Exciting matters in Electroconvulsive Therapy

Studies on seizure thresholds

Jeroen Antonius van Waarde

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Exciting matters in Electroconvulsive Therapy

Studies on seizure thresholds

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Introduction

Electroconvulsive therapy offers exciting subject matters for the human brain, clinicians and scientists

"Het was alsof ze feestvierde op den bodem van een diepen put,
waaruit nooit iemand verlost werd. Soms dacht zij, dat dit op de hel leek,
waar de verdoemden het laatste oordeel afwachten en zich verdooven door
feestgedruisch in kunstlicht, daar Gods zon hun niet meer gegund is."

Frederik van Eeden, Van de koele meren des doods, 1900.

"It was as if they were celebrating at the bottom of a deep well,
from which no person would ever be redeemed.
Sometimes she thought that this resembled hell,
where the doomed await their final verdict and benumb themselves by feasting
in artificial light, as they are no longer blessed with God's sun."

Frederik van Eeden, The Cool Lakes of Death, 1900.

———

"Depressie gaat nergens over; het is een lege archiefkast.
Ik heb eindeloos gezocht naar een oorzaak van mijn somberheid,
maar ik kom er gewoon niet achter."

Mike Boddé, Pil, 2010.

"Depression deals with nothing; it is an empty filing cabinet.
I have searched endlessly for a cause of my sorrow,
but I just can't understand it."

Mike Boddé, Pill, 2010.

The suffering of depressed patients is enormous. It also poses an important burden on their significant others and on society as a whole. Clinicians are therefore being urged to relieve these conditions as soon as possible. To that purpose, effective psychotherapeutic, psychopharmacologic and other biological interventions, such as electroconvulsive therapy (ECT), are available. Observing a quick response to a course of ECT in a psychotic depressed patient is astonishing. ECT may restore the patient's normal mood, but at the same time may provoke anxiety and a sense of shame or stigmatization. Frequently, ECT is accompanied by more or less impairing cognitive side effects.

For clinicians and scientists, ECT is fascinating and raises many research questions concerning the effects of this treatment on the functioning of the brain. This thesis reports on our daily practice in which we treat severely ill depressed patients, while simultaneously doing clinical research. To further improve the understanding and the effectiveness of ECT, the electrical dose, which elicits the seizure activity (defined as seizure threshold [ST]), is the subject of this thesis.

1. Clinical aspects of ECT

1.1 Indications for and use of ECT in the Netherlands

In the Netherlands, the use of ECT is limited, functioning mostly as the 'treatment-of-last-resort' for severely ill patients suffering from (psychotic and/or pharmacotherapy resistant) depression, mania, