT seems to have a faster antidepressant effect than low-dose BF ECT. The ECT effectiveness of RUL ECT treatment was lower in real-life heterogeneous patient groups than in homogeneous patient samples used in experimental efficacy trials.

2. REVIEW OF LITERATURE

2.1. Depression

Depression may be considered as a normal human emotion, a symptom of a somatic illness, a neuropsychiatric illness or one of the main symptoms of mood disorders. Depression often recurs (Angst et *al*., 1996), it is associated with an increased risk of suicide (Harris and Barraclough, 1997), and causes much disability (Wells et *al*., 1989). The risk of suicide in follow-up studies of affective disorder has decreased compared to that reported in previous reviews (O'Leary et *al*., 2001). The availability of ECT and antidepressants (ADs) may have contributed to this decrease, but it cannot be assumed that ECT can be prescribed for all patients. Depressive illness has been the fourth leading global cause of disability-adjusted life years (DALYs) in 1990 and it has been predicted it will be the second leading cause of DALYs in 2020 (Murray and Lopez, 1997).

2.1.1. Clinical evaluation

Different criteria for mood disorders have been used over the last decades. The criteria according to Feighner et *al*. (1972), and the Research Diagnostic Criteria (RDC) (Spitzer et *al*., 1978) have included criteria for both primary and secondary depression. Secondary major depression occurs in a person who has a preexisting non-affective psychiatric disorder (which may or may not still be present), or a serious or life-threatening medical illness, which precedes and parallels the symptoms of depression contrary to primary depression. In Finland, the criteria according to the International Classification of Diseases (ICD, version 10, World Health Organization, 1992) are officially used for mood disorder diagnostic. On the other hand, depression studies have widely used the criteria for mood disorders of the Diagnostic and Statistical Manual of Mental Disorders (DSM) [American Psychiatric Association (APA)]. The latest version (DSM-IV) (APA, 1994) has been used in the studies which make up this thesis.

DSM-IV defines a mood disorder as a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual and that is associated with present distress (e.g., a painful symptom) or disability (i.e., impairment in one or more important area of functioning) or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom.

The DSM-IV mood disorders are as follows: 1) mood disorder due to a general medical condition, 2) substance induced mood disorder, 3) bipolar I disorder, 4) bipolar II disorder, 5) schizoaffective disorder, 6) cyclothymic disorder, 7) major depressive disorder, 8) dysthymic disorder, 9) adjustment disorder with a depressed mood and 10) depressive disorder not otherwise specified. The term major depression indicates that the depressive disorder is severe.

Diagnoses for major depressive disorders and for bipolar I disorders include a major depressive episode. A major depressive episode has a duration of at least two weeks, and it represents a change from previous functioning. The major depressive episode includes at least five of the following nine symptoms: either 1) a depressed mood or 2) markedly diminished interest plus associated symptoms 3) significant weight loss or weight gain when not dieting 4) insomnia or hypersomnia 5) psychomotor agitation or retardation 6) fatigue or loss of energy 7) feelings of worthlessness or excessive guilt 8) diminished ability to think or

concentrate, or indecisiveness and 9) suicidality. The nine symptoms, occurring nearly every day during the episode, are the A criteria for a DSM-IV major depressive episode. The criteria for a major depressive episode are somewhat different according to the ICD 10 criteria, e.g. the most typical symptoms include in addition to a depressed mood, and loss of interest and enjoyment also reduced energy leading to increased fatiguability and diminished activity.

A major depressive episode may occur with melancholic (endogenous), atypical, catatonic, or psychotic features. The DSM-IV criteria for major depressive episode with melancholia are symptoms no. 1 or 2 and 3 of no. 3-8: 1) loss of pleasure in all or almost all activities, 2) lack of reactivity to usually pleasurable stimuli, 3) depression regularly worse in the morning, 4) early morning awakening, 5) marked psychomotor retardation or agitation, 6) significant anorexia or weight loss, 7) excessive or inappropriate guilt, 8) a distinct quality of the depressed mood. The psychotic features found in a major depressive episode according to DSM-IV includes delusions or hallucinations and according to ICD-10 delusions, hallucinations, or depressive stupor. The clinically different subtypes may be also biologically different. It has been suggested that especially psychotic depression may be a distinguishable nosological entity that warrants separate treatment algorithms (Petrides et *al*., 2001). Estimates for the frequency of occurrence of psychotic depression range from 14% in a community sample (Johnsson et *al*., 1991) up to 54% in clinical practice, particularly in treatment-resistant depressed patients (Dubosky and Thomas, 1992). Relapse rates are higher and occur earlier in psychotic depressed patients than in nonpsychotic depressed patient. Regarding neurophysiological aspects, psychotic depression has been found to occur more often among abnormal EEG (62%) than normal EEG (39%) patients (Malaspina et *al*., 1994).

A major depressive episode can be categorised as severe based on depressive symptoms, on scores on a depression rating scale, e.g. Hamilton Rating Scale for Depression (HDRS, Hamilton, 1967), and Montgomery and Åsberg Depression Rating Scale (MADRS, Montgomery and Åsberg, 1979), on a need for hospitalisation, on depressive subtypes, on a functional capacity, on the level of suicidality and on the impact that the depression has on the patient (Sonawalla and Fava, 2001).

As many as 30% to 40% of patients with major depressive disorder are unresponsive to AD medication (Fava, 2000; Kornstein and Schneider, 2001). At present, there are no commonly accepted standards for defining medication resistance. Guscott and Grof (1991) emphasize that the problem of treatment-refractory depression has to do primarily with the diagnostic-treatment process than with patient variables. The questions which should be considered are as follows: 1) Is the diagnosis correct? 2) Has the patient received adequate treatment? 3) Was a rational stepped-care approach used? 4) How was outcome measured? 5) Is there a coexisting medical or psychiatric disorder that is interferring with response to treatment? and 6) Are there factors in the clinical setting that are interfering with treatment?

The clinical characteristics of depression is further influenced by several biological, psychological and social factors, and by the presence of comorbid psychiatric or medical illnesses (Weissman et *al*., 1996; Parker and Kalucy, 1999; Roulloin, 1999).

Recent studies have found that depression is also a risk factor for somatic illnessess such as coronary heart disease (Ferketich et *al.* 2000) and for cardiac mortality (Seiner and Mallya, 1999). This mortality may be decreased by appropriate treatment of depression (Seiner and

Mallya, 1999). Regarding an increased risk for sudden death, high levels of QT variability occurs on the electrocardiograms (ECGs) of the patients with an elevated risk for sudden death. The increased QT variability has also been found in depressed patients (Yeragani et *al*., 2000).

2.1.2. Epidemiology

Recent studies have found one-year prevalence rates for a major depressive episode to range from 10.1% to 4.5% **(Table 1)**.

Table 1. One-year prevalence rates for a major depressive episode

Reference	Total prevalence (%)	Females (%)	Males (%)	Total prevalence (%) with clinical significance criteria
Regier et *al*., 1984	5.8			4.5
Kessler et *al*., 1994	10.1			6.4
Lindeman et *al*., 2000	9.3	10.9	7.2	
Ayuso-Mateos et *al*., 2001	6.7	8.0	4.9	
Kringlen et *al*., 2001	7.3	9.7	4.1	
Pirkola et *al*., 2002	5.0	7.0	4.0	
Narrow et *al*., 2002				4.5

Prevalence rates were found to be lower if they were based on the clinical significance of depressive disorders (Narrow et *al*., 2002). This may be important for estimating the needs for different treatment.

2.1.3. Etiology

The causes of mood disorders are unknown (see Kaplan and Saddock, 1998). The causative factors can be artificially divided into biological, genetic, and psychosocial, but this division is artificial because the three realms most likely interact with each other.

The monoamine hypothesis, which was first proposed in 1965, holds that monoamines such as norepinephrine and serotonin are deficient in depression and that the action of antidepressants depends on increasing synaptic availability of these monoamines (Schildkraut, 1965). Although the data are not yet conclusive, amino acid neurotransmitters [particularly γ-aminobutyric acid (GABA)] and neuroactive peptides (particularly vasopressin and the endogenous opiates) have been implicated in the pathophysiology of mood disorders (see Kaplan and Saddock,1998). Major depression is a familial disorder, and its familiality mostly or entirely results from genetic influences (Sullivan et *al*., 2000). Environmental influences specific to an individual are also etiologically significant (Sullivan et *al*., 2000; Kendler et *al*., 2001)

2.1.4. Functional Neuroanatomy

Functional abnormalities in the frontal, subcortical, and limbic structures are associated with mood disorders (Mayberg, 1997; Soares and Mann, 1997). The frontal lobes make up approximately one-third of the total cortical area of the brain and mediate critical social functions such as planning, regulation of behaviour, and drive. Furthermore, there is specific

neuropsychological and neurobehavioral evidence for significant prefrontal cortical dysfunction in depression (Sweeney et *al*., 1998; Merriam et *al*., 1999). Dysfunction of the prefrontal cortex, particularly with respect to its role in modulating limbic activity, may produce many of the symptoms seen in clinical depression (George et *al*., 1994). Mayberg (1997) has suggested that dorsal neocortical decreases and ventral paralimbic increases characterize both healthy sadness and depressive illness. Concurrent inhibition of overactive paralimbic regions and normalization of hypofunctioning dorsal cortical sites is suggested to be necessary for disease remission, whether facilitated by psychotherapy, medication, or electroconvulsive therapy. Also in bipolar disorder, the available data indicates that abnormalities in specific frontal-subcortical brain circuits seem likely (Strakowski et *al*., 2000).

2.1.5. Neurophysiological aspects

Clinical neurophysiology examines the functions of the nervous system in the clinical setting. The neurophysiological effects of depression on the brain function can be evaluated by means of electroencephalography (EEG), by quantitative EEG (QEEG), by evoked potentials (EPs), by magnetoencephalography (MEG), by polysomnographic recordings and most recently by means of transcranial magnetic stimulation (TMS). Both spontaneous and event-related activity can be studied as well as generators of that activity or the profile of the sleep.

EEG. The spontaneous EEG activity has been divided into to the following frequency bands: beta activity (greater than 13 Hz), alpha rhythm (between 8 and 13 Hz), theta activity (between 4 and 7.5 Hz), and delta activity (less than 4 Hz) (see Niedermeyer, 1987). Theta and delta activity are the components of the slow-wave activity. The alpha rhythm occurs maximally over the posterior regions of the head and is blocked by eye opening. The presence of delta rhytms is considered to be a sign of pathology in an alert state.

The role of neurophysiological methods in evaluation of the clinical brain function of depressed patients is not established as yet. The role of the EEG methods in the study of affective disorders has primarily considered to be in ruling out organic mental disorders (Brenner et *al*., 1989; Nuwer, 1997). In general, abnormalities in EEG are nonspecific. It has been concluded that EEG can help detect excess slow activity in organic disorders such as dementia but EEG is not yet able to help in the diagnosis of other disorders, such as schizophrenia or depression (Nuwer, 1997). In patients with endogenous major depressions, standard pretreatment clinical EEGs have been found to be abnormal in 19 percent of patients (Malaspina et *al*., 1994). It is further emphasized that the ability of any QEEG procedure to make psychiatric diagnoses or to discriminate between various groups of psychiatric patients and normal subjects is not well established (Nuwer, 1997). In contrast, Hoffman et al. (1999) considers that QEEG can be useful for the evaluation and understanding of psychiatric disorders by referring to a review by Hughes and John (1999). Regarding earlier studies, e.g. Abrams and Taylor (1979) have found that the proportion of abnormal EEGs was twice as great among schizophrenics as among affectives. Schizophrenics had more temporal abnormalities and affectives had more parieto/occipital abnormalities. Boutros (1996) have suggested that increased illness severity and increased number of medications and dosages may be accompanied with an increased amount of diffuse EEG slowing. One focus of neurophysiological studies in patients with mood disorders has been laterality or asymmetry regarding the brains hemispheres. In major depression, cerebral asymmetry (alpha suppression) as measured by EEG has been found to occur so that there is less left frontal

activation and greater right frontal activation (Davidson, 1992). On the other, Bruder et al. (1997) have found that the lateralization of EEG activation in depressed patients is dependent on the comorbid anxiety disorder in question.

There is strong evidence that many psychotropic medications may modulate the brain's function as measured by EEG. Epileptiform discharges on the EEG and increased slow-wave activity can be induced by neuroleptic medication, TCAs, and lithium (Holmes and Korteling, 1993). Lithium is one of the agents that induce most significant changes of the EEG (Struve, 1987). In contrast, chloralhydrate may induce only a little increase in beta activity (Holmes and Korteling, 1993). A dose-dependent effect of sertraline has been found on the pharmaco-EEG profile (Saletu and Grunberg, 1988).

MEG. MEG is a modern neurophysiological method used in human brain research (Reeve et *al*., 1989; Hari, 1993; Hämäläinen et *al*., 1993; Salmelin and Mäkelä, 1995; Mäkelä, 1996; Reite et al., 1999). MEG recordings pick up tiny extracranial magnetic fields associated with electric currents in synchronously active cortical neurons. When a very sensitive instrument is used to measure these generated magnetic fields, the magnetic energy is converted back into an electrical signal. The detection of these very weak fields requires superconductivity, i.e. the use of a super quantum interference device (SQUID). In the SQUID devices, superconductivity is obtained by bathing the detectors in liquid helium at –269 degrees Celsius. Modern MEG instruments allow detection of magnetic field patterns produced by brain activitity simultaneously over the whole scalp. MEG allows non-invasive monitoring of ongoing human cortical activity on a millisecond time scale. The spatial resolution capacity of MEG is reasonable. Making measurements for patients is simple, and painless. MEG also has a capacity to localize generators of the cortical activity of the the brain.

Both EEG and MEG evidently reflect postsynaptic currents in the pyramidal cortical cells. However, there are essential differences between EEG and MEG methodology in measuring the spontaneous brain activity. While EEG detects electric potentials, MEG picks up tiny extracranial magnetic fields associated with electric currents in synchronously active cortical neurons with a good spatial resolution (Hari, 1993). MEG is most sensitive to currents with components tangential to the head surface, i.e. to currents flowing predominantly in the fissural cortex, whereas EEG is sensitive to both radial and tangential currents (Hari, 1993). About two-thirds of the human cortex is embedded in fissures, and thus can be studied with MEG better than with EEG. Magnetic fields traverse the skull and scalp unaffected, whereas EEG signals are blurred by layers of different electric conductivities. Furthermore, the location of the reference electrode affects the recorded EEG signals, but MEG signals are reference free.

The clinical utility of MEG includes presurgical mapping of sensory cortical areas and localization of hypoperfusion areas of the brains of stroke patients (Mäkelä, 1998; Reite et *al*., 1999). Psychiatric disorders are principally suitable for MEG research (Mäkelä, 1996). However, little data exist e.g. on how depression affects spontaneous brain activity as measured by MEG. Reite et *al*. (1999) have found altered cerebral lateralization being associated with psychoses of schizoaffective disorder and bipolar I disorder. Llinas et *al*. (1999) have found that nine patients suffering from chronic, severe and therapy-resistant neurological or neuropsychiatric disorders (four patients with Parkinson's disease, one patient with tinnitus, two patients with neurogenic pain and two patients with major

depression) had increased slow-wave rhytmicity in the theta range, in conjunction with a widespread and marked increase of coherence among high-and low-frequency oscillations.

2.1.6. Treatment

An active treatment of depression directed at remission, i.e. at removal of essentially all symptoms instead of reduction of the symptoms by 50% or some a greater percentage, i.e. to achieve response (see APA, 2000), is an important task in improving the long-term prognosis in depression (Baldwin, 2000).

In the acute phase, pharmacotherapy, psychotherapy, a combination of medications plus psychotherapy, or ECT treatments can be used (see APA, 2000). The selection of an initial treatment modality should be influenced by both clinical (e.g., severity of symptoms) as well as other factors (e.g., patient preference). If preferred by the patient, AD medications may be provided as an initial primary treatment modality for mild major depressive disorder. AD medications should be provided for moderate to severe major depressive disorder unless ECT is planned. A specific, effective psychotherapy alone as an initial treatment modality may be considered with moderate clinical confidence for patients with mild to moderate major depressive disorder. Cognitive behavioral therapy and interpersonal therapy are the psychotherapeutic approaches that have the best documented efficacy in the literature for the specific treatment for major depressive disorder. With substantial clinical confidence, the combination of a specific effective psychotherapy and medication may be useful as an initial treatment choice for patients with psychosocial issues, interpersonal problems, or a comorbid personality disorder together with moderate to severe major depressive disorder. In the acute phase, the response rates with AD medications often range from 50% to 75% of patients (APA, 2000). The proportion of patients with major depressive disorders who respond to ECT has previously been found to range from 80% to 90% (see Abrams, 1997). ECT should be considered with substantial clinical confidence for patients with major depressive disorders with a high degree of symptom severity and functional impairment or for cases in which psychotic symptoms or catatonia are present (see APA, 2000). With moderate clinical confidence, ECT may also be the treatment modality of choice for patients in whom there is an urgent need for response, such as patients who are suicidal or refusing food and nutritionally compromised (see APA, 2000). The presence of comorbid general medical conditions that preclude the use of AD medications, a prior history of positive response to ECT, and patient preference are other important considerations that may indicate the use of ECT (see APA, 2000). ECT is often used for depressive patients who have not responded to AD medication. Medication resistant patients may show at least a 50% likelihood of a satisfactory response to ECT (Prudic et *al*., 1990).

2.2. Electroconvulsive therapy (ECT) treatment

2.2.1. Development of modern ECT practice

History. ECT is an electrical induction of a series of generalized motor seizures for therapeutic purposes. Before electrical induction of seizures in humans, non-electric convulsive treatments induced e.g. by camphor and pentylenetetrazol were used by von Meduna since 1934 (Kalinowsky, 1986; Endler, 1988). Meduna's idea of convulsive therapy was based on the frequent observation that catatonics and other schizophrenic patients would temporalily lose their psychotic symptomatology after spontaneous seizures whatever their cause. Thus, ECT was originally applied to schizophrenics, and only later was it realised that

it gives even better results in patients with depression. ECT was first implemented in April 1938 by Cerletti and Bini for a human patient who probably suffered from schizophrenia (Kalinowsky, 1986). Only the third stimulus, which was higher than the two first stimuli, was followed by a complete seizure, after which the previously mute patient began to talk. He had a good remission after a series of treatments and could be followed for two years.

Change of use of ECT as a function of time. At the end of the 1950s, the use of ECT decreased considerably with the introduction of AD medication until the early 1980s (Thompson and Blaine, 1987). A survey of practice in California between 1977 and 1983 indicated that 1.12 persons per 10000 in the general adult population were treated with ECT (Kramer, 1985). The rate was 3.86 persons per 10000 among people aged 65 years and older. The overall increase in the use of ECT in the United States between 1980 and 1986 was fully attributable to its greater use in elderly patients (Thompson et *al*., 1994). The authors suggest that this increase occurred because of cardiovascular and other relative contraindications to AD medication in the elderly. In Finland, ECT was introduced as early as the end of the 1930s (Achte, 1983). Huuhka et *al*. (2000) investigated the clinical use of ECT in the 1940s, 1960s, and 1990s in Pitkäniemi Hospital. The authors found that the use of ECT decreased from about 14% to 2% of all inpatients between the two first time points but remained at the same level between the two latest data points. Over the last few years ECT has become a routine method for patients hospitalized because of depression in many countries.

Attitudes and ethical aspects. There exists a lot of negative attitudes against ECT (Harrigan, 1999). It has been suggested that ECT is an unscientific treatment and a symbol of authority of the old psychiatry. Movies that deal with ECT have had a negative influence towards ECT. ECT has been shown on film as a progressively more negative and cruel treatment, leaving the impression of a brutal, harmful, and abusive manoeuvre with no therapeutic benefit (McDonald and Walter, 2001). Furthermore, there seems to be a significant negative biases against ECT among medical students. As high as forty percent of the students feel that psychiatrists often misuse ECT, while 31% actually thought ECT was used to punish violent or uncooperative patients (Clothier et *al.*, 2001). Joyce Jackson (1995), who has been treated with ECT, emphasizes that the stigma that she feel as a result of having had ECT is not only the most severely adverse effect but also the only long-term adverse effect that she have experienced from ECT.

Recent reports of the ethics of ECT focus on the necessity to obtain informed consent from the patients (APA, 1990; Reiter-Theil, 1992; see Royal College of Psychiatrists, 1995; Ekholm and Heikman, 1999; see APA, 2001). This method guarantees the rights of the patients by best means and also necessitates the physicians to give the patients their best available information on ECT.

Low rates of use of ECT in Finland. In addition to the study of Huuhka et *al*. (2000), there are three studies which show a low use of ECT in depressive patients. Isometsä et *al*. (1994) have found that among suicide victims with current major depression 3% had received ECT. Suominen et *al*. (1998) have found that none of the suicide attempters with major depression had received ECT treatment either during the month just before their attempted suicides or during a one-month period after the attempt. Among Finnish patients with major depression who were granted a disability pension, 11 (4%) of the 277 patients had received ECT (Isometsä et *al*., 2000).

Indications for ECT. Depressive states are the main indication for use of ECT at present (see Royal College of Psychiatrists, 1995; see APA, 2001). Regarding patients with depression, ECT is often used for severe psychotic or melancholic depressions, in patients who are intolerant of or resistant to their AD medication, and/or in patients who are suicidal. ECT has an acute beneficial effect on suicidal patients but the data showing a long-term beneficial effect is weak (Prudic and Sackeim, 1999; Sharma, 2001). Catatonia**,** regardless of its cause, has been repeatedly treated successfully with ECT (see APA, 2001). For mania, ECT continues to be an effective treatment. A combination of ECT plus antipsychotic agents has been found to be at least as efficient as a combination of lithium and antipsychotic medication (Small et *al*., 1988). In drug-treatment-resistant cases, reported response rates are about 80% (Mukherjee et *al*., 1994; Daly, 1997). During the last years, interest in the use of ECT in schizophrenia has again increased **(**Tharyan, 1999**)**. In the United States, schizophrenia and related conditions (schizophreniform and schizoaffective disorders) constitute the second most common diagnostic indications for ECT (see APA, 2001). Case studies concerning antiepileptic treatment with ECT have been reported since the 1940s in patients with epilepsy (Gonzalez, 1997). ECT has powerful anticonvulsant properties (Coffey et *al*., 1995b; Sackeim, 1999). The anticonvulsant effect has been associated with the ECT-induced rise in seizure threshold. The rise in ST has found to be from 25 to 200% during a course of treatment (Sackeim et *al*., 1987a). Furthermore, ECT may be beneficial e.g. for symptoms of patients with idiopathic Parkinson's disease (Andersen et *al*., 1987; Rasmussen and Abrams, 1991), for patients with neuroleptic malignant syndrome (Trollor and Sachdev, 1999), for patients with refractory obsessive compulsive disorder, and for a subgroup of patients with chronic pain (Rasmussen and Rummans, 2002).

Technical development. During the first years of ECT, the treatment was generally accepted in spite of the frequent complication of fractures. In 1951, succinylcholine became available as a safe muscle relaxant for used during ECT. To save the patient distress from paralysis of the respiratory muscles, barbiturate anesthesia prior to the muscle relaxant became an essential part of the ECT anesthesia. The place of unmodified ECT, i.e. treatment without anesthesia, has been questioned as being an unacceptable practice since the 1970s (McCleave and Blakemore, 1975).

The amnestic effects of the conventional bitemporal (BT), i.e., bilateral (BL) sine wave ECT has been a great challenge for ECT research (see Abrams, 1997). Based on this valuable work, brief pulse stimulus and unilateral electrode placement has been widely introduced (see e.g Abrams, 1997). The beneficial effects of RUL ECT as compared with BT ECT on cognitive function has been emphasized (Weiner et *al*., 1986; see Abrams, 1997).

An opportunity to evaluate the effects of BT stimulation exclusive of the temporal lobes arose with the suggestion of Inglis (1970) that seizures induced with electrodes placed over the front of the head should improve mood but have less effect on memory than other techniques. At the beginning of the 1970s, Abrams and Taylor (1973) used anterior bifrontal (ABF) ECT. Some years later, Weaver (1976) reported, using a theoretical model, that BT ECT induced maximal current density in frontal areas of the brain instead of the areas between the stimulus electrodes. ABF ECT disappeared from the ECT landscape until a modified version was introduced (Lawson et *al*., 1990; Letemendia et *al*., 1993; Bailine et *al*., 2000). With this modern bifrontal (BF) ECT, the distance between electrodes is wider than with ABF. In addition to BF ECT, an asymmetric bilateral right frontotemporal left frontal stimulus electrode placement was introduced in the 1990s (Manly and Swartz, 1994; Swartz,

1994) but no controlled trials have been carried out with this ECT technique. Low-dose BF ECT as compared with low-dose RUL ECT and low-dose BT ECT has been shown to spare patients from cognitive side-effects without a concomitant impairment in efficacy (Lawson et *al*., 1990; Letemendia et *al*., 1993). Similar result have been reported by Bailine et *al*. (2000) using BT and BF ECT both dosed at equal doses, i.e. 1.5 times, relative to the seizure threshold level. However, the role of BF ECT has so far been considered to be experimental (see APA, 2001**)**.

Most of recent ECT research has been carried out on depressive patients. However, the required technique of ECT may be different e.g. for manic or schizophrenic patients. In the treatment of depression by ECT, the initial ECT stimulus dose can be chosen using two alternative methods (see Abrams, 1997). Firstly, the ECT dose can be given individually as obtained by a dose titration method (see e.g. Sackeim et *al*., 1987a) by which the individual seizure threshold is measured. Secondly, one can use a method of a predetermined dose, e.g. a fixed high dose method for RUL ECT treatment (Abrams et *al*., 1991; McCall et *al*., 2000a), or a dose based on parameters which have some relationship with the seizure threshold level, e.g. the age of the patient (age-based dosing) (Swartz and Abrams, 1994; see Abrams, 1997). In contrast to RUL ECT, conventional BT ECT has not found to be as sensitive on the dosing methods (see Abrams, 1997).

Practice guidelines for prescribing ECT. The APA has published recommendations for ECT on three different occasions (see APA, 1978; see APA, 1990; see APA, 2000). The first report aimed to standardize the practice of ECT. One of its most important contributions was to insist on the routine use of anaesthesia, muscle relaxation, and oxygenation in ECT. Furthermore, the first report favored unilateral ECT. The second report emphasized the importance of electrode placement/stimulus dose combination in optimizing therapeutic efficacy and minimizing cognitive effects. This report pointed out that using unilateral ECT, low electrical doses are usually associated with low efficacy. However, specific recommendations about how high above the threshold to deliver unilateral ECT could not be made, as studies concerning this issue were in a rather preliminary state at that time. The latest report provides recommended dosing range (2.5 to 6 times the threshold) for right unilateral ECT. Guidelines for prescribing ECT has been published twice by The Royal College of Psychiatrists (1989; 1995). Based on the recommendations by the APA (1990), Heikman (1995) has published recommendation on ECT for Finnish physicians.

2.2.2. Mechanism of action

ECT's mechanism of action is still not fully understood. Over a hundred theories have been offered to account for the efficacy of ECT, and skepticism has been expressed about the possibility of uncovering its mode of action in part because ECT by provocation of generalized seizures produces a wide variety of effects to neurophysiological, to neurotransmitter/neurochemical, and to neuroendocrine systems. Therefore, it is essential to be able to isolate those neurobiological changes that accompany therapeutically effective forms of stimulation from nonspecific changes intrinsic to seizure induction.

The functional changes induced by ECT are both ictal (recorded during ECT seizures) and interictal (recorded during waking).

There is a lot of data suggesting the role of frontal lobes in the mechanism of action of ECT. Weaver (1976) reported, using a theoretical model, that BT ECT induced maximal current density in frontal areas of the brain instead of the areas between the stimulus electrodes. Animal studies have pointed out the role of the frontal lobes in the mechanism of action of ECS (e.g. Nutt et *al*., 1989). Nutt et al. have found that ECS enhances a tonic throughput of norepinephrine in the frontal cortex and dopamine in striatum. Letemendia et *al*. (1993) have suggested that BF ECT by avoiding the temporal regions of the brain may spare both verbal and non-verbal cognitive functioning and by inducing maximal current density in the frontal regions may achieve full therapeutic advantage.

During the seizures, using single photon emission tomography (SPECT) and blood-flow tracers, it has been found that ECT increases regional cerebral blood flow (rCBF) (Bolwig et *al*., 1977). The findings regarding interictal rCBF are not uniform; both reductions (Silfverskiöld et *al*., 1987; Nobler et *al*., 1994) and increases (Bonne et *al*., 1996; Bonne and Krausz, 1997) has been observed. Furthermore, the efficacy of ECT treatment has been reported to be associated both with a reduction, (Nobler et *al*., 1994) or an increase (Petracca et *al*., 1995; Bonne et *al*., 1996; Bonne and Krausz, 1997) of postictal rCBF. In positron photon emission tomography (PET) studies, ECT has been shown either to decrease the cerebral metabolic rate for glucose (CMRglu) (Henry et *al*., 2001), or have no effect on the CMRglu (Yatham et *al*., 2000). Thus, the findings on interictal CBF seem to be contradictory.

In order to understand the mechanism of action of ECT, one has to also remember that ECT alleviates symptoms of depression, mania, psychosis, and motor disturbances. This may reflect the possibility that ECT does not act uniformly in all its indications (Fink, 1993a).

In animal studies of electroshock treatments (ECS), seizure activity may last essentially longer than in humans and may be accompanied with different effects on the brain (Devanand et *al*., 1994). Second, the findings within animal studies seem to be inconsistent (Newman et *al*., 1988). Third, the relevance of neurochemical changes in the brains of normal rodents to the clinical effects of ECT in depressed or otherwise ill humans has been questioned (Lerer, 1999). Those are the three main reasons why I have excluded most of the animal studies conducted from this thesis.

An interesting question is whether AD medication and ECT share some common mechanisms in their actions. The time to achieve maximal response may be more rapid with ECT than with psychotropic medication (Nobler et *al*., 1997; see APA, 2001). On the other hand, ECT and psychotropic medications may have some overlap in their mechanism of actions. Many resistant patients to TCAs respond to ECT but their response rates seem to be reduced compared to that of patients without established medication resistance (Prudic et *al*., 1990). Failure to respond to one or more adequate medication trials have been shown to predict a diminished rate of ECT response (Prudic et *al*., 1996). Furthermore, the resistance to AD treatment may be dependent on the type of AD medication used: patients with resistance to TCAs have been found to be more resistant to ECT than patients with resistance to SSRIs (Prudic et *al*., 1996).

ECT has to be given as a course of several treatments to induce its beneficial effects. In some patients, the response of the initial two treatments has found to be associated with the overall change at the end of the course (see Royal College of Psychiatrists, 1995). It is also found

that there is no any significant prophylactic value in giving extra ECT after clinical improvement in the hope of preventing relapse (Barton et *al*., 1973). The efficacy of ECT is not long-lasting. Sackeim et *al*. (2001) have found that without active treatment, virtually all remitted patients relapse within 6 months of stopping ECT.

2.2.3. Neurophysiological aspects in mechanism of action of ECT

Several studies are providing a growing body of evidence of the relationship between the response to ECT and both ictal and interictal EEG. The studies appear to be consistent in pointing to the importance of neurophysiological changes in the prefrontal cortex as a potential mediator of the antidepressant response to ECT (Krystal and Weiner, 1999).

Seizure. It was long suggested that an induction of an epileptic seizure by ECT is essential for the efficacy and EEG changes of ECT (Ottosson, 1960). However, there nowadays exist strong evidence that the occurrence of a generalized seizure does not guarantee a good response to ECT (Sackeim et *al*., 1993).

Seizure duration. Seizure duration per se is considered to be an unreliable guideline for effective treatment (Sackeim et *al*., 1987c; Sackeim et *al*., 1991; Nobler et *al*., 1993; Kales et *al*., 1997; Sackeim, 1999; see APA, 2001). In order to be a clinically adequate seizure, it has been suggested that a seizure should have a duration at least of 15-25 seconds (Weiner et *al*., 1991; Krystal and Weiner, 1994; see Royal College of Psychiatrists, 1995; see APA, 2001). Importantly, brief seizures may be due to either insufficient or markedly suprathreshold stimulus intensity (Sackeim et *al*., 1991; Frey et *al*., 2001). On the other hand, short seizures are likely to occur in older patients (Sackeim et *al*., 1991; Boylan et *al*., 2000) as well as later in the ECT course (Kales et *al*., 1997). The process underlying the reduction in seizure duration through a course of ECT may not be related to antidepressant efficacy (Kales et *al*., 1997).

Ictal EEG findings. It has been shown that the ictal EEG characteristics of seizures induced by barely suprathreshold unilateral ECT (a low-efficacy treatment) are different compared to seizures induced by bilateral ECT and unilateral ECT administered at a high intensity relative to seizure threshold (high-efficacy treatments) (Krystal and Weiner, 1999). Treatments with high efficacy are accompanied with 1) higher amplitudes of 2–5 and 5–13-Hz activity immediately after the stimulus, 2) greater immediate poststimulus interhemispheric coherence, 3) a shorter time to the onset of the onset of high-amplitude slow waves, 4) increased amplitude of 2–5 and 13–30 Hz activity in the midictal portion of the seizure, 5) more regular midictal slow-wave shape (or signal predictability over time), 6) more pronounced postictal suppression, and 7) less postictal interhemispheric coherence.
A relationship between postictal suppression and likelihood of clinical improvement has also been observed by Suppes et *al*. (1996) and by Nobler et *al*. (2000). However, in the study of Nobler et *al*. (2000) all associations between ictal EEG changes and clinical outcome were weak, and were dependent on manipulations of ECT technique. In contrast, Luber et *al*. (2000) found that effective forms of ECT resulted in a topography where ictal delta power was accentuated in prefontal EEG sites. Despite the relationship between clinical outcome and ictal EEG changes induced by ECT, the data has not been considered sufficient to give guidelines for a clinician for ECT dosing (see APA, 2001).

Inter-ictal EEG slow-wave activity. EEG slow-wave activity induced by ECT has been investigated widely since 1940 (see Abrams, 1997). The global increase or lateralization of

this activity induced by modern brief-pulse stimuli is not associated with the efficacy of treatment (Weiner et *al*., 1986; Abrams et *al*., 1992; Sackeim et *al*., 1996). Instead, the efficacy has been related to induction of post-convulsive EEG delta (0.5-3.5 Hz) activity using QEEG over prefrontal regions (topography pattern 1) (Sackeim et *al*., 1996). Similar relationship with more primitive EEG techniques has been found as early as in the 1950s by Roth (1952) and by Fink and Kahn (1957). Fink and coworkers saw the development of the EEG slow-wave activity as evidence that a persistent change in brain chemistry had occurred, which was necessary but not sufficient for clinical improvement. The increase in EEG slow-waves was suggested to indicate that the cerebral biochemistry was altered, thereby allowing physiological adaptive processes to modify the expression of psychoses. The changes in the EEG slow-wave activity have been shown to vary with the method of seizure induction, and with the number of seizure administered (see Abrams, 1997). Furthermore, the induced slow-wave activity has been shown to resolve within several weeks after the treatment (Kolbeinsson and Petursson, 1988; see Abrams, 1997).

Inter ictal MEG slow-wave activity. There are two studies which have found that the ECT-induced slow-wave activity can be measured also by MEG (Salmelin et *al*., 1997; Sperling et *al*., 2000).

Global EEG and MEG slow-wave activity and subcortical pacemakers. The global EEG slow-wave activity has been presumed to reflect an effect from subcortical pacemakers (Streriade et *al*., 1990). Using MEG, Llinas et *al*. (1999) suggest that the slow-wave activity in patients with Parkinson's disease, with tinnitus, with neurogenic pain and with major depression may indicate presence of a thalomocortical dysrythmia. Even unilateral thalamic lesions have been shown to decelerate cortical MEG rhythms bilaterally (Mäkelä et *al*., 1998). Under the influence of increased inhibition, thalamocortical neurons oscillate at about 6 Hz instead of their normal frequency of around 10 Hz (Steriade et *al*., 1990). Inhibitory mechanisms are thought to be important in mediating the therapeutic effects of ECT (Sackeim et *al*., 1994; Sackeim et *al*., 1996).

Modulation of the slow-wave activity. To understand how the cortical slow-wave activity is modulated may be even much more difficult than determing the electric field distributions induced by ECT. It has been suggested that adrenergic, cholinergic, and histaminergic neurotransmitter systems are involved in the expression of the slow-wave activity of the ECT process (see Fink, 1985). Regarding cholinergic neurotransmission, the relationship between changes in choline-containing coumpounds signal from hippocampus have been shown to be altered by ECT (Ende et *al*., 2000). The evidence of enhancement of serotonin transmission induced by ECT in the human central nervous system is not well known (Mann, 1998). In the most recent study, ECT in humans has not been found to induce an increase in the sensitivity of post-synaptic 5-HT_{1A} receptors in the hypothalamus (Shapira et *al*., 2000). 5-HT_{1A}-receptor sensitization induces a decrease in the number of 5-HT_{2A} receptors that are found to be elevated in depressive patients (Soares and Mann, 1997). Furthermore, a clinically successful ECT has found to be associated with changes in vascular perfusion and GABAergic neurotransmission (Mervaala et *al*., 2001). On the other hand, Krystal and Weiner (1999) point out that the anterior EEG slowing is not a categorical marker for therapeutic ECT but may actually reflect some other type of neuronal process, e.g. an increase in neurotrophic factor or a change in function of cortical-subcortical circuits, which is linked to clinical improvement. Subcortical involvement with ECT is based on both indirect and direct measures. As an indirect measure, ECT has found to accelerate heart rate

and raise blood pressure (see Abrams, 1997). As more direct measures, ECT has been found to have an effect on neurohormones (Sattin, 1999; Sundblom et *al*., 1999), on human thalamus as reflected in MRI T_2 relaxation times (Diehl et *al*., 1994) and on human hippocampus as reflected in choline-containing coumpounds by MRS (Ende et *al*., 2000).

During the seizures, using single photon emission tomography (SPECT) and blood-flow tracers, it has been found that ECT increases regional cerebral blood flow (rCBF) (Bolwig et *al*., 1977). The findings regarding interictal rCBF are not uniform; both reductions (Silfverskiöld et *al*., 1987; Nobler et *al*., 1994) and increases (Bonne et *al*., 1996; Bonne and Krausz, 1997) has been observed. Furthermore, the efficacy of ECT treatment has been reported to be associated both with a reduction, (Nobler et *al*., 1994) or an increase (Petracca et *al*., 1995; Bonne et *al*., 1996; Bonne and Krausz, 1997) of postictal rCBF. In positron photon emission tomography (PET) studies, the findings 24 hours after last ECT on regional cerebral metabolic rate for glucose (rCMRglu) have been negative (Volkov et *al*., 1988; Guze et *al*., 1991). ECT has been found to decrease the rCMRglu during the week after ECT (Nobler et *al*., 2000), or to have no effect on the rCMRglu after a one weeks follow-up period (Yatham et *al*., 2000).

Seizure threshold. The term seizure threshold (ST) refers to the minimum instrument setting (dose) required to induce a generalized seizure (see Royal College of Psychiatrist, 1995; see APA, 2001). Seizure threshold is affected by many factors affecting electrical impedance, and the excitability of brain neurons (**Table 2**). It is generally accepted that the most useful and valid measure of seizure theshold is in units of charge [coulomb, C = current (amperes, A) x time (seconds, s)] (see APA, 1990; see Royal College of Psychiatrist, 1995; see Abrams, 1997; see APA, 2001), but seizure threshold may also be described in units of energy (Joules, J), stimulus intensity (mC/s), voltage (volts/V) or current (milliampers, mA).

Table 2. Factors affecting seizure threshold level

Factor	Effect	References
Age (increasing)	Raise	Sackeim et *al*., 1987a, b and c; Coffey et *al*., 1995a
Anesthetic medication (increasing dose)	Raise	see e.g. APA, 2001
Anticonvulsants	Raise	see e.g. APA, 2001
AD medication	Lower / No effect / Raise	Warrington, 1992 / Boyer and Feighner, 1992 / Watanabe et *al*., 1998
β-blockers	Raise ?	see e.g. APA, 2001
Benzodiazepines	Raise? / No-effect	see e.g. APA, 2001 / Boylan et *al*., 2000
Brain region: frontal / limbic strutures	High /low	Sackeim, 1994
Caffeine (pretreatment given iv.)	No effect	McCall et al., 1993a
Dehydration	Raise ?	see e.g. Royal College of Psychiatrists, 1995.
ECT-dynamic impedance (increasing)	Lower	Sackeim et *al*., 1994; Coffey et *al*., 1995a
ECT- increasing number of treatments	Raise	Sackeim et *al*., 1987a, Coffey et *al*., 1995b
ECT-previous course within last month	Raise ?	see e.g. Royal College of Psychiatrists, 1995
ECT-electrode contact with scalp (poor)	Raise	see e.g. APA, 2001
ECT-electrode placement (bilateral vs. unilateral)	High vs. low	Sackeim et *al*., 1987a, Coffey et *a*l., 1995a
ECT-stimulus pulse width (short vs. long)	Lower	Swartz and Manly, 2000
Hyperventilation (low carbon dioxide saturation)	Lower ?	see e.g. Royal College of Psychiatrists, 1995.
Neuroleptic medication	Lower	Coffey et. *al*., 1995a; Minabe et *al*., 1998; Woolley and Smith, 2001
Oxygen saturation of blood (low)	Raise ?	see e.g. Royal College of Psychiatrists, 1995.
Sex: male / female	Raise / lower	Sackeim et *al*., 1987a, Coffey et *al*., 1995a
Differences in thickness, anatomy, and resistance of the skull	Individual	Sackeim et *al*., 1994
Theophyllin	Lower ?	see e.g. Royal College of Psychiatrists, 1995

Regardless of how ST is defined, it is important to recognize that it is not absolute. The level for BT ST level has shown range from 25 mC to 800 mC or more and that for RUL ST level from 25 mC to 300 mC (Sackeim et *al*., 1991).

Although the biological counterpart of the individual ST is not well known, there is evidence that ST may be a modulator of the effects of electrical stimulation on both clinical outcome

(Sackeim et *al*., 1993; Sackeim et *al*., 2000a) and neural tissue (Sackeim et *al*., 1996). Changes in appearance of frontal EEG slow-wave activity corresponding to the efficacy of ECT have been found to be dose-dependent relative to the seizure threshold level (Sackeim et *al*., 1996). Regarding prolactin response, a moderate dose (3 times ST-level) RUL ECT stimulation has been found to cause a larger prolactin response than low threshold-level treatment (Zis et *al*., 1993).

Relationship between seizure duration and seizure threshold. In ECT, seizure duration is not a direct measure of a seizure threshold. For example, a decrease in the duration of seizures have been found in patients receiving BZD medication (Pettinati et *al*., 1990) but the effects of BZDs may be more complicated towards ST (Sackeim et *al*., 1991; Boylan et *al*., 2000). On the other hand, seizure duration at the first ECT treatment has been found to be inversely related to RUL and BT ST levels (Sackeim et *al*., 1987c; Sackeim et *al*., 1991; Coffey et *al*., 1995a). The relationship between seizure duration and initial ST level has not yet been studied in BF ECT.

Neurophysiological aspects in mechanisms of ECT-induced cognitive side-effects. There are some findings that suggest different mechanisms for the ECT-induced beneficial effects and cognitive side-effects. It has been suggested that ECT-induced memory impairment is to a large extent a direct effect of the electrical stimulus and not to the seizure in mediating the beneficial effects (Ottosson, 1960). On the other hand, Sackeim et *al*. (2000b) have suggested that the neural system subserving the therapeutic and adverse cognitive side-effects of ECT are distinct. The ECT-induced memory dysfunction has been suggested to result from neuronal insults due to excessive release of excitatory amino acids and activation of their receptors (Chamberlin and Tsai, 1998).

2.2.4. Efficacy of ECT as shown by different types of studies

The efficacy of ECT in major depression has been shown in open trials (see APA, 2001), in ECT vs. medication comparisons, in ECT vs. sham ECT studies, and in ECT technique studies.

ECT vs. sham ECT studies. It has been shown that real ECT has a better outcome as compared with treatment with anesthesia but without electrical stimulus, i.e. sham ECT in all (Freeman et *al*., 1978; Johnstone et *al*., 1980; West, 1981; Brandon et *al*., 1984; Gregory et *al*., 1985) but one study (Lambourn and Gill, 1978). In the study of Lambourn and Gill (1978), brief-pulse unilateral ECT was not better than sham ECT.

ECT vs. medication comparisons. ECT has found to be a more effective treatment than AD medication in mixed age and geriatric populations (Avery and Lubrano, 1979). In the meta-analysis of Janicak et *al*. (1985), it is reported an average response rate to ECT that was 20% higher than that of TCAs and 45% higher than that of MAOIs. Markowiz et *al*. (1987) have shown that depressed patients given ECT had mean hospital stays that were 13 days shorter than those given AD medication. On the other hand, Piper (1993) consideres that the data on outcome between ECT and TCA medication is inadequate to support the claim that one treatment is superior to the other because of numerous methodological weaknesses in the studies. Later, in a comparison of elderly depressed patients treated with ECT or pharmacotherapy, Philibert et *al.* (1995) have found higher rates of mortality and significant depressive symptoms in the pharmacotherapy group after a long-term follow-up.

Furthermore, ECT has found to be superior to paroxetine in medication-resistant major depression in terms of both degree and speed of response (Folkerts et *al.*, 1997).

ECT technique studies. The outcome of ECT in the treatment of depression has been found to be highly dependent on the ECT technique used **(Table 3)**.

Table 3. Outcome of the recent ECT studies in depression

ECT stimulus dosing method	Response	Reference
BT, at 50% above ST	87 % for study completers	Petrides et *al*., 2001
BF and BT, 1.5 times ST level	Equal efficacy, BF induced less global cognitive impairment	Bailine et *al*., 2000
RUL at 50%, 150% and 500% at above ST. BT at 150 % above ST.	65 % for both RUL at 500% above ST and BT at 150% above ST	Sackeim et *al*., 2000a
RUL at 2.25 times ST, and RUL at a fixed high dose (403 mC)	67% for fixed high dose and 39% for RUL 2.25	McCall et *al*., 2000a
RUL at 2.5 ST	Response rate 31%	Ng et *al*., 2000
RUL ECT at 2.25 times ST and FHDM (403 mC)	The FHDM resulted in a faster response.	McCall et *al*., 1995
Low dose RUL, BT, and BF ECT. No DTM.	BF ECT was superior to both BT and RUL ECT.	Letemendia et *al.*, 1993
RUL ECT and BT ECT, both dosed both at just above ST level and at 2.5 times the ST level	The response rate for low-dose RUL was 17% as compared with 43% for RUL at 2.5 the ST level, and 65 % for high-dose BT and 63% for low-dose BT.	Sackeim et *al*., 1993
FHDM (378 mC) for RUL and BT ECT	No significant difference between RUL and BT ECT, although there was a trend for faster improvement with BT ECT.	Abrams et *al*., 1991
Low-dose (relative to the initial ST level) BT and RUL ECT	BT was markedly superior in short-term symptom reduction.	Sackeim et *al*., 1987b

The selection criteria for depression-efficacy studies using ECT may have caused a major bias (McCall et *al*., 2000b). Most of the depressive patients treated in clinical practices are not included to those studies. On the other hand, a comparison between BF ECT and adequate doses of RUL ECT has not been carried out. BF ECT has been shown to spare both verbal and nonverbal cognitive functions better than RUL ECT treatment if the stimulus is dosed just above individual seizure threshold (Lawson et *al.*, 1990; Letemendia et *al*., 1993). The ST level RUL ECT which has been used as a comparison group for BF ECT has shown to have a poor outcome in the treatment of major depression (Sackeim et *al*., 1993).

2.2.5. Side-effects and contraindications

ECT is generally a safe treatment. Cognitive and cardiovascular side-effects are the most important ones. Although no absolute contraindication exists for ECT (see APA, 2001), the risk/benefit analysis must be done especially carefully with patients who may have increased intracranial pressure, or recent myocardial infarction.

Brain damage. Structural brain imaging and postmortem neuropathologic studies provide no evidence that ECT produces brain damage (Coffey 1991 et *al*.; Coffey, 1994; Devanand et *al*., 1994). A classic amnestic syndrome involving anterograde and retrograde amnesia implicates a dysfunction in medial temporal lobe structures, especially the hippocampus (Squire, 1986; Sackeim et *al*., 1992; Sobin et *al*., 1995). ECT is not likely to induce hippocampal atrophy or cell death, which could be reflected in the *N*-acetylaspartame signal (Ende et *al*., 2000). On the other hand, measurement of magnetic resonance imaging T_2 relaxation times have been found to be increased in the thalamus after ECT (Diehl et *al*.,

1994). The increased T_2 relaxation times reflect increase in brain water content perhaps secondary to a breakdown of the blood-brain barrier. This process may be related to the memory impairment following ECT.

Cognitive side-effects. ECT is associated with a transient postictal confusional state and with a longer period of anterograde and retrograde memory interference (see Abrams, 1997). The anterograde memory impairment, involving rapid forgetting of newly learned material, typically resolves in a few weeks after cessation of treatment (Stoudemire et *al*., 1995). Some degree of retrograde amnesia, involving loss of memory for information learned before ECT, may be long-lasting, particularly for recent memories, at least for patients receiving bilateral ECT (Weiner et *al*., 1986; McElhiney et *al*., 1995; see Abrams, 1997). Patients occasionally report more pervasive and persistent cognitive disruption, the basis of which is uncertain (Squire and Slater, 1983; Squire, 1986). The effects of ECT on non-memory cognitive side-effects are not well studied. In most cases, cognitive functioning after recovery from the acute effects of ECT becomes better than prior to ECT (Krueger et *al*., 1992; Calev et *al*., 1995; Brodaty et *al*., 2001). This may be due to recovery from the cognitive impairment caused by the depression. Brodaty et *al.* (2001) suggest that that mechanism is present even in elderly patients, i.e. for old (≥ 65 years) and for very old (≥ 75 years) patients.
Squire and Zouzounis (1986) have suggested that the advantage of brief-pulse ECT on memory function in clinical practice is probably achieved only if treatment is dosed close to the individual seizure threshold. More recently, Sackeim et *al.* (1993) have shown that RUL ECT treatment with stimuli dosed at 2.5 times the seizure threshold level compared with that to threshold-level treatment induces a longer immediate disorientation phase, which increases the risk of retrograde amnesia following ECT (Sobin et *al*., 1995). On the other hand, according to Abrams (2002) there is no clear evidence in the literature that some long-term cognitive side-effects persist after brief-pulse ECT.

Mortality. When mortality occurs with ECT, it typically happens immediately after the seizure or during the posictal period. The rate of mortality is estimated to be approximately the same as that associated with minor surgery (see APA, 2001). Published estimates from large and diverse patient series over several decades report up to 4 deaths per 100000 treatments (see APA, 2001). Regarding longitudinal follow-up studies, some evidence has shown that mortality rates following hospitalization are lower among depressed patients who received ECT than among patients who received other treatment modalities or no treatment at all (Avery and Winokur, 1976; Philibert et *al*., 1995) although there is also a report that found no advantage for ECT (Black et *al*., 1989).

Cardiovascular complications. ECT may cause a variety of cardiovascular complications including cardiac arrest, arrhytmias, ischemias, hypertension, and hypotension (Dec et *al*., 1985; see APA, 2001). Cardiovascular complications are the most common cause of medical morbidity and mortality with ECT in those presenting cardiovascular disease (Zielenski et *al*., 1993). Myocardial ischemia can be produced by hemodynamic changes during ECT in 8% of patients not known to have preexisting cardiac dysfunction (Alexopoulos et *al*., 1984). 'Recent' myocardial infarction is believed to represent a risk for reinfarctation during ECT (see APA, 2001). The concept of 'recency' is, however, difficult to define. For example, the risks at six weeks after a mild myocardial infarction without adverse sequaele may be less than those present at six months after a severe, complicated infarction.

Prolonged apnoea. This is a rare condition accompanied with slow metabolism of succinylcholine (Packman et *al*., 1978).

Prolonged seizures. The lengths of seizures defined as prolonged ones, are those longer than 200 seconds (Coffey et *al*., 1995a), longer than 180 seconds (see APA, 2001), and longer than 120 seconds (Greenberg, 1985; see Royal College of Psychiatrists, 1995; see Abrams, 1997). Prolonged seizures may be harmful especially for brain function and therefore they should be terminated either with iv-bzd or with the anesthetic used (see APA, 2001). Fink (1993b) has suggested that up to 1% of induced seizures may be prolonged. Coffey et *al*. (1995a) have found that 7% of their patients had prolonged EEG seizures. The frequency of prolonged EEG seizures has reported to be nearly 18% in the study of Mayur et *al*. (1999). They conclude that there was a potential risk of missing prolonged EEG seizures in 6.4% of the patients if motor monitoring alone was used.

Tardive seizures. They are spontaneous seizures that occur within hours after ECT. This condition must be remembered in cases where the consciousness or vital functions of an ECT-patient are disturbed especially later on the treatment day (see APA, 2001).

Nonconvulsive status epilepticus. ECT may be accompanied with an abrupt onset of delirium, unresponsiveness or agitation (Solomons et *al*., 1998). If not detected, epileptic activity without motor manifestations may cause severe brain damage.

Cerebrovascular complications. ECT-induced cerebrovascular complications are notably rare (Hsiao et *al*., 1987).

Headache, muscle soreness and nausea. These are common, and short-lasting side-effects which are mainly treated by symptom-relieving agents (see APA, 2001).

Hypomanic switch. ECT may switch a depressive episode to hypomania or mania (see APA, 2001) in at most 4% of patients treated with ECT (Devanand et *al*., 1992).

ECT may cause also other side-effects which are reviewed e.g. by APA (2001).

2.2.6. Prediction of efficacy of ECT in depression

No reliable biological marker exists to predict efficacy of ECT (see Abrams, 1997). Therefore, prediction of outcome of ECT in depression is based on the technique of ECT intended to be used and on the clinical characteristics of depressed patients. However, no significant clinical predictors were found for 130 patients with unipolar major depressive disorder treated at a university teaching hospital in the study of Lam et *al*. (1999).

Age. Findings regarding the effects of age on short-term efficacy of ECT are inconsistent. Some studies have reported that advancing age can be used to predict good response to ECT (Black et *al*., 1993; Wesson et *al*., 1997; Tew et *al*., 1999; O'Connor et *al*., 2001) while other studies have not found this relationship (Brodaty et *al*., 2000), and other studies have found a more rapid response in younger patients (Shapira and Lerer, 1999).

Subtype of depression. ECT has found to be highly effective in major depressive disorder with psychotic features (Kantor et *al*., 1977; Pande et *al*., 1990; Petrides et *al*., 2001).

However, Sobin et *al*. (1996) found that the therapeutic advantage of effective forms of ECT was similar across the depression subtypes; patients who lacked both psychosis and retardation showed this pattern. Regarding melancholia, recent research (Sackeim and Rush, 1995; see APA, 2001) has not confirmed the previous finding that melancholic depression predicts a good response to ECT (Carney et *al*., 1965).

Duration of episode. A long duration of a current depressive episode has been shown to predict a diminished rate of ECT response (Black et *al*., 1993; Prudic et *al*., 1996).

Severity of depression. Patients with a less severe depression has found to have a poorer response to ECT (Hamilton and White, 1980).

Secondary depression. It has been shown that patients with secondary depression are less likely to recover from an index depressive episode (Coryell et *al*., 1985) and are more likely to receive inadequate treatment (Black et *al*., 1987) than patients with primary major depression. Moreover, patients with secondary depression have been found to have a poorer response to ECT treatment than patients with a primary depressive disorder (Davidson et *al*., 1980; Zorumski et *al*., 1986; Black et *al*., 1987; Black et *al*., 1993). Zorumski et *al*. (1986) found that patients with alcohol dependence and secondary depression had a favorable response to ECT. However, concurrent alcohol dependence diminishes the likelihood that depression will respond to treatment (Mueller et *al*., 1994).

Comorbid personality disorder. Patients with and patients without a personality disorder have been found to have similar short-term response to ECT (Zimmerman et *al*., 1986). On the other hand, depressed patients with borderline personality disorder may have a poorer outcome on some measures (DeBattista and Mueller, 2001). After a 6-month follow-up period, depressed patients with a personality disorder have been found to be more symptomatic (Zimmerman et *al*., 1986) although the acute phase of depression may have been effectively treated with ECT (DeBattista and Mueller, 2001).

Use of psychotropic medication during ECT. When patients take BZDs during a course of unilateral ECT, the maximum therapeutic response may be compromised (Pettinati et *al*., 1990). Combining ECT and antipsychotic agents may have synergistic effects (Klapheke, 1993). There is little known about the combined clinical effects of AD medication and ECT (Pritchett et *al*., 1993).

Resistance to antidepressant medication. Patients who had failed to respond to adequate pre-ECT pharmacotherapy have found to be substantially less likely to respond to ECT than patients who had not received adequate pharmacological trials before ECT (Prudic et *al*., 1990; Prudic et *al*., 1996). This relationship was not found in the study of Lam et *al*. (1999). In the most recent study, Huuhka et *al*. (2000) have found that only 56% of the highly selected treatment refractory patients with depressive disorders responded to ECT in 1997 in contrast to the fact that almost all unselected depressive patients in 1955 and 1964 benefited from ECT.

2.2.7. Prediction of adverse-effects of ECT in depression

Patients with preexisting cardiac illness, compromised pulmonary status, or medical complications after earlier courses of anesthesia or ECT are especially likely to be at

increased risk (Zielinski et *al*., 1993; see Abrams, 1997). Furthermore, patients with low baseline heart rates might be likely to show bradyarrhytmia during treatment (Swartz and Manly, 1999).

Patients vary considerably in the extent and severity of their cognitive side effects following ECT (see Abrams, 1997; Austin et *al*., 2001). Available information about the factors that contribute to the individual differences is limited (Pettinati and Rosenberg, 1984; Calev et *al*., 1989; Krueger et *al*., 1992; Austin et *al*., 2001).

Age. Elderly patients may be at greater risk for more persistent confusion and greater memory deficits during and after ECT treatment (see Abrams, 1997).

Global cognitive impairment prior to ECT. Among depressed patients without known neurologic disease or insult evidence has indicated that the extent of pre-ECT global cognitive impairment (as measured by MMSE scores) predicts the magnitude of retrograde amnesia for autobiographic information at long-term follow-up (see Abrams, 1997).

Concomitant medication. Lithium and high doses of anesthetic medications may exacerbate ECT-induced cognitive side-effects (see Abrams, 1997).

Post ECT disorientation. A longer immediate disorientation phase increases the risk of retrograde amnesia following ECT (Sobin et *al*., 1995).

Known brain abnormalities. MRI findings of basal ganglia lesions and severe white matter hyperintensities have been linked to the development of an ECT-induced delirium (Figiel et *al*., 1990).

ECT technique. Selection of ECT technique may increase vs. decrease the severity of adverse cognitive side effects, i.e use of sine wave vs. brief pulse stimulus waveform, use of BL vs. RUL electrode placement, use of grossly suprathreshold vs. low-dose stimulus intensity, spacing of treatments 3-5 times per week vs. to a fewer frequencies and use of multiple seizures per session vs. single seizure per session, respectively (see Abrams, 1997; see APA, 2001).

2.2.8. Prescription of ECT in depression

A decision to use of ECT should be based on a risk/benefit analysis for the specific patient. This analysis considers the diagnosis of the patient, and the severity of the presenting illness, the patients treatment history, the anticipated speed of action and efficacy of ECT, the medical risks and anticipated adverse effects, and the likely speed of action, efficacy and safety of alternative treatments (see APA, 2000). Although no absolute contraindication exists for ECT (see APA, 2001), the risk/benefit analysis must be done especially carefully with patients who may have increased intracranial pressure, or recent myocardial infarction.

Together with the risk/benefit analysis, concept of primary and secondary use of ECT should be considered according to recommendations by the APA (2001). Primary use of ECT, i.e. use of ECT prior to a trial of psychotropic agents, includes, but is not necessarily limited to, the following situations: where a need for rapid, definitive response exists on either medical or psychiatric grounds; or when the risks of other treatments outweigh the risks of ECT; or

when a history of poor drug response and/or good ECT response exists for previous episodes of the illness; or patient preference. The criteria for secondary use of ECT are as follows: In other situations, a trial of an alternative therapy should be considered prior to referral for ECT. Subsequent referral for ECT should be based on at least the following: treatment failure (taking into account issues such as choice of agent, dosage, and duration of trial, adverse effects which are unavoidable and which are deemed less likely and/or less severe with ECT, and deterioration of the patient's condition such that the criterion (where a need for rapid, definitive response exists on either medical or psychiatric grounds) is met. In clinical practice, indications for secondary use than those of primary use are more often met in the treatment of depressed patients with ECT.

Regarding use of ECT in special populations, ECT is a relatively safe and effective procedure in patients aged 75 or more (Gormley et *al*., 1998). Furthermore, ECT is a relatively safe and effective treatment during pregnancy if steps are taken to decrease potential risks (Miller, 1994). In young persons, there is limited information about use of ECT (Walter and Rey, 1999).

Regarding use of ECT in high-risk populations, ECT is an effective and relatively safe procedure when careful attention has been paid to each patient's medical and anesthesia needs (Rabheru, 2001). ECT is associated with a transient rise in intracranial pressure and blood-brain barrier permeability (see Abrams, 1997). For these reasons, patients with intracranial-space-occupying lesions, evidence of increased intracranial pressure or cerebrovascular fragility, e.g., unstable vascular aneurysm, are at substantially greater risk and should only receive ECT after careful general medical, neurological, or neurosurgical evaluation (Krystal and Coffey, 1997; see, APA 2001). Other high-risk-patients may be those with recent myocardial infarction, recent intracranial hemorrhage, retinal detachment, pheochromocytoma and an American Society of Anesthesiologists (ASA) level 4, i.e. a patient with an incapacitating systemic disease that is a constant threat to life or level 5, i.e. a moribund patient not expected to survive 24 hours with or without operation, ratings.
There are many case reports showing the safety of ECT in high risk patients such as patients with a recurrent brain tumor (Kohler and Burock, 2001), with a metallic skull plate (Madan and Anderson, 2001), and with an automatic internal cardioverter-defibrillator (Lapid et *al*., 2001).

Pre-ECT evaluation. ECT treatment should be carried out according to the principles of the informed consent procedure (see APA, 2001). In order to reduce the fears against of ECT, the patient should have the possibility to visit the treating room and the personnel of the ECT treatment team. Furthermore, appropriate laboratory tests and physical examinations plus specialist consultations needed should be carried out according to the latest recommendations (see Royal College of Psychiatrists, 1995; see APA, 2001).

Anesthesia for ECT. To prevent harmful effects of seizure on musculoskeletal and cardiovascular systems, the patients are given muscle relaxants (see APA, 2001). Succinylcholine is the most used agent. The use of a relaxant necessitates the use of an anesthetic. Methohexital, a short-acting barbiturate, has been the drug of choice over the last few decades. Methohextial is no longer manufactured and thiopenthone and propofol have replaced it. The seizures during propofol anesthesia are shorter than during methohexital (Swartz, 1992; Malsch et *al*., 1994; Martensson et *al*., 1994), and etomidate anesthesia (Stadtland et *al*., 2002). However, the reduction in seizure duration using propfol anestehesia

has not shown to impair the outcome of ECT treatment (Malsch, 1994; Martensson et *al*., 1994). In addition to relaxant and anesthetic, an anticholinergic (atropine or glycopyrrolate) is often used for ECT anesthesia. The application of an electrical stimulus results in vagal stimulation regardless of whether a seizure is induced. This parasymphatetic discharge almost invariably results in decreased heart rate unless patients are premedicated with an anticholinergic agent (see Abrams, 1997). Seizure induction produces a sympathetic conversion from bradycardia. However, for various reasons, subconvulsive stimulation with increased risk to asystole can happen at any time during ECT. Beta-blockers by unopposing the parasympathetic discharge induced by ECT may increase the risk to asystole (McCall, 1996). Oxygenation is recommended prior, during and after the ECT to prevent any harmful effects of ECT (see APA, 2001).

ECT devices. Modern ECT devices deliver a bi-directional square wave brief-pulse stimuli and are equipped with EEG and ECG monitoring (see Royal College of Psychiatrists, 1995; see APA, 2001). The decision how the device is used for the treatment of patients, should be decided by the treating physician based on the clinical status of the patient.

Electrode placement / stimulus intensity. The combination of electrode placement and stimulus intensity is the most important technical factor in treatment with ECT. Since the two cannot be separated in discussions of efficacy and cognition, they are essentially one topic (see APA, 2001). BT ECT may predispose to long-lasting cognitive side-effects. However, when a rapid effect of ECT is necessary, the BT ECT may be the optimal choice also today (see APA, 2001). In other cases, RUL ECT has been recommended since 1990 (see APA, 1990). RUL ECT at a moderate dose (100-200%) above seizure threshold (ST) has been often used as the initial standard treatment based on the previous recommendations (see APA, 1990; see Royal College of Psychiatrists, 1995). On the other hand, Sackeim et *al*., (1993) have found that RUL ECT at the threshold-level dose has an extremely poor efficacy. Increasing the dose to 2.5 the seizure threshold level increases the efficacy of the RUL ECT, although not to the level of the BT ECT. In the most recent study of Sackeim et *al*. (2000a), high-dose RUL (6 times ST level) was as effective as BT ECT. BF stimulus has been shown to spare both verbal and nonverbal cognitive functions better than BT and RUL ECT treatment if the stimulus is dosed just above the individual seizure threshold (Lawson et *al*., 1990). However, the place of BF ECT in the treatment of depressive patients has not yet been established.

The initial ECT stimulus dose can be chosen using two alternative methods. Firstly, the ECT dose can be given individually as obtained by a dose titration method (DTM) (see e.g. Sackeim et *al*., 1987a) by which the individual seizure threshold is measured. Secondly, one can use a method of predetermined dose, e.g. a fixed high dose method for RUL ECT treatment (Abrams et *al*., 1991), or a dose based on parameters which have some relationship with the seizure threshold level, e.g. the age of the patient (see Abrams, 1997). Age-based dosing has two clinical applications. In the age method (AM), the dose (mC) equals the age (years) of the patient multiplied by 5.0 (Swartz and Abrams, 1994), and in the half-age method (HAM) the dose (mC) equals the age (years) of the patient multiplied by 2.5 (Petrides and Fink 1996). Unilateral ECT is more dose sensitive than BT ECT (see APA, 2001). In routine clinical BT ECT practice, Gangadhar et *al*. (1998) have suggested that the ‘formula’ method using age alone may be appropriate.

There is an ongoing debate on whether to use the DTM or the method of predertimened dose. Those who are for the DTM, emphasize the value of individual dosing. Those who are against the DTM, consider that the DTM is a technically difficult method, the DTM may be an unreliable method because many factors affect ST level, and subconvulsive stimuli, which are a part of the DTM method, may be accompanied with cardiovascular or cognitive side-effects (see Royal College of Psychiatrists, 1995; see Abrams, 1997; see APA, 2001). In the recent studies, subconvulsive stimulation has not been found to induce any adverse cognitive (Prudic et al., 1994) or severe cardiovascular consequences (McCall et al., 1994).

Monitoring the ECT seizure. Monitoring seizure activity is done routinely by modern ECT devices. EEG directly measures the brains electrical activity and therefore, it has suggested that EEG is the standard against which other techniques must be measured (see Abrams 1997; Mayur et *al*., 1999). Furthermore, prolonged and tardive seizures may not be accompanied with motor manifestations (Parker et *al*., 2001). On the other hand, interpretation of EEG requires experience and education. EEG may be sensitive to different artifacts. Furthermore, EEG amplitude may decrease gradually rather than abruptly, and then it is difficult to determine exactly when the seizure ends. In these cases, the practitioner will need to rely on clinical signs (resumption of spontaneous breathing, and return to baseline heart rate) to know that the seizure is over. If low ECT stimuli are used, it is possible that there exist no recordable EEG seizure activity. This may be due to the low EEG seizure regularity at the ST-level (Krystal et *al*., 1993; McCall, 1998). In cases of low seizure regularity, the individual waves may bear no resemblance to their immediate neighbours.

Motor seizure monitoring can be done by direct visual observation or by inflating a blood pressure cuff above the peak systolic pressure to block of distribution of relaxant to a distal part of the limb in order to see an unmodified seizure (see Royal College of Psychiatrists, 1995; see APA, 2001).

Modern ECT practice includes both EEG and motor seizure monitoring methods.
In addition, seizure duration can be estimated using ECG. ECT-induced tachycardia has been found to be highly correlated with both motor and EEG seizure estimates (Larson et *al*., 1984).

Frequency of treatments. ECT is typically administered three times weekly; less frequent administration has been associated with less cognitive impairment but also a prolonged period until onset of action (Lerer et *al*., 1995; Shapira et *al*., 1998; see APA, 2001). The change between the two methods can be done based on the clinical status of the patient.

ECT and concurrent medication. Because of a lack of controlled studies, the clinician often has to make decisions based solely on clinical needs. It is often necessary to provide symptomatic relief against anxiety at least until the therapeutic effects of ECT are manifest. There is a standard recommendation that BZD's are to be avoided in patients receiving ECT (see APA, 1990). Concomitant use of BZDs and ECT may lessen the efficacy of treatment (Ottosson, 1960; Standish-Barry et *al*., 1985; Greenberg and Pettinati, 1993). The maximum therapeutic response may be compromised especially during a course of unilateral ECT (Pettinati et *al*., 1990). However, the empiric data on the impaired efficacy with BZD and ECT is weak (Sackeim et *al*., 1991), and there is some evidence that depressed patients with marked anxiety may, in any case, have a poorer rate of ECT response (Pande et *al*., 1990). If BZDs are used, the preferred agent is lorazepam in doses up to 3 mg/day with a minimum

duration of between 8 to 12 hours between the last administration of medication and ECT administration (Sackeim et *al*., 1991).
Combining ECT and antipsychotic agents may have synergistic effects (Klapheke, 1993).
The 1990 APA report cautioned against concomitant use of AD medication and ECT. However, there is in general little known about the combined clinical effects of ADs and ECT (Pritchett et *al*., 1993) but also little is known about the synergistic effects between AD medication and ECT (Nelson and Benjamin, 1989; Lauritzen et *al*., 1996). In one male patient, the combined use of venlafaxine and ECT has been found to cause a prolonged bradycardia (Agelink et *al*., 1998) whereas Bernando et *al*. (2000) have found that combined venlafaxine and ECT appears to be safe. For patients with severe and recurrent mood disorder, complete discontinuation of lithium may not be advisable (APA, 2001). The decision to continue lithium during ECT should be made on a case-by-case basis. It is possible that the risk of neurotoxity increases at higher serum lithium levels and that it might be reduced by keeping lithium levels in the low-to-moderate therapeutic range.

Continuation / maintenance ECT. High relapse rates after ECT are perhaps the biggest problem of the ECT practice (Sackeim et *al*., 2001). Petrides et *al*. (1994) have found that in psychotic depression, about 42 percent of the patients had a relapse of depression during a one year follow-up period. In the most recent study by Sackeim et *al.* (2001) it was found that without active treatment, virtually all remitted patients relapse within 6 months of stopping ECT. High relapse rates are not surprising given that most patients are medication resistant, and ECT is usually withdrawn at the moment it becomes effective (McCall, 2001). Although continuation/maintenance ECT is an option in preventing relapse, it may not be a practical solution for persons still in their productive years, and it is resource-intensive (McCall, 2001). The strategies regarding continuation/maintenance ECT clearly need future studies (see APA, 2001; Sackeim et *al.*, 2001).

3. AIMS OF THE STUDY

The general aim of this thesis was to study neurophysiological changes and clinical outcome in depressed patients receiving either RUL or BF ECT. BF ECT is an experimental ECT technique which has so far found to have a low cognitive risk/benefit ratio. The mechanism of action of ECT is still not fully understood but recent EEG data indicate that ECT-induced changes in terms of slow-wave activity over prefrontal lobes may play an essentially important role. Regarding ECT dosing, there is an ongoing debate on the optimal combination of the placement and dose of the stimulus. One central question concerns the value for estimating an individual seizure threshold, i.e. the use of the DTM, as compared using a method of a predetermined dose based e.g. on the age of the patients (age method, AM) or use of a fixed high-dose (FHDM) method. Furthermore, both clinical and neurophysiological aspects of the measured seizure threshold need to be studied more specifically. Unfortunately, recent ECT efficacy studies have excluded many groups of patients who are treated with ECT in clinical practice. Therefore, ECT research is clearly needeed in a pragmatic sample of depressive patients.

The specific aims of the studies (I-V) are as follows:

1. To study ECT-induced changes in the spontaneous MEG slow-wave activity (0.5-3 Hz and 3-7 Hz) both of the frontal and occipital cortex, and to study further, if the induced changes might have any relationship to the clinical outcome on the ECT treatment.

2. To study the relationship between initial seizure threshold and seizure duration in depressive patients for RUL and BF ECT.

3 To compare the DTM and the predetermined dose methods in terms of stimulus dose in relation to the initial seizure threshold for RUL and for BF ECT patients. Regarding predetermined dose methods, AM was used both for RUL and BF patients and FHDM only for RUL patients.

4 To compare the outcomes for low-dose BF ECT, high-dose RUL ECT, and moderate dose RUL ECT in patients with a pure major depression.

5 To study the effectiveness of RUL ECT in a pragmatic heterogeneous patient population as compared with that in patients with pure major depression.

4. PATIENTS AND METHODS

4.1. Study design

This prospective study was carried out between November 1994 and February 1997 in two phases, i.e. in a preliminary phase (from November 1994 to October 1995), and in a randomized phase (from October 1995 to February 1997). All the study patients were more than 20 years old and had been hospitalized because of depression at the Lapinlahti Hospital of the Department of Psychiatry of Helsinki University Central Hospital, and they gave their informed consent for the study. During the same time period, there were a total of 1655 hospitalizations at the Lapinlahti Hospital.

All ECT treatments were given or supervised by an ECT treatment unit (ECT-T-U). The ECT-T-U included two treating psychiatrists [Eila Sailas, and Pertti Heikman (P.H.)], an ECT treatment nurse (Inge Taskinen), and the anesthesiologists from the Intensive Care Unit of Helsinki University Central Hospital. Pre-ECT evaluation for standard short-term generalized anaesthesia was done for all the patients referred by the attending physicians to the ECT-T-unit. All study patients were stimulated using standard RUL and BF titration schedules (**Table 4.**).

Table 4. The dose titration schedules for RUL and BF ECT

	RUL stimulus					BF stimulus				
	Dose	**Current**	**Pulse width**	**Frequency**	**Duration**	**Dose**	**Current**	**Pulse width**	**Frequency**	**Duration**
	mC	A	ms	Hz	s	mC	A	ms	Hz	s
First level	25.2	0.9	1.0	30	0.47	50.4	0.9	1.0	30	0.93
Second level	50.4	0.9	1.0	30	0.93	100.8	0.9	1.0	30	1.87
Third level	75.6	0.9	1.0	30	1.4	151.2	0.9	1.0	50	1.68
Fourth level	100.8	0.9	1.0	30	1.87	201.6	0.9	1.0	50	2.24

The patient is stimulated using an increased stimulus dose with an interval about 30 s between the stimuli until she or he has a generalized ECT-induced epileptic discharge.
The seizure threshold is defined as the ECT stimulus which elicits a generalized convulsive activity lasting for at least 25 s.

All the clinical evaluations and the pre-ECT EEG recordings, pre-ECT MRI recordings and MEG recordings prior, during and after ECT were done blinded to ECT treatments.
The attending physicians completed a structured questionnaire formulated for the pre-ECT evaluation according to the recommendations of the APA (1990). This questionnaire was used during the whole study period as a referral (N = 140) to the ECT-T-U.
Fifty-eight patients were not recruited to the study. Twenty-three patients did not receive ECT: twelve patients refused to have ECT, four patients had present alcohol abuse, one patient had present abuse with BZDs, and six patients were in partial remission. Thirty-five patients were excluded: two patients did not give their consent to the study, five patients received outpatient ECT, one patient received BT ECT for schizophrenia, three patients were treated because of severe catatonia at the Meilahti hospital with BT ECT, one patient could not have methohexital anesthesia due to methohexital allergy, fourteen patients were not

stimulated with the standard RUL and BF ECT schedule (in five cases due to technical problems, in two cases due to a higher than the standard initial RUL dose and in seven cases due to a higher initial BF dose), six patients were treated with age based dosing, and three patients continued with their AD medication. Thus, 82 patients entered the study. DSM-IV diagnoses are based on the semi-structured clinical interviews made either by E.S. or P.H, always prior to ECT. The collection of psychiatric history included a symptom checklist for criteria of major depressive episode.

The psychotropic medication which had failed to achieve remission, was continued with stable doses during the entire ECT treatment course to eliminate the withdrawal effects of medication on the MEG signal. In studies II and III, psychotropic medication was either kept stable or reduced by the attending physician. For clinical studies IV and V, the antidepressant medication had to be discontinued beforehand. The minimum wash-out period was five days. For an antidepressant trial to be considered adequate in Studies IV-V, the threshold for sufficient duration was a minimum of 4 weeks at or above the threshold for the usual dosages of antidepressants (see APA, 2000).

The study protocol was approved by the Ethics Committee of the Department of Psychiatry of Helsinki University Central Hospital according to the principles of the Helsinki declaration.

4.2. Patients

All the 82 patients who entered the study fulfilled the inclusion and exclusion criteria for studies II and III as shown in **Table 5**.

Table 5. Inclusion and exclusion criteria to the Studies I - V

	Study I	Studies II and III	Study IV	Study V	
Time period used for inclusion the patients to Studies I-V (month/year)	6/95-6/96	11/94-2/97	10/95-2/97	10/95 -2/97	
Number of included patients	7	82	24	Group 1 16	Group 2 24
Inclusion criteria					
Age (years)	20-50	> 20	> 20	> 20	> 20
Major depressive episode	yes	not necessary	yes	yes	yes
Unipolar (U) / bipolar (B) depression	U	U and B	U and B	U and B	U and B
Severity of depression on MADRS or HDRS scale	MADRS >25	no limit	HDRS > 16	HDRS > 16	no limit
AD wash out at leat 5 days prior to ECT	No	not necessary[a]	yes	yes	yes
Exclusion criteria					
Previous ECT during a 6 or 3 months' period	6 months	3 months	3 months	3 months	3 months
Pre-ECT EEG recording (abnormal/normal)	abnormal	No criteria	no criteria	no criteria	no criteria
Pre-ECT MRI imaging (abnormal/no criteria)	abnormal	No criteria	no criteria	no criteria	no criteria
Lithium medication	yes	no	no	no	no
History of rapid-cycling bipolar illness[b]	yes	no	yes	yes	no
History of alcohol abuse during previous year	yes	no	yes	yes	no
History of schizophrenia	yes	no	yes	yes	no
History of schizoaffective disorder	yes	no	yes	yes	no
History of any other concurrent psychosis	yes	no	yes	yes	no
History of a severe medical illness	yes	no	yes	yes	no
History of a neurological illness	yes	no	yes	yes	no

[a] The AD medication was either stable or reduced by the attending physician.

[b] At least four mood episodes occur during the previous 12 months' period.

The selection criteria for studies I, IV and V are also shown in **Table 5**.
In Group 2 of Study V, four patients had had a mild major depressive episode, eight patients had a history of alcohol abuse during the previous year, six patients had a history of schizophrenia, schizoaffective disorder or another psychotic disorder which was not part of the mood disorder (four patients had psychotic disorder not otherwise specified, and two schizoaffective disorders), two patients had a history of a neurological illness (one patient had cerebellar ataxia, and the other ischemic cerebrovascular disease) and four patients had a history of a severe medical illness (three patients had hypertensive cardiovascular disease with concomitant risk factors: one had an aortic homograft, one a history of epilepsy, and one a risk for esophageal reflux, and one patient had coronary artery disease with coronary artery bypass grafting).

4.3. Technique of the ECT treatment

Prepare for ECT. Patients were given an opportunity to express their concerns and questions on ECT treatment to the attending physicians, psychiatric nurses, and the members of the ECT-T-U according to the recommendations by APA (2001). The patients were prepared for ECT treatments in the same way during the whole study period. The stimulation sites were cleansed with alcohol, wiped dry, and thereafter conductive gel (Hellige) was applied over the treatment surfaces of the stainless steel electrodes. The static impedance (skin-to-electrode contact) was measured before each treatment. The impedance was according to the recommendation of the THYMATRON-DGx manual (Swartz and Abrams, 1994) at least 100 and less than 3000 ohms prior to all stimulations.

Anaesthesia. ECT anesthesia included standard medication, i.e., atropine (0.4 mg), methohexital (0.75 mg/kg), and succinylcholine (0.5 mg/kg). All medications were given intravenously. The doses of medications were allowed to be adjusted individually on clinical grounds. The patients were oxygenated (100% O_2, 35% face mask), and their cardiovascular function (heart rate, and blood pressure) was monitored using a Cardiocap™ II anesthesia monitor (Datex).

Stimulus electrodes. For RUL ECT, a flat and a concave stimulus electrode, and for BF ECT, two concave stimulus electrodes, both hand held and ~5 cm in diameter, were used.

Electrode placements. In the RUL ECT, we used d'Elia ECT stimulus placement (d'Elia and Perris, 1970), whereas in the BF ECT, the midpoints of both electrodes were about 5 cm above the lateral angles of the orbits on both sides (Lawson et *al*., 1990; Letemendia et *al*., 1993).

Seizure threshold measurement. The initial ST level was defined as the ECT stimulus dose (mC) which elicited a generalized motor convulsive activity lasting for at least 25 s that could be observed by the ECT-T-U. The adjustment of the starting dose on the basis of electrode placement was based on the previous RUL (McCall et *al*., 1993b; Rasmussen et *al*., 1994) and BF (Letemendia et *al*., 1993) studies. The first stimulus (25.2 mC) in the RUL ECT group was the lowest stimulus level of the THYMATRON-DGx device, whereas the stimulus level in the BF ECT group (50.4 mC) was set to be lower than the standard initial dose (120 mC) used in the study by Letemendia et *al*. (1993). The schedules for the RUL and BF ECT were as follows: 25.2, 50.4, 75.6, and 100.8 mC for RUL ECT; 50.4, 100.8, 151.2,

and 201.6 mC for BF ECT (**Table 4**). The stimuli (pulse width 1 ms) were repeated at about 30 s intervals until the patient had a generalized (bilateral) motor convulsive activity lasting for at least 25 s. The motor seizure duration was measured by an ECT nurse using a stopwatch from the end of the stimulus to the end of the last clonic movement. The ST was defined as that ECT stimulus dose of the titration procedure which elicited such a seizure.

ECT was administered 3 times per week. In the second and subsequent treatments of study IV, the stimulus was dosed in the RUL ECT group either at five times the initial ST level (400% above the ST level, RUL ECT 5) or at 2.5 times the ST level (150% above the ST level, RUL ECT 2.5) and in the BF ECT treatment at the ST level (just above the ST level, BF ECT 1.0). For study V, RUL ECT 5 and RUL ECT 2.5 were used. The treatments were continued with fixed stimuli, making sure that the motor seizure duration exceeded 25 s. If the generalized motor seizure was shorter, the patient was restimulated after approximately 60 s with a 25% greater charge, and if no seizure occurred, restimulation was given after about 30 s.

ECT seizure monitoring. Our primary seizure monitoring method was direct visual observation of a motor seizure. One-channel THYMATRON EEG seizure monitoring was done with standard THYMATRON electrodes including measurement of seizure duration and also seizure quality measures, i.e. seizure energy index, seizure concordance index and postictal suppression index (Swartz and Abrams, 1994). Prior to each ECT treatment, the gain of the EEG channel was adjusted for each patient to obtain clearly visible recordings. Bifrontal linkage (Fp1-Fp2) was used in the preliminary phase, and right frontopolar (Fp2-FM1) linkage was used both in the preliminary and randomized phase. The other channel of the Thymatron device was used for EMG recording. Due to an insufficient number of reliable EMG registrations, we could not use the EMG data for statistical analyses.
Generally, the use of the cuff-method in motor seizure monitoring (Addersley and Hamilton, 1953) is recommended (see APA, 2001). However, for this thesis, direct motor seizure monitoring was used. The seizure threshold measurement with up to three restimulations may take a longer time than other treatments during the ECT treatment course. Therefore, the cuff-method may include the potential risk of a prolonged ischemic period. An additional side-effect with the cuff-method may be the risk for fractures in patient with osteoporosis. Furthermore, the benefit of using the cuff method is dependent on the dose of relaxant used. With a succinylcholine dose of 1.0 mg/kg or more, motor movements of the ECT-induced seizure are generally mild and may be altogether absent (Weiner et *al*., 1991). Such a high dose is indicated e.g. in patients with abdominal aortic aneurysm (Goumeniouk et *al*., 1990). Partial muscle paralysis achieved with succinylcholine doses of 0.5-1.0 mg/kg has been shown in general to allow for direct observation of motor seizures (Enns and Karvelas, 1995). Regarding absolute doses of succinylcholine, doses from 20 to 50 mg of succinylcholine have been found to give a safe degree of paralysis but still allow observation of the motor seizure (Letemendia et *al*., 1993). Furthermore, convulsive movements have been found in some cases to end later in other parts of the body than in the cuffed extremity (Barrington and Lambourn, 1987; Couture et *al*., 1988). ECT anesthesia for the Studies in this thesis included the standard low dose of succinylcholine (0.5 mg/kg). This dose was allowed to be adjusted individually on clinical grounds.

ECT device. The same square-wave, brief-pulse, constant current device (THYMATRON-DGx™, Somatics Inc., Lake Bluff, IL, U.S.A) was used for all patients.

4.4. Clinical evaluations

Attending physicians. The attending physicians evaluated under supervision by the senior physician the clinical status of the patients prior, during, and after the course of treatment. The ECT treatment course was finished (IV and V) when 1) a patient had two or fewer of the nine symptoms for DSM-IV major depressive episode A criteria, or 2) no further improvement occurred after two consecutive treatments during the courses of ECT.

Extra raters. Three extra raters (Irja Idman, Heikki Katila and Kristian Wahlbeck) evaluated the severity of a major depressive episode using the MADRS scale (I) and HDRS scale (IV and V) prior, during, and after the course of treatment. Interrater reliability between these three raters was tested thrice during the study.

The psychiatric nurses. The psychiatric nurses used MMSE scales (Folstein et *al*., 1975) for evaluation of the global cognitive functionig (IV and V).

4.5. EEG, MRI and MEG recordings

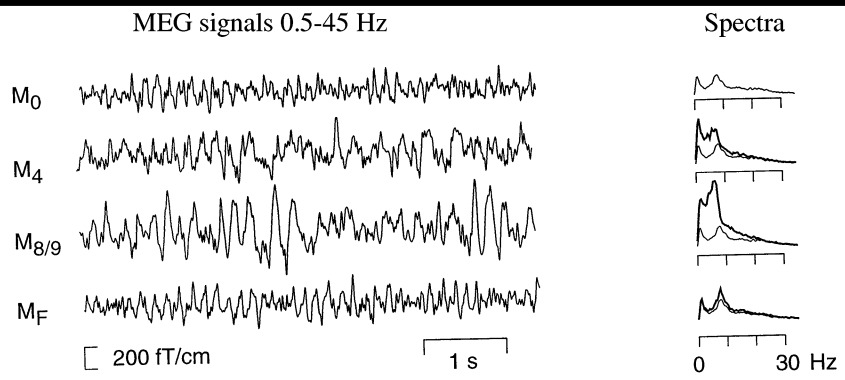
This thesis includes neurophysiological data for depressive patients on spontaneous brain activity (EEG and MEG) prior to ECT. ECT-induced EEG activity was recorded ictally, i.e. during seizures. Between treatment sessions and after the course of ECT treatment, spontaneous brain acitivity was recorded by MEG. We have not used measurements of evoked potentials or polysomnographic recordings.

A Siemens Magnetom SP 42 (Erlangen, Germany) was used to obtain the 1-Tesla magnetic resonance images (MRI) prior to ECT (I).

All MEG recordings (I) were performed in the magnetically shielded room of the Low Temperature Laboratory, Helsinki University of Technology. Magnetic spontaneous brain activity (0.5-45 Hz) was recorded with a whole-scalp neuromagnetometer (Neuromag-122™, Neuromag Ltd., Finland; Ahonen et *al*., 1993), which uses planar SQUID gradiometers coupling most strongly to the currents just below the recording site. We did not use a co-registering technique with MRI. Instead, MRI (I) was used to exclude structural abnormalities of the brain.

The 122 sensors of Neuromag-122™ are arranged in a helmet-shaped array, with two orthogonal sensors in each of the 61 measurement sites. Magnetic spontaneous cortical activity was measured for 4 min when the patient was relaxed with her eyes open and for 4 min with her eyes closed. The exact location of the subject's head with respect to the sensors was determined by measuring the magnetic signals produced by small currents delivered to three coils attached to the scalp. The locations of the coils with respect to the nasion and periauricular points were obtained with a 3-D digitizer. Frequency spectra at each sensor were calculated from 4-min recordings of spontaneous magnetic activity during the eyes-open period by advancing a 3.4 s time window in 1.7 s steps and averaging the spectra (**Figure 1**).

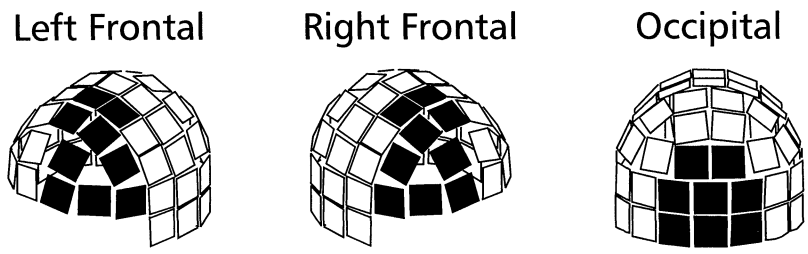
Figure 1. Spontaneous brain activity and corresponding spectra using MEG



The first measurement (M0) was done prior to the first ECT treatment and the next ones 24 to 48 hours after the fourth ECT treatment (M4), and the eighth or ninth treatment (M8/9). An additional fourth measurement was done for five patients (1, 4, 5, 6 and 7, see Table 8) after the one-month follow-up period (MF).

We compared the spectral magnitudes averaged for the left frontal (LF), and right frontal (RF) subregions, both consisting of 9 sensor pairs, and over the occipital subregion (O) of 8 sensor pairs (**Figure 2**). The mean spectral power was studied within 0.5-3 Hz (delta), and 3-7 Hz (theta) frequency bands. The frontal MEG activity was compared with the occipital activity (anteroposterior gradient) by dividing the frontal spectral amplitude by the amplitude of the occipital activity in the same frequency band. The left and right fronto-occipital ratios (LF/O, RF/O) were calculated separately.

Figure 2. The black rectangles of the measurement helmet show the Left Frontal, the Right Frontal and the Occipital subregions.



The spectral values (in fT/cm *vHz*) before treatment were used as the baseline (100%), and the percentage from the baseline level was calculated both for the subregions and the LF/O and the RF/O at M4, at M8/9, and at MF. Changes in the MADRS score were calculated as a decrease (%) from the pretreatment level at M4 and M8/9.
This thesis did not aim to study modulation of the spontaneous brain activity as measured by MEG.

4.6. Statistical analyses

In all studies, non-parametric tests were used if the variables were not normally distributed (Wilk-Shapiro-test). Other indications for non-parametric statistics are as follows: the values both for seizure threshold (II and III) and for the age-groups are more ordinal than continuous variables (III), the subgroup comparisons included small number of patients (III), and use of an estimate for the number of treatments (ENT) for patients who had markedly poor response to eight randomized ECT treatments and were therefore treated with the BT ECT (IV and V).
Randomization (IV and V) was done by computer (Medstat, version 2.12) using a block randomization (six patients per block). Assignment was concealed until administration of the first ECT treatment. For study IV, the patients were randomized to RUL 5, RUL 2.5, and BF 1. For Study V, after the patients were selected to Group 1 and Group 2, they were randomized to RUL 5, and RUL 2.5.

The results (Tables**)** are expressed as medians [(means), minumum -maximum value)].

Analyses in Study IV were done among study completers. In study V, analyses were performed from the intent-to-treat (ITT) sample using the last-observation-carried-forward (LOCF) method. For this analysis, we included both study completers and non-completers who had received at least one ECT treatment after randomization. For five patients, post-ECT HDRS scores were not available. For these patients, the HDRS ratings and number of randomized treatments were as follows: HDRS 4, six; HDRS 4, eight; HDRS 4, twelve; pre-ECT HDRS, one; pre-ECT HDRS, three. Regarding MMSE analysis, pre-ECT MMSE scores were not available for four patients. For three patients post-ECT MMSE scores were not available. The MMSE ratings and number of randomized treatments for these three patients were as follows: MMSE 4, eight; pre-ECT MMSE, three; MMSE 4, seven. As a sensitivity analysis, we also performed an analysis among study completers who had HDRS and MMSE ratings both prior and after the course of the randomized treatment.

All tests were two-tailed, and the statistical significance level was set at $\alpha = 0.05$. Statistical computations were performed with the BMDP New System (BMDP Statistical, Software, Inc, Los Angeles, California, 1994). Because of a lack of appropriate tests in the BMDP New System, we used for the confidence interval analysis the CIA (Software for Confidence Interval Analysis, BMJ 1989, London) (II), for the analysis of multiple comparisons of the Kruskal-Wallis test the BMDP Classic Release 7 (1993) (III and IV), for the comparison of nominal data with small cell frequencies Fisher-Freeman-Halton's exact test the StatXact (Cytel Software corp., Cambridge, MA, 1999) (Study IV), and for the ANCOVA the SPSS for Windows 10.0 (SPSS Inc., Chicago, USA) (V).

Two-group comparisons were made for nominal variables with Fisher's Exact Test (II and V), and with Fisher-Freeman-Halton's exact test (IV). For non-nominal variables, two-group comparisons were done with the two-tailed paired t-test (I), with the Mann-Whitney *U* test

(II, III, IV and V), with the independent sample t-test (V), and with the Analysis of covariance (ANCOVA)(V). Three-group comparisons were done with the Kruskall-Wallis test (III and IV). Correlations were done with simple linear regression (I) or with Spearman rank correlation (r_s) (II and III).

The main outcome measures of this thesis are shown in **Table 6**.

Table 6. Outcome measures of studies I-V

Outcome measure	Number of the study
ECT-induced change (%) in frontal and occipital MEG slow-wave activity	I
Relation between change in MEG slow-wave activity (%) and MADRS score (%)	I
Initial ST levels (mC) in RUL and BF ECT	II & III
Relation between seizure duration (s) and initial RUL ST and BF ST	II
Comparison between ECT dosing methods	III
Age (year) / ST (mC) ratio at different RUL ST and BF ST levels	III
A fixed high dose (378 mC) / ST ratio at different RUL ST levels	III
Comparison of number of treatments (ENTs) between BF ECT 1, RUL ECT 2.5 and RUL ECT 5	IV
Comparison of number of treatments (ENTs) between Group 1 and Group 2	V
Comparison of HDRS change (%) and number of responders between BF ECT 1, RUL ECT 2.5 and RUL ECT 5	IV
Comparison of HDRS change (%) and number of responders between Group 1 and Group 2	V
Change of ECT treatment randomized	IV and V
MMSE change (%)	IV and V
MMSE change negative	IV and V
Cognitive risk	IV and V
Cognitive risk and nonresponse	IV and V

The estimated number of treatment (ENT) was given a score of 14 (IV and V) because the maximal number of the randomized treatments was 13, determined on a clinical basis. Regarding the HDRS and MMSE ratings (IV and V), the scores prior to ECT treatment were used as the baseline values, and the percentage of change by the randomized treatments was calculated after the last treatment (HDRSL%, and MMSEL%, respectively). Patients were considered to have responded to treatment if they had scores of less than ten for their HRSDL ratings. Study V additionally provided that HDRSL% was at lest 60. On the other hand, the patients were considered to have a cognitive risk if they had any worsening in the MMSE total score, i.e., MMSEL% < 0. The possibility of concomitant occurrences of cognitive risk (yes/no) and nonresponse (yes/no) were calculated for all patients.

5. RESULTS

5.1. Patients and methods

The clinical data for study patients are shown in **Table 7**. One Study II and III patient participated also in Study I. Four study II and III patients were treated again during the study period and participated then in Study IV (two patients) and in Study V (two patients).

Table 7. The clinical characteristics of the study patients

	Study I	**Study II and III**	**Study IV**	**Study V**
Number of patients	N = 7	N = 80	N = 22	N = 40
RUL ECT/BF ECT	4/3	50/30	15/7	40/0
Age (years)	34.0 (35.1, 24-46)	48.0 (48.9, 24-77)	56.5 (56.0, 39-68)	52.0 (53.0, 28-77)
Sex (F/M)	6/1	53/27	13/9	25/15
Previous ECT (yes/no)	0/7[a]	23/57[b]	9/13[b]	12/28[b]
Psychotic features (yes/no)	2/5	18/62	4/18	5/35
Unipolar/bipolar depression	7/0	71/9	17/5	34/6
Duration of current episode (wk)[c]			23.0 (46.1, 5-104)	52.0 (54.3, 8-104)
MADRS (baseline)	31 (31.9, 22-42)			
HDRS (baseline)			27.5 (27.2, 16-40)	24.0 (25.3, 13.0-42.0)
MMSE (baseline)			27.0 (26.3, 19-30)	27.0 (27.2, 19-30)
Pre-ECT EEG (normal/abnormal)	7/0	63/7		
Use of BZDs the day prior to ECT (yes/no)		58/22		
Use of BZDs during the course of ECT (yes/no)	6/1			
Dose of lorazepam-equivalent during the ECT course (mg)			0.8 (1.0, 0.0-3.0)	0.8 (1.1, 0-3.0)
Use of neuroleptic medication the day prior to ECT (yes/no)		49/31		
Use of neuroleptic medication during the ECT course (yes/no)	5/2			
Dose of chlorpromazine during the ECT course			27.6 (64.9, 0.0-320.3)	19.2 (60.3, 0-320.3)
Dose of chloralhydrate during the ECT course			1.1 (1.1, 0.0-2.1)	1.0 (1.0. 0-2.1)
Use of ADs the day prior to ECT (yes/no)		21/59[d]		
Use of ADs during the ECT course (yes/no)	3/4			
Number of AD trials during the current episode			2.0 (2.1, 1-6)	2.0 (2.2, 1-7)
Prior adequate AD treatments (yes/no)			17/5[e]	34/6

[a] refers to a six months period; [b] refers to a three months period; [c] an upper limit of 104 weeks was used. [d] 14/16 for BF ECT and 7/43 for RUL ECT, p = 0.0032, [e] the number of prior adequate antidepressant treatment trials was different between RUL ECT 5, RUL ECT 2.5 and BF ECT (8/0 vs. 6/1 vs. 3/4, p = 0.022.
The patients (I-V) continued with their somatic medications prescribed prior to ECT.

The clinical and treatment parameters (II and III) were similar for the RUL and BF ECT groups except for the use of AD medication the day prior to the first ECT treatment. The BF ECT patients were more often on AD medication; nine patients were on SSRIs (three RUL and six BF patients), eight patients were on TCAs (three RUL patients and five BF patients), one BF patient had a combination of SSRI and TCA, and three patients were on moclobemide (one RUL and two BF patients). The number of prior adequate antidepressant treatment trials was different between RUL ECT 5, RUL ECT 2.5 and BF ECT (IV). The Group 1 patients (V) tended to be older ($t = 1.99$, $df = 38$, $P = 0.0539$), had higher baseline HDRS scores ($t = 2.74$, $df = 38$, $P = 0.0093$), and lower baseline MMSE scores ($P = 0.0053$) than Group 2 patients.

Clinical and ECT data for Study I are shown in **Table 8**.

Table 8. Clinical and ECT data of the ECT/MEG study (Study I)

Patient	1	2	3	4	5	6	7
Age (years)	28	41	46	34	24	44	29
Sex (M/F)	F	F	F	F	F	F	M
Use of BZDs (yes/no)	y	y	y	y	y	n	y
Use of neuroleptics (yes/no)	y	y	y	n	y	n	y
Use of ADs (yes/no)	n	y	y	n	y	n	n
ECT stimulus placement	RUL	BF	BF	RUL	BF	RUL	RUL
Initial seizure threshold (mC)	50.4	50.4	50.4	25.2	50.4	50.4	25.2
Charge (mC)[a]	204.4	82.8	81.0	114.8	53.2	219.0	100.8
Motor seizure duration (s) [a]	45	50	50	47	54	47	44
MADRS at M_0	42	36	31	30	33	29	22
MADRs at M_4	33	23	20	13	26	19	12
MADRS at $M_{8/9}$	6	26	11	6	4	18	8

[a] Averaged per treatment up to $M_{8/9.}$

Characteristics of treatment and seizure parameters for the first treatment session including the initial ST measurement (II and III) are shown in **Table 9**.

Table 9. Treatment and seizure parameters at the first ECT treatment (Studies II & III)

Atropine (mg) [a]	0.40 (0.42, 0.30-0.50)
Methohexital (mg) / body weight (kg) [a]	0.82 (0.90, 0.61-1.64)
Succinylcholine (mg) / body weight (kg) (N = 79) [a, b]	0.52 (0.57, 0.35 - 1.02)
Initial ST (mC) level	50.4 (63.3, 25.2-151.2)
RUL ST level (n = 50)	50.4 (49.9, 25.2-75.6)
BF ST level (n = 30)	100.8 (85.7, 50.4-151.2)
Number of subconvulsive stimuli (0/1/2/3)	21/48/11/0
Static impedance (Ω)[a, c]	1605.0 (1507.6, 320.0-2440.0)
Motor seizure duration (s)	53.0 (54.9, 30.0 - 95.0)
EEG seizure duration (s) (N = 74)	64.5 (67.9, 28.0 - 138)
Suppression index (N = 74)	82.5 (79.2, 30-97)

Due to non-randomization of the patients to RUL and BF ECT, no statistical comparisons were made between any of the seizure or seizure threshold measure between the two stimulus electrode placements.

[a]The differences between RUL and BF ECT were not statistically significant.

[b]One patient was excluded because of use of mivacurium (0.07 mg/kg iv dose) as muscle r elaxant.

[c]Refers to skin to electrode contact.

Treatment and seizure parameters during ECT course (IV and V) are shown in **Table 10.**

Table 10. Treatment and seizure parameters during the course of the ECT treatment (Studies IV and V)

	Study IV				Study V		
	Whole sample	RUL ECT 5	RUL ECT 2.5	BF ECT 1.0	Whole sample	Group 1	Group 2
RUL ECT 5 / RUL ECT 2.5	8/7				20/20	8/8	12/12
RUL ECT / BF ECT	15/7				40/0		
Initial ST level (mC)	50.4 (64.1, 25.2-151.2)	50.4 (53.5, 50.4-75.6)	50.4 (54.0, 25.2-75.6)	100.8 (86.4, 50.4-151.2)	50.4 (52.3, 25.2-75.6)	50.4 (55.1, 25.2-75.6)	50.4 (50.4, 25.2-75.6)
Charge (mC)	147.6 (185.6, 75.6-378.0)	252.0[a] (277.7, 252.0-378.0)	126.0 (146.1, 75.6-241.2)	120.4 (119.9, 100.8-151.2)	241.2 (208.0, 75.6-378.0)	241.2 (218.5, 75.6 -378.0)	191.5 (200.6, 75.6-378.0)
Duration of seizures, motor (s)	41.3 (41.5, 35.3-48.0)	38. 8 (40.1, 35.3-46.0)	43.6 (44.1, 41.1-48.0)	40.1 (40.7, 36.0-47.4)	43.2 (42.8, 28.7-56.4)	42.3 (41.1, 28.7-48.0)	43.5 (43.9, 32.3-56.4)
Duration of seizures, EEG (s)	51.3 (54.0, 37.3-141.4)	46.4 (58.6, 38.3-141.4)	55.9 (54.3, 43.8-59.3)	51.0 (48.4, 37.3-56.8)	50.8 (53.3, 28.0-141.4)	51.9 (54.8,28.0-141.3)	50.4 (52.3, 36.2-77.8)
Subconvulsive treatments, no. patients		1[b]	0	4			

Parameters except those for the intial seizure threshold refer to median (mean, minimum-maximum) values after the first treatment.

[a] $p = 0.0004$ (252 vs. 126 vs.120.4). RUL ECT 5 > RUL ECT 2.5, and RUL ECT 5 > BF ECT 1.0, $p < 0.05$.

[b] 1/7 vs. 0/7 vs. 4/3, $p = 0.044$.

5.2. Attrition

Of the included 82 patients, two BF patients (II and III) were excluded. The first one (a 54 year-old woman, P 1) had at the first subconvulsive stimulus a 20-s asystole which resolved spontaneously without complications. The patient was not restimulated. She had a history of hypertension treated with beta blockers, and prior to ECT, she had had doxepine withdrawal for six days. The second one (a 63 year-old woman, P 2) did not exhibit a clinical seizure of adequate duration even at the highest stimulation level.

Two patients (P 1 and P 3) out of 24 (8%) could not complete the Study IV and were considered to be dropouts. P3 (RUL ECT 2.5) was excluded after seven ECT treatments because of ventricular extrasystole.

Six out of 40 patients (15%)(V), one in Group 1 (P 3) (6%) and five (P4, P5, P 6, P 7 and P 8) in Group 2 (21%) were non-completers. In Group 2, one RUL ECT 5 patient (P 4) had to discontinue the course of the treatment after three treatments because of regurgitation of gastric contents, one RUL ECT 2.5 patient (P 5) after the first treatment because of a hypomanic switch, two RUL ECT 5 patients (P 6 and 7) after three treatments because of high elevations of blood-pressure, and one RUL ECT 2.5 (P 8) patient after three treatments

due to alcohol abuse. The decision to discontinue ECT treatment was made by the patient in one case, by the anesthetist in four cases, and by the attending physician in one case.

5.3. Neurophysiological aspects

Study I. The ECT-induced MEG changes are shown in **Table 11.** In LF, the ECT treatment did not induce any statistically significant MEG changes.

Table 11. The ECT-induced MEG slow-wave change (%)

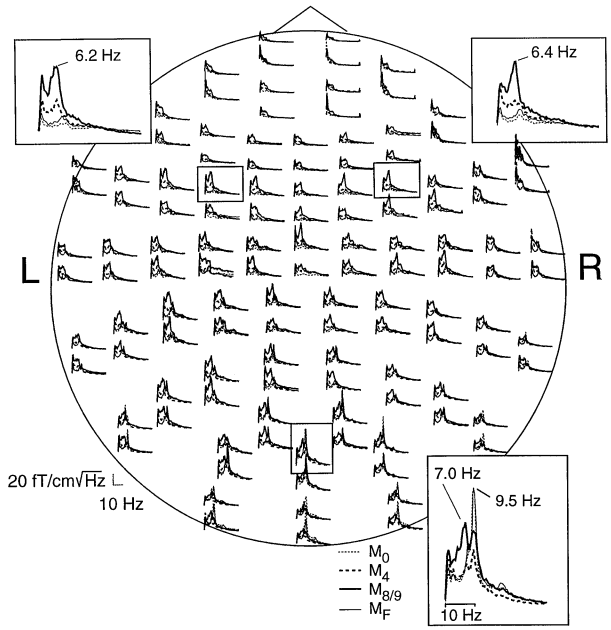
	M_4	$M_{8/9}$	M_F
LF	NS	NS	NS
RF	NS	theta range: 141.2 (179.7, 119.7-276.4) p = 0.018	NS
O	theta range: 129.3 (142.9, 84.0-210.6) p = 0.040 delta range: 130.7 (129.7, 89.7-163.8) p = 0.021	theta range: 165.1 (206.8, 85.2-423.4) p = 0.042	NS
LF/O	NS	NS	NS
RF/O	NS	NS	NS

NS, non significant, $p > 0.05$.
M_4 refers to time period 24 to 48 hours after the fourth ECT, $M_{8/9}$ refers to the same time period after eight or nine treatments, and M_F refers to the measurement after a one-month follow-up period.

Patient 4, displayed in **Figure 3**, showed the most prominent change after nine treatments in her theta activity in the LF (382%) and RF (276%) subregions. The change in O was 213%.

The increase was more prominent in the theta than in the delta band both at M4 (131.6 ± 44.4% vs 114.1 ± 40.1%, $p = 0.019$) and at M8/9 (179.7 ± 65.5% vs 130.7 ± 64.3%, $p = 0.026$) in RF. In other comparisons at M4, at M8/9, or at MF, there were no statistically significant differences between changes in theta and delta activities.

Figure 3. Whole-scalp spectral distribution (122 sensors) before ECT (M_0), and after 9 treatments ($M_{8/9}$) of patient 4. The nose points upwards, and the recording surface is flattened. L indicates the left side and R the right side of the head. The enlarged inserts from one sensor in the left and right frontal and in the occipital subregions show spectra also after 4 treatments (M_4) and after 1 month of ECT (M_F).



There was an inverse correlation between seizure duration measures (motor and EEG) and the ST level in the RUL ECT group (motor: r_s = -0.29, 95% CI, -0.53 to -0.017, p = 0.038; EEG, r_s = -0.29, 95% CI, -0.53 to -0.0030, p = 0.048) (II). However, the inverse correlation was not found in the BF ECT group (motor: r_s = -0.046, 95% CI, -0.40 to 0.32, p = 0.81; EEG: r_s = 0.061, 95% CI, -0.33 to 0.44, p = 0.76, respectively) (**Table 12**).

Table 12. Relation between initial seizure threshold level and seizure duration

Motor seizure duration (s)

RUL ECT				BF ECT			
	N	Median	Range		N	Median	Range
	50	57	30-95		30	48.5	32-73
Seizure threshold level (mC)				Seizure threshold level (mC)			
Low (25.2)	9	72	46-95	Low (50.4)	12	50	32-73
Moderate (50.4)	33	56	30-82	Moderate (100.8)	15	48	37-63
High (75.6)	8	53.5	37-67	High (151.2)	3	46	46-55
Very High (100.8)	0			Very high (201.6)	0		

EEG seizure duration (s)

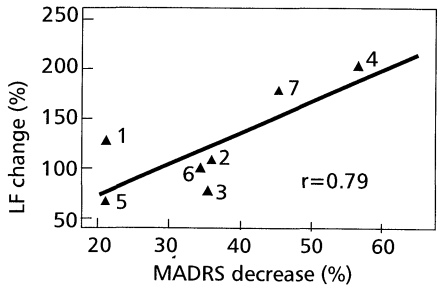
RUL ECT				BF ECT			
	N	Median	Range		N	Median	Range
	48	70	28-138		26	57.5	40-92
Seizure threshold level (mC)				Seizure threshold level (mC)			
Low (25.2)	8	90	62-135	Low (50.4)	10	53	40-92
Moderate (50.4)	33	65	28-110	Moderate (100.8)	13	58	44-86
High (75.6)	7	65	49-138	High (151.2)	3	57	50-72
Very High (100.8)		0		Very high (201.6)	0		

5.4. Clinical aspects

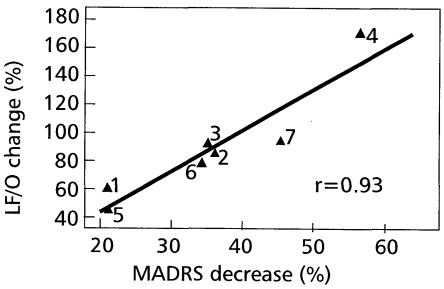
The mean (SD) MADRS scores both at M4 (20.0, 20.9, 12-33) and at M8/9 (8.0, 11.3, 4-26) decreased from the pretreatment level (31.0, 31.9, 22-42) (35.8 ± 12.6%, p = 0.0001 and 63.9 ± 23.4%, p = 0.0014 respectively) (I). The increase of theta activity in LF correlated positively with the decrease of the MADRS score (r = 0.79, p = 0.036, y = 3.2x + 8.0) at M4 (**Figure 4a**). The correlation was also significant between the LF/O change and in the MADRS score (r = 0.93, p = 0.0020, y = 2.9x -16.3) (**Figure 4b**). The RF theta change did not show any statistically significant relationship with the decrease in the MADRS score (r = 0.30) at M4, but the change in the RF/O correlated significantly with the decrease in the MADRS score (r = 0.82, p = 0.025, y = 1.3x + 46.6). Other correlations between changes in the MEG slow-wave activity and in the MADRS score were not statistically significant.

Figure 4. The correlation between the improvement in depression [decrease (%) of the Montgomery-Åsberg Depression Rating Scale (MADRS) score from the pretreatment level] and the change in the magnetoencephalography (MEG) activity [% from baseline level (100%)] after four treatments. Patient number given at individual data points refer to Table 8.

a. Correlation between the left frontal (LF) subregion and MADRS score reduction.



b. Correlation between the left frontooccipital (LF/O) ratio and MADRS score reduction. The LF/O indicates the MEG activity in the left frontal subregion divided by the activity in the occipital activity.



The number of patients (male/female) at the different seizure threshold levels were: 2/7 at 25.2 mC, 9/24 at 50,4 mC, 6/2 at 75,6 mC, and 0/0 at 100,8 mC in the RUL ECT group, and 3/9 at 50,4 mC, 6/9 at 100,8 mC, 1/2 at 151,2 mC, and 0/0 at 201,6 mC in the BF ECT group (III).

The correlation between the ST and the age was relatively poor both in the RUL ECT group (r_s = 0,31, p = 0.027, Spearman rank correlation), and in the BF ECT group (r_s = 0.35, p = 0.054) (**Table 13**). In the RUL ECT group, there was a significant correlation between the seizure threshold level and the age of the men (r_s = 0.64, p = 0.0061) whereas there was no correlation between the seizure threshold level and the age of the women (r_s = 0.098). In the BF ECT group, there was a tendency for inverse correlation between the ST level and the age of the men (r_s = - 0.47, p = 0.17), and a significant correlation between the ST level and age of the women (r_s = 0.59, p = 0.0064).

The age of patients tended to increase in relation to their ST levels both in the RUL ECT group (p = 0.081, Kruskal-Wallis test), and in the BF ECT group (p = 0.060) **(Table 13**). The age/ST ratio decreased relative to the ST level both in the RUL ECT group (p < 0.0001, Kruskal-Wallis test), and in the BF ECT group (p = 0.0005). Using multiple comparison for the Kruskal-Wallis test, the age/ST at the lowest ST level was higher than that at the second or third level both in the RUL ECT and in the BF ECT group. The age/ST at the second level was not different from the age/ST at the third level in the RUL ECT group, or in the BF ECT group. The FHDM/ST ratio was ≥ 5 in the RUL ECT group at all ST levels the highest level being 15 (**Table 13**).

Table 13. The relation of age-base dose and fixed high dose to the initial seizure threshold (ST)

	Age (y)		Age/ST		HAM/ST		AM/ST		FHDM/ST ratio
ST (mC)	Median	Range	Median	Range	Median	Range	Median	Range	
RUL ECT	48.5	28-69							
25.2	46	29-61	1.8 [a]	1.2-2.4	4.4 [a]	2.9-6.1	9.0 [a]	6.0-12.0	15.0
50.4	48	28-68	1.0	0.6-1.4	2.5	1.4-3.4	5.0	3.0-7.0	7.5
75.6	57.5	44-69	0.8	0.6-0.9	1.9	1.5-2.3	4.0	3.0-4.5	5.0
BF ECT	47.0	24-77							
50.4	41.5	24-63	0.8 [b]	0.5-1.3	2.1 [b]	1.2-3.1	4.1 [b]	2.5-6.5	
100.8	46	32-77	0.5	0.3-0.8	1.1	0.8-1.9	2.3	1.5-4.0	
151.2	66	57-68	0.4	0.4-0.5	1.1	0.9-1.1	2.2	2.0-2.5	

FHDM, fixed high dose method: ECT dose = 378.0 mC; [a] p < 0.0001; [b] p = 0.0005.

The age/ST ratio by gender was different relative to the ST level both in the RUL ECT group (for men, 1.5, 0.9, and 0.8, p = 0.034; for women, 1.8, 1.0, and 0.6, p = 0.0002, Kruskal-Wallis test), and in the BF ECT group (for men, 1.3, 0.4, and 0.4, p = 0.043; for women, 0.7, 0.5, and 0.4, p = 0.026) (study III). Using multiple comparison for the Kruskal-Wallis test, both men and women in the RUL ECT group had a higher age/ST ratio at the first level stimulation level than at the third level. The ratio at the first level for women was higher than at the second level. In the BF ECT group, the comparisons between subgroups were not statistically significant.

In the Study III, the seizure threshold by age was found to be different for men in the RUL ECT group (p = 0.0089, Kruskal-Wallis test) and for the women in the BF ECT group (p = 0.0078) (**Table 14**). Using multiple comparison for the Kruskal-Wallis test, the seizure threshold (BF ECT group) for women in the youngest age group was lower than that in the oldest age group. The comparison between other subgroups was not statistically significant.

Table 14. Median (range) initial seizure threshold (mC) by age and gender

	RUL ECT		BF ECT	
Age (y)	Male	Female	Male	Female
10-29	25.2 [a]	50.4 (50.4-50.4)	100.8	50.4 (50.4-50.4) [b]
	N = 1	N = 2	N = 1	N = 4
30-59	50.4 (25.2-75.6)	50.4 (25.2-75.6)	100.8 (50.4-151.2)	100.8 (50.4-100.8)
	N = 12	N = 23	N = 8	N = 12
60-85	75.6 (75.6 - 75.6)	50.4 (25.2-50.4)	50.4	126.0 (100.8-151.2)
	N = 4	N = 8	N = 1	N = 4

[a] p = 0.0089, [b] p = 0.0078.

In the RUL ECT group (III), the patients on neuroleptics had a lower ST level (median 50.4, mean 46.2) than those without the medication (median 50.4, mean 55.4, p = 0.031, Mann-

Whitney *U* test). In the BF ECT group, the patients on benzodiazepines had a higher ST level (median 100.8 mC, mean 92.0) than those not using benzodiazepines (median 50.4, mean 64.8 mC, p = 0.05). Other calculations regarding ST by psychotropic medication were statistically non-significant.

Even though more patients responded to the high dose RUL treatment than to moderate dose RUL or BF treatments, the treatment groups were not statistically different (number of responders/nonresponders between RUL ECT 5, RUL ECT 2.5, and BF ECT 1.0: 7/1 vs. 3/4 vs. 3/4, p = 0.12; median/mean change in the HDRS scores: 72.9% / 70.5% vs. 59.5% / 57.8% vs. 64.3% / 44.8%, p = 0.30, respectively) (IV). Patients treated with BF ECT 1.0 received more treatments than patients treated with RUL ECT 5 (12 vs. 7, p < 0.05). The change of the MMSE scores or the likelihood of the occurrence of a simultaneous cognitive risk and nonresponse did not differ between the ECT techniques (**Table 15**).

Table 15. Clinical outcome of studies IV and V

	Study IV				Study V		
	Whole sample	RUL ECT 5	RUL ECT 2.5	BF ECT 1.0	Whole sample	Group 1	Group 2
HDRS (baseline)	27.5 (27.2, 16-40)	29.0 (29.1, 20-40)	27.0 (27.9, 22-37)	27.0 (24.4, 16-29)	24.0 (25.3, 13-42)[a]	29.0 (28.6, 20-40)	23.0 (23.0, 13-42)
HDRS, after last ECT	9.0 (10.6, 3-22)	8.0 (8.4, 3-19)	15.0 (12.0, 5-22)	10.0 (11.9,5-21)	13.0 (12.9, 3-27)	9 (10.2, 3-27)	13 (14.6, 8-27)
HDRS change (%)	68.9 (58.3, –31-88)	72.9 (70.5, 35-88)	59.5 (57.8, 27-82)	64.3 (44.8, –31-82)	47.9 (45.6, –5.6-87.5)[b]	68.9 (64.3, 26.7-87.5)	34.5 (33.1, –5.6-70.0)
Responders (yes/no)	13/9	7/1	3/4	3/4	12/28[c]	10/6	2/22
Change of ECT treatment randomized (yes/no)	3/19	0/8	1/6	2/5	3/37	1/15	2/22
Number of treatments, ENT	8.0 (9.2, 4-14)[d]	7.0 (7.3, 4-12)	8.0 (9.6, 7-14)	12 (11.0, 6-14)	8.0 (7.7, 1-14)	7.5 (8.3, 4-14)	8.0 (7.4, 1-14)
MMSE baseline	27.0 (26.3, 19-30)	25.5 (25.0, 19-29)	27.0 (27.0, 26-29)	27.0 (27.0, 24-30)	27.0 (27.2, 19-30)	27.0 (26.0, 19-29)	28.5 (28.1, 25-30)
MMSE after last treatment	26.5 (26.5, 20-30)	25.0 (25.9, 22-30)	28.0 (27.3, 23-30)	26.0 (26.6, 20-30)	27.5 (26.6, 21-30)	27.5 (26.6, 22-30)	27.5 (26.6, 21-30)
$MMSE_{L\%}$	0.0 (1.2, –16.7-26.0	2.4 (4.0,–12-26)	0.0 (1.1, –12-15)	0.0 (–1.9, –17-7)	–1.5 (–1.8, –22.2-26.0)[e]	1.9 (2.7, –12.2-26.0)	–3.2 (–5.3, –22.2-4.0)
Cognitive risk (yes/no)	8/14	4/4	2/5	2/5	18/18	6/10	12/8
Cognitive risk and nonresponse (yes/no)	1/21	0/8	1/6	0/7	11/25[f]	1/15	10/10

[a] p = 0.0093, [b] p < 0.0001, [c] p = 0.0004, [d] p = 0.033, [e] p = 0.016, [f] p = 0.0091.
Positive values on percentage change indicate a better cognitive functioning as compared with the baseline. Cognitive risk = MMSE change < 0%, nonresponse = HDRS scores after last ECT ≥ 10, and in addition (Study V), the improvement in HDRS scores at least 60%.

The number of responders vs. nonresponders was higher in Group 1 than in Group 2 both in the ITT analysis (10/6 vs. 2/22, P = 0.0004, Table 3) and among study completers (10/5 vs. 2/14, P = 0.0032) (**Table 15)** (V).

The improvement in HDRS score was higher in Group 1 than in Group 2 both in the ITT analysis and among study completers (64.3% vs. 33.1%, t = 4.56, df = 38, P = <0.0001; 64.6% vs. 35.9%, t = 3.71, df = 29, P=0.0009, respectively). Using ANCOVA with pre-ECT HDRS scores as a covariate, the difference was statistically significantly different in the ITT sample (P = 0.0016), and among study completers (P = 0.0076), and remained statistically significantly different when both the pre-ECT HDRS scores and age were used as covariates both in the ITT sample (P = 0.0036, Table), and among study completers (P = 0.0152).

Three patients received a course of BT treatment due to a markedly poor response to the randomized RUL ECT treatment. The number of BT patients was not statistically significantly different between Group 1 and Group 2 (1/15 vs. 2/22, P = 1.0).

The number of treatments was not different between Group 1 and Group 2 in the ITT sample (Table) or among study completers (median, mean, range: 8.0, 8.3, 4-14 vs. 8.0, 8.8, 4-14, P = 0.5844).

The mean MMSE scores improved in the Group 1 patients in contrast to impairment in the Group 2 patients both in the ITT sample and among the study-completers (2.7% vs. -5.3%, t = -2.53, df = 34, P = 0.0159; 2.6% vs. -6.9%, t = -2.52, df = 27, P = 0.0178, respectively). Using ANCOVA with pre-ECT MMSE scores as a covariate, the difference did not remain statistically different in the ITT sample (P = 0.2518), and among study completers (P = 0.2333). The difference was non-significant also with pre-ECT MMSE scores and age as covariates in the ITT sample (P = 0.1803), and among study completers (P=0.0961).

The likelihood of the occurrence of a simultaneous cognitive risk and non-response was significantly higher for Group 2 than for Group 1 in the ITT sample (10/10 vs. 1/15, P = 0.0091, Table 15) and among the study completers (8/6 vs. 1/14, P = 0.0052).

The ten patients in Group 2 who had simultaneous cognitive risk and non-response were included in Group 2 because of their mild major depressive episode (n = 4), because of their history of previous non-affective psychosis (n = 2), because of alcohol abuse (n = 2), and because of severe medical illness (n = 2). Nine of them had had adequate antidepressant treatments during the current major depressive episode.

6. DISCUSSION

In this thesis, I have been able to demonstrate a relationship between MEG slow-wave activity and clinical outcome of ECT, an inverse relationship between seizure duration and initial ST level in RUL ECT but not in BF ECT, the individual value of using a DTM in RUL and BF ECT, a faster response to high-dose RUL ECT than low-dose BF ECT, and a lower RUL ECT response in a heterogeneous depression goup as compared to that in a homogenous group of patients with major depressive episodes.

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6.1. Sample

All the study patients had been hospitalized because of depression. The severity of the episode ranged from mild to severe. Twenty-three percentage of the patients had depression with psychotic features. This is in agreement with the previous studies showing a range from 16% up to 54% for psychotic depression in clinical practice (Dubosky and Thomas, 1992). All the study patients participating in the clinical studies (IV and V) had had at least one treatment with AD medication (**Table 7**). The sample of depressive patients in this thesis was made more representative than the previous ECT efficacy studies (Bailine et *al*., 2000; McCall et *al*., 2000a; Sackeim et *al*., 2000a) by including the comorbid patient group and also patients with mild major depressive episodes. Recent efficacy studies have made the analyses using study completers. In addition to this method, an ITT-analysis was carried out in Study V. The differences between the outcomes of these two methods were however small.

6.2. Limitations and confounding factors

The small sample size is a clear limitation of the MEG study. However, I assume that a relative low modulation of MEG signal may explain the finding that a relationship between clinical outcome and MEG changes was found after four treatments but no longer after eight or nine treatments. Regarding the finding on the prefrontally accentuated EEG slow-wave activity in ECT responders (Sackeim et *al*., 1996), the effect of the applied methods, the spatial origin, the mechanism of the induced slow-wave activity and the functional significance of the ECT induced EEG activity has been challenged (Volavka and Czobor, 1996). Although the EEG and the MEG methods are different, the questions raised by Volavka and Czobor concern MEG as well.

The interactions between ECT and psychotropics in cerebral physiological and clinical effects are not well known. The patients in the MEG study continued the medications they had used prior to their ECT treatments to eliminate the withdrawal effects of the medication on the MEG signal. In the clinical Studies (IV and V), the AD medication was discontinued before ECT but patients were allowed to use lorazepam, chlorpromazine and/or chloralhydrate (**Table 7**). Concomitant use of BZDs and ECT may lessen the efficacy of treatment in depression (Greenberg and Pettinati 1993). In the clinical Studies (IV and V), the doses of lorazepam were at the same level as in the efficacy studies of Sackeim et *al.* (1993 and 2000a). At present, there is little known about the combined clinical effects of both antipsychotic agents and ADs and ECT (Klapheke, 1993; Pritchett et *al*., 1993; see APA, 2001).

Due to non-randomization and different titration schedules, I did not carry out any statistical comparisons between RUL and BF seizure measures in the Studies II and III. The non-

randomization might have caused a selection bias towards the two ECT groups because many factors affect ST level (**Table 2**). The RUL and BF ECT groups were, however, different only in respect to the use of ADs (**Table 7**). The BF ECT patients were more often on AD medication. Nine patients were on SSRIs (three RUL and six BF patients), eight patients were on TCAs (three RUL patients and five BF patients), one BF patient had a combination of SSRI and TCA, and three patients were on moclobemide (one RUL and two BF patients). TCAs may lower the ST level (Warrington, 1992) whereas SSRIs have been found to have no effect on the ST level (Boyer and Feighner, 1992). On the other hand, SSRIs have been found to increase the ST of rats (Watanabe et *al*., 1998). Thus, the effect of ADs on our findings can not be excluded. The use of neuroleptics has been found to be associated with a lower ECT ST level (Coffey et *al*., 1995a). In our RUL and BF groups, the number of patients on neuroleptics between the two groups was not different. Regarding BZDs, a mean average lorazepam dose of 0.85 mg in the 48 hours prior to ECT has not been found to be associated with the initial ST level (Boylan et *al*., 2000). Our approximate median dose equivalents for lorazepam in the 24 hours prior to ECT were 1.0 mg both for the RUL and BF groups. However, the clinical equivalent doses of BZDs may not be the same as the equivalent doses regarding their effects on ST. Furthermore, different inter-electrode distances between RUL and BF ECT and regional differences in the thickness of the skull may have been other confounding factors (Sackeim et *al*., 1994).

Cognitive side-effects of RUL or BF ECT may not be optimally detected with the MMSE alone (Calev et *al*., 1995; see Abrams, 1997; Austin et *al*., 2001). The MMSE grossly assesses global cognitive status, and not the central cognitive effects of ECT, particularly retrograde amnesia. Furthermore, more specific measures of executive functioning and parietal lobe functioning would be necessary to evaluate fully the cognitive side-effects of BF and RUL ECT, respectively. Unfortunately, specific recommendation regarding an optimal instrument to evaluate the cognitive side-effects of ECT is not available (see APA, 2001). However, the impact of ECT on cognition, particularly orientation and memory, should be assessed in terms of both objective findings and patient report prior, during, and after the ECT course.

6.3. Mechanism of action of ECT

Dysfunction in the frontal cortical-subcortical circuits has been found to be associated with mood disorders (Mayberg, 1997; Soares and Mann, 1997; Strakowski et *al*., 2000). According to Mayberg (1997), concurrent inhibition of the overactive paralimbic regions and normalization of hypofunctioning dorsal cortical areas are necessary for disease remission, whether facilitated by psychotherapy, medication or ECT. ECT has been shown to induce accentuation of the interictal EEG slow-wave activity in the frontal cortex. This change has been found to have a relation to clinical outcome of ECT treatment (Roth, 1952; Fink and Kahn, 1957; Sackeim et *al*., 1996). Therefore, the MEG study (I) focused on this specific ECT-induced neurophysiological change in the brain function.

Sackeim et *al*. (1996) have found that the efficacy of ECT was linked to the induction of delta band of the EEG slow-wave activity in the prefrontal cortex (topographic pattern 1). This pattern revealed the ECT-responders among non-responders. In the present MEG study, the increase in the postconvulsive left frontal MEG activity in the theta band correlated with the efficacy of the ECT treatment after four treatments (**Figure 4**) although the induced mean activity was not significantly increased. The relationship between MEG change and efficacy was significant also as measured by the left frontal to occipital (LF/O) and right frontal to

occipital (RF/O) changes in the MEG activity. The bilateral MEG findings showing the frontal accentuation of induced MEG activity (I) are in agreement with the topographic pattern 1 (Sackeim et *al*., 1996). The relation between efficacy of ECT treatment and increase in postconvulsive frontal slowing as measured both by EEG (Sackeim et *al*., 1996) and by MEG (I) were not dependent either on the electrode placement or on the stimulus dose. The changes in the EEG slow-wave activity have been previously shown to vary with the method of seizure induction, and with the number of seizures administered. In contrast, both the QEEG measure (Sackeim et *al*., 1996) and the MEG measures (I) may be more constant markers for efficient ECT treatments and clearly merit further studies.

The present MEG study found outcome-related changes both in the left frontal cortex and in left and right frontal cortex as measured by LF/O and RF/O ratio. The role of the left frontal cortex particularly has been empasized by some studies in the pathogenesis of depressive disorders (George et *al*., 1994; George et *al*., 1995; Pascual-Leone et *al*., 1996). Direct stimulation of left prefrontal cortex by rapid-rate TMS, the treatment given without anesthesia, has been found to be beneficial in some depressive patients (George et *al*., 1995; Pascual-Leone et *al*., 1996). In major depression, cerebral asymmetry (alpha suppression) as measured by EEG has been found to occur so that there is less left frontal activation and greater right frontal activation (Davidson, 1992). On the other, Bruder et *al*. (1997) have found that the lateralization of EEG activation in depressed patients is dependent on the comorbid anxiety disorder. Using MEG, Reite et *al*. (1999) have found altered cerebral lateralization being associated with psychoses of schizoaffective disorder and bipolar I disorder. A lower activity on the left than right hemisphere has been found in patients with major depression also with TMS measurements (Maeda et *al*., 2000). However, Mayberg et *al*. (1999) have found that recovery from depression involves especially the right frontal cortex. Moreover, in the most recent TMS treatment study it was found that TMS given over right prefrontal cortex of depressive patients is beneficial (Klein et *al*., 1999). The recent ECT studies have not found a relationship between lateralized EEG changes and ECT efficacy (Weiner et *al*., 1986; Abrams et *al*., 1992; Sackeim et *al*., 1996). Thus, the relationship between the left hemispheric accentuation of the ECT-induced MEG changes and clinical outcome (I) clearly needs further studies.

The MEG study (I) showed a change both in theta and delta frequency bands. The change in postconvulsive MEG theta activity correlated with the clinical outcome whereas in the EEG/ECT studies (Roth, 1952; Fink and Kahn, 1957; Sackeim et *al*., 1996), the clinical outcome has been found to correlate with the EEG delta activity. This difference might be explained by different dose-dependent effects of ECT on thalamic pacemakers based on the facts that thalamic pacemakers modulate the cortical rhythms of the brain (Steriade et *al*., 1990), ECT affects thalamus (Diehle et *al*., 1994) and ECT induces neurohormone responses in a dose-dependend manner (Zis et *al*., 1993; Devanand et *al*., 1998; Lisanby et *al*., 1998). Delta activity has been found to be induced by higher mean stimulus intensities, i.e. by doses from 140mC to 318 mC (Sackeim et *al*., 1996) whereas theta activity has been shown to appear using lower intensities, i.e. by the doses of 95 mC (Sackeim et *al*., 1996) and by the mean dose of 122 mC in the present MEG study.

The MEG findings in individual patients (**Figure 3**) might support at least partly a theory assuming that the spatial distribution of reduced functional activity following ECT is largely determined by the topography of seizure onset and that the reduction of functional activity in anterior frontal regions is critical to the ECT efficacy (Sackeim, 1994; Sackeim et *al*., 1996).

Sackeim has suggested that the exceeding of the individual ST in frontal lobes is the key factor to the efficacy of ECT. In the present MEG study, the high-dose RUL ECT treatment induced the most prominent change of the anteroposterior gradient and best recovery from depression of the patient number 4. This finding may indicate, that the dose of RUL ECT stimulus had reached the level where the anterior frontal tissue participates in seizure initiation. Low dose RUL ECT seizures may in general originate in perirolandic (motor strip) regions which have the lowest seizure threshold in the brain (Sackeim et *al*., 1994; Sackeim, 1994). The low-dose BF ECT treatment (I) was relatively inefficient in inducing an increase in frontal slow-wave activity although the stimulus electrodes were placed frontally. Thus, the low-dose BF ECT may have been able to initiate seizures mainly in perirolandic region.

The excellent temporal and reasonable spatial resolution and the possibility to directly study signals from different brain subregions and make comparisons between them are clear advantages for the MEG recordings. Co-registering techniques which are capable to detect ECT-induced changes accurately also in deep brain structures may be of special value in the future. [^{123}I] ADAM with SPECT seems to have such a capacity (Kauppinen et *al*., 2002). Therefore, our research group is going to start an ECT study combining neurophysiological and SPECT methods to further test the neuroanatomical model of depression by Mayberg (1997). Although speculative, I consider that both the topography of seizure onset and the dose-dependent effects of ECT on thalamic pacemakers are essential in the mechanism of action of ECT.

6.4. Initial RUL and BF ST levels

The first ECT treatment given to a human patient included measurement of his individual ST level (Kalinowsky, 1986). Since then, the knowledge concerning ST measurement has been increased essentially. The individual ST is not absolute but is effected by many factors as indicated in **Table 2**. Therefore, the technical factors of the ECT treatment affecting ST level (I-V) were standardized to the maximum level. Regarding clinical factors, the control over confounding factors is more difficult.

The initial ST of the RUL ECT has shown to vary in the range from 25mC to 300 mC (Sackeim et *al*., 1991). In this thesis, the range was from 25.2 mC to 75.6 mC. All ST measurements (II and III) were carried out at the first treatment session in contrast to the study of Sackeim et *al*. (1991). In general, the ST level increases individually during the course of the treatment (Sackeim, 1999**)**. In consider, that that fact explains the difference in variance to a great extent. The protocol for ST measurement (II and III) was the same for both women and men, and the doses at the three first stimulus levels were identical to those of McCall et *al.* (1993a), and Rasmussen et *al*. (1994). However, both McCall et *al*. and Rasmussen et *al.* used a shorter interval (20 sec. vs. 30 sec.) between subconvulsive stimuli than the Studies II and III, and additionally, Rasmussen used a shorter stimulus pulse width (0.5 ms vs. 1.0 ms). The RUL ST level (II and III) is however quite similar to the low values among studies using brief-pulse stimuli and the d'Elia stimulus placement (Malitz et *al*., 1986; Sackeim et *al*., 1987a; McCall et *al*., 1993b; Sackeim et *al*., 1993; Rasmussen et *al*., 1994; Coffey et *al*., 1995a; Enns and Karvelas, 1995).

The starting BF stimulus dose (50.4 mC) was adjusted at a clearly lower level than that (~115 mC) used previously by Letemendia et *al*. (1993). In spite of this, 40% (12/30, 3 men and 9 women) of BF patients seized surprisingly already for the first stimulus. Thus, a lower

starting dose, e.g. 25.2 mC, especially for women may be sufficient for BF ECT if a Thymatron machine with similar stimulus parameters (**Table 4**) is used as in this thesis. If the initial BF ST level really would be lower, the seizures might be longer, and might have an inverse relationship to the stimulus dose in a similar manner as that found in previous studies using RUL and BT ECT (Sackeim et *al*., 1987c; Sackeim et *al*., 1991; Coffey et *al*., 1995a). Also the efficacy of such a low-dose BF stimulus might be lower than that been found previously (Letemendia et *al*., 1993).

Apart from finding patients with low STs, the DTM is useful in detecting patients with exceptionally high STs also in BF ECT. One of our BF ECT patients had an exceptionally high ST, i.e. higher than 201.6 mC. Patients with markedly high ST levels have been found to be rare (Krystal et *al*., 2000) if the confounding factors have been minimized.

6.5. Relation between ST and seizure duration

The Study II found an inverse relationship between the duration of seizures and the initial ST level in seizures after RUL stimuli just like in the previous studies (Sackeim et *al*., 1987c; Sackeim et *al*., 1991; Coffey et *al*., 1995a) (**Table 12)**. The inverse relationship after RUL stimuli (II) could be found both in the analysis of motor and EEG data. However, no relationship was found after BF stimuli. The correlation was so poor (r_s = - 0.05 for motor seizures and r_s = 0.06 for EEG seizures) that it could not be due to insufficient statistical power. The lack of an inverse relationship may indicate that we have overestimated the first level of the BF schedule. Both for RUL and BT ECT, where the stimulus is given over the temporal lobes, a higher initial stimulus dose induces a shorter seizure. Given this relation, it has been suggested that the measurement of RUL and BT ST assesses more than individual or treatment condition differences in the degree to which current is shunted away from the brain. ST measurement has been suggested to incorporate assessment of one or more dimensions that reflect endogenous neural processes that determine seizure duration (Sackeim et *al*., 1987c). Thus, future studies using a lower initial BF ST may show whether the biological counterparts for the RUL and BF STs really are different.

6.6. Outcome: impact of ECT dose and characteristics of patients

An active treatment of depression should result in remission instead of resulting in response (see APA, 2000). This aim was best fulfilled using the high-dose RUL ECT in patients with pure major depressive episodes (**Table 15**, IV) and worst in the heterogeneous depression goup (**Table 15**, V, Group 2). The response rates were 88% and 8%, respectively. The proportion of patients with major depressive disorder who have responded to ECT in the recent ECT studies has been found to range from 17% up to 87% (Sackeim et *al*., 1993; McCall et *al*., 2000a; Ng et *al*., 2000; Sackeim et *al*., 2000a; Petrides et *al*., 2001). The 17% response rate (Sackeim et *al*., 1993) was achiewed using the 'just above ST level' RUL ECT treatment whereas the 87% response rate was achiewed using the BT ECT dosed at 50% above ST level (Petrides et *al*., 2001). The abysmal response rate of the patients in the Study V is lower although the RUL stimuli (V) were higher than in the study of Sackeim et *al*. (1993). Thus, the outcome of RUL ECT treatment is dependent both on the ECT dose and on the characteristics of the patients.

6.7. Value of the ST measurement

The latest report of APA (2001) suggests that the dosing range for RUL ECT stimulus should be from 2.5 to 6 times the ST level. This recommendation is mainly based on the studies of Sackeim and coworkers (1993 and 2000a). In the later study, Sackeim et *al*. have found that the best cognitive risk/benefit ratio as compared with other ECT techniques was achiewed when the RUL ECT treatment was dosed at 6x ST level. The DTM allows to give for the second treatment an exact dose relative to the initial ST level. However, all ECT reseachers do not support the use of the DTM but prefer to methods based on the predetermined doses (see Abrams, 1997). In the present study, both the age method and the fixed high dose method would have guided to give effective RUL ECT treatment to all the patients (**Table 13**). The stimulus dosed at 5 times the ST level would have led us to give to the study II and III patients a stimulus dose which would have been less than the fixed high doses, i.e. 378 mC and 403 mC, used previously (Abrams et *al*., 1991 and McCall et *al*., 2000a, respectively).

The patients both in the RUL ECT and BF ECT groups with low STs would have received higher doses in relation to the initial ST than other patients if the age based dosing or the FHDM (only RUL ECT) had been used. Only a moderate correlation between age and seizure threshold was found in the RUL ECT group as in the previous studies (Sackeim et *al*., 1987a; McCall et *al*., 1993a; Beale et *al*., 1994; Coffey et *al*., 1995a; Enns and Karvelas, 1995). The correlation between age and seizure threshold in the BF ECT group was even poorer. In the RUL ECT group the relation between seizure threshold and age was stronger in men than in women (**Table 14**). This finding is in agreement with those of Dykes and Scott (1998), and Sackeim et *al*. (1991).

In the patients with the lowest STs (25.2 mC) the doses based on the AM and the FHDM would have been very high. Such doses have been found to impaire global cognitive functioning more than the benefit of the treatment (McCall et *al*., 2000a). Furthermore, the doses would have been even underestimated in these patients because 'their true ST' was either at the measured level or somewhere below it. The number of patients who had an adequate seizure at the first stimulus level (18%) is in agreement with the finding (15%) of the Columbia University group (Sackeim et *al*., 1987a).

According to Letemendia et *al.* (1993), BF ECT is safe and effective when dosed just above the individual ST level. The HAM would have guided us to give nearly the dose recommended by Letemendia et *al.* (1993) to patients with moderate (100.8 mC) to high STs (151.2 mC). In patients with low STs (50.4 mC), both the HAM and the AM would have given significantly higher doses. The clinical meaning of this speculation may, however, be of little value because Letemendia et *al.* (1993) did not use any DTM in their dosing analyses. Thus, it is not clear that the BF ECT doses in the study of Letemendia et *al*. (1993) were 'just above ST level'. In contrast, their BF ECT doses might have been at a clearly higher level relative to the intial ST level. The lack of the inverse relationship between the seizure duration and initial BF ST level in the study II and the relatively slow response induced by the low-dose BF ECT in the study IV (**Table 15**) support the possibility that the initial BF ST level may be at a lower level than has been suggested previously.

6.8. Comparison between RUL and BF ECT

The high dose (5x ST level) RUL ECT had a good short-term antidepressant effect in patients with major depression (IV). This finding is in agreement with the results of recent RUL ECT studies **(**McCall et *al*., 2000a; Sackeim et *al*., 2000a). The response rate (88%) was nearly identical to that of 87% in the recent BT ECT study (Petrides et *al*., 2001). The high-dose RUL-ECT had a faster antidepressant effect than the low-dose BF ECT. Moreover, the higher response rate with high-dose RUL ECT compared to either moderate dose RUL or low-dose BF ECT is clinically significant. All the patients treated with high-dose RUL ECT had had an adequate antidepressant trial during the current major depressive episode, whereas only three of seven BF ECT patients did. Prudic et *al*. (1996) have found that patients who previously had failed one or more adequate AD medication trials are less likely to respond to subsequent ECT than patients not to known to be medication resistant. Thus, all Study IV findings suggest the superiority of high-dose RUL ECT over low-dose BF ECT.

The low-dose BF ECT had a more gradual effect on the depressive symptoms of the patients than high-dose RUL ECT treatment (IV). The slow BF response may only be secondary to the fact that "just above threshold" BF but moderate and high dose RUL ECT were used. Moreover, the mean HDRS percentage improvement scores of BF ECT (IV) were lower than those of the BF ECT in the studies of Letemendia et *al*. (1993) and Bailine et *al*. (2000) (45% vs. 74% and 77%, respectively). All BF patients (N = 24) in the study of Bailine et *al*. (2000) reached remission by a mean of six ECT treatments, whereas only three out of seven of our BF ECT patients achieved remission using similar criteria. The relatively poor outcome of the BF ECT (IV) is at least partly due to the mean low stimulus level (120 mC) as compared with that (164 mC) in the study of Letemendia et *al*. (1993). In addition, four out of seven of our BF patients needed restimulations due to inadequate seizures during the ECT treatment course. This finding indicates that at least some of the treatments have been given with too small stimulus doses.

6.9. Outcome of RUL ECT in depression

The Study V shows that the patients with low severity of a major depressive episode or with a variety of somatic or psychiatric comorbidities (Group 2) have a significantly lower response rate to RUL ECT (8%) than patients with a pure, moderate to severe major depressive episode (63%). The Group 2 included those patients who have been excluded from the recent efficacy studies (McCall et *al*., 2000a; Sackeim et *al*., 2000a). The abysmal response rate in Group 2 is based upon quite strict response criteria, i.e., a decrease of at least 60% in HDRS scores from baseline and a post-ECT score less than ten. For comparison, the mean percentage improvement in HDRS was 33% in Group 2 as compared with 64% in Group 1. This difference is also both clinically and statistically significant.

Why did the two depression groups have such different antidepressant responses to the RUL ECT? A long duration of a current depressive episode (Black et *al*., 1993; Prudic et *al*., 1996), and failure to respond to one or more adequate medication trials have been shown to predict a diminished rate of ECT response (Prudic et *al*., 1996). In this study, there were no differences between these variables in the depression groups. Furthermore, when patients take BZDs during a course of unilateral ECT, the maximum therapeutic response may be compromised (Pettinati et *al*., 1990). The mean dose of lorazepam (1.1 mg/d) of the patients (V) was at the same level as in the previous efficacy studies (1.0 mg/d, and 1.2 mg/d) (Sackeim et *al*., 2000a; Sackeim et *al*., 1993, respectively). In Study V, the mean dose of lorazepam was not different between the depression groups. Findings regarding the effects of

age on short-term efficacy of ECT have been somewhat inconsistent. Some studies have reported that advancing age can be used to predict good response to ECT (Black et *al*., 1993; Tew et *al*., 1999) while other studies have not found this relationship (Brodaty et *al*., 2000). Thus, the higher mean age of our Group 1 patients may have had some beneficial effect on their treatment outcome as compared to Group 2 patients, but on the other hand, the lower mean age in Group 2 may reflect a greater burden of co-morbidity leading to earlier referral for ECT. The patients in Group 2 had less severe depression than those in Group 1. None of the patients who were included in the analysis because of a mild major depression (Group 2) responded to the ECT treatment. This finding is in agreement with that of Hamilton and White (1960) and questions, in general, the usefulness of RUL ECT in patients with a major depression of low severity.

Many of the patients in Group 2 had secondary major depression (Feighner et *al*., 1972; Spitzer et *al*., 1978), i.e. they had some preexisting non-affective psychiatric disorder (which may or may not still be present), or a serious or life-threatening medical illness, which precedes and parallels the symptoms of depression. Specifically, eight patients had a history of alcohol abuse during the previous year, six patients had a history of schizophrenia, schizoaffective disorder or another psychotic disorder which was not part of the mood disorder (four patients had psychotic disorder not otherwise specified, and two schizoaffective disorders), two patients had a history of a neurological illness (one patient had cerebellar ataxia, and the other ischemic cerebrovascular disease) and four patients had a history of a severe medical illness (three patients had hypertensive cardiovascular disease with concomitant risk factors: one had an aortic homograft, one a history of epilepsy, one a risk for esophageal reflux, and one patient had coronary artery disease with coronary artery bypass grafting). It has been shown that patients with secondary depression are less likely to recover from the index depressive episode (Coryell et *al*., 1985) and are more likely to receive inadequate treatment (Black et *al*., 1987) than patients with primary major depression. Moreover, patients with secondary depression have been found to have a poorer response to ECT treatment than patients with a primary depressive disorder (Davidsson et *al*., 1980; Zorumski et *al*., 1986; Black et *al*., 1987; Black et *al*., 1993). Zorumski et *al*. (1986) found that patients with alcohol dependence and secondary depression had a favorable response to ECT. However, concurrent alcohol dependence diminishes the likelihood that depression will respond to treatment (Mueller et *al*., 1994). The subgroups in Study V were too small for any statistical analyses but one may conclude that the lack of ECT efficacy in Group 2 was due to the prevalence of secondary depression in this group especially as the effect of ECT was lower in Group 2 than in Group 1 also after an adjustment for initial differences in severity of depression and age between the two groups. This finding is in agreement with the suggestion that it is likely that ECT does have specific brain effects that affect individuals differently because their individual substrate differ (Fink, 1993a).

6.10. Side effects of ECT

None of the ECT treatments (I-V) were fatal. ECT may cause a variety of cardiovascular complications including cardiac arrest, arrhytmias, ischemias, hypertension, and hypotension (Dec et *al*., 1985; Prudic et *al*., 1987; Zielinski et *al*., 1993; Rice et *al*., 1994). One excluded BF ECT patient (P1, Studies II, III and IV) had a 20-s asystole despite of premedication with atropine. The asystole resolved spontaneously. The patient had a history of hypertension treated with beta blockers, and prior to ECT, she had had doxepine withdrawal for six days. The subconvulsive stimulus accompanied with vagal stimulation despite use of atropine and

use of the beta blocker may have contributed to the occurrence of asystole as suggested by McCall (1996). Furthermore, ventricular extrasystole was found in one RUL ECT 2.5 patient (IV) and high elevations of blood pressure in two patients treated with RUL ECT 5 (V). The ECT-induced increases in heart rate and systolic blood pressure have been found to increase the rate pressure product (RPP), i.e. an index of myocardial oxygen demand (Mayur et *al*., 1998). Furthermore, ECT has been found to increase the QT dispersion, i.e., maximal QT interval minus minimal QT interval. This increased heterogeneity of ventricular repolarization may be associated with enhanced vulnerability to arrhythmias during ECT (Guler et *al*., 1998). In the study of Mayur et al. (1998) none of the cardiac-healthy patients (n = 95) had any clinically observable cardiac complications with ST level (mean dose 68 mC) RUL ECT. The RUL ECT doses of Studies IV and V were significantly higher. Therefore, there is a need to further study cardiovascular side-effects induced by suprathreshold RUL ECT. On the other hand, the cardiovascular monitoring of the patients during the ECT treatments was continuous and effective.

Abrams (see 1997) points out that when increasingly higher doses become routine for RUL ECT in order to maximise therapeutic impact, objective memory deficits may become manifest. Some of the RUL ECT patients with low seizure thresholds (II and III) would have been treated with stimulus doses more than ten times their individual ST level if the AM would have been used. All RUL patients with low ST levels would have received a very high (15x ST) RUL ECT dose if the FHDM (Abrams et *al*., 1991) would have been used. McCall et *al*. (2000a) have found that when the RUL ECT stimulus is dosed at approximately 8-13x ST level compared with dosing at 3-5x ST level, global cognitive disturbances increase more than the antidepressant response does. Facilities vary considerably in many aspects of ECT practice, often clearly departing from the standards in the field (Prudic et *al*., 2001). Prudic et *al.* (2001) have found that the more intensive the form of ECT used at facilities, the less intensive the assessment of ECT-induced cognitive side effects. Therefore, I suggest that no FHDM (dose ≥ 378 mC) should be used if the RUL ST level has not been estimated.

The high-dose RUL ECT, despite its therapeutic advantages, did not result in greater MMSE impairment after ECT than the moderate dose RUL or the low-dose BF ECT (IV). BF stimulus has been shown to spare both verbal and nonverbal cognitive functions better than BT and RUL ECT treatment if the BF stimulus is dosed just above the individual ST level (Lawson et *al*., 1990). However, Study IV suggests that such a dose may have a slow response and therefore, higher doses may be required. Then, both profile and amount of cognitive side-effects may become more evident in BF ECT.

The patients (I-V) had no prolonged seizures (>180 seconds) as measured either using motor seizure monitoring or using the automated EEG monitoring of the Thymatron ECT device. The lack of prolonged seizures (I-V) is in disagreement with the study of Mayur et *al*. (1999). They found that prolonged seizures using only motor seizure monitoring would have been missed in about 6% of patients. However, also I recommend a routine use of EEG seizure monitoring to detect prolonged seizures which can occur without motor manifestations but still can be harmful for the function of the brain.

One patient (V) had to discontinue the course of ECT treatment because of a hypomanic switch. The low switch rate (1%) in this thesis is in agreement with that (≤ 4%) reported by Devanand et *al*. (1992).

One patient (V, Group 2) had to discontinue the course of ECT because of regurgitation of his gastric contents. This rare side-effect of ECT may predispose to aspiration pneumonia (see Royal College of Psychiatrists, 1995). We did not use a nasogastric tube before anesthesia. Thus, the beneficial effect of this proposed method can not be answered by this study.

6.11. Risk and benefit analysis of ECT

This study clearly demonstrates that both cardiovascular and cognitive side-effects must be included in the risk and benefit analysis of the ECT treatment. Four patients discontinued their ECT treatments because of cardiovascular complications. Furthermore, the possibility for simultaneous worsening in global cognitive status and nonresponse to RUL ECT treatment was found to be significantly high for depressive patients with comorbid conditions or with low severity of depression. In the clinical practice, comorbidity is common. Until there are more studies on depressive patients with co-morbidity or low symptom severity, the risk/benefit ratio has to be assessed individually in different subgroups of patients with major depression.

7. CONCLUSIONS

Study I. The findings support the possibility that an efficient ECT treatment regardless of ECT stimulus placement and stimulus dose induces a relative accentuation of frontal MEG slow-wave activity.

Study II. In contrast to RUL ECT, the seizure duration does not show any association with the threshold level BF ECT stimulus. The lack of an inverse relationship for BF ECT may be due to our overestimation of the first stimulus level and also to the use of too large increments between stimuli. Thus, it can not be excluded that lower BF doses might induce longer seizures accompanied with impaired efficacy.

Study III. Patients with different seizure thresholds would be treated differently if the predetermined dose is used both for RUL ECT and BF ECT groups. Especially, patients with low seizure thresholds are in danger of being treated with supra-high stimulus doses. The safety of such doses is questionable. We recommend the use of the dose titration method, i.e. measurement of the individual seizure threshold in the first ECT treatment, followed by an ECT treatment relative to it. Only the dose titration method allows us to standardize the ECT stimulus dose relative to the initial seizure threshold level.

Study IV. High-dose (5x ST) RUL ECT has a faster antidepressant effect than low-dose (1.0x ST) BF ECT. BF placement has to be considered as experimental, and it can not be recommended for routine clinical use until further trials are completed. The cognitive risk/benefit ratio using different BF stimulus doses should be further studied with more sensitive neuropsychological methods.

Study V. The good response to RUL ECT of the patient group with major depression without co-morbidity was not found in a heterogeneous co-morbid patient group. Most of the patients in this group had secondary major depression. In addition, patients with a low severity of major depression have a high risk/benefit ratio and this makes the RUL ECT treatment unjustified for them. More research is needed to clarify the response to ECT treatment in different subgroups of patients with major depressive episodes.

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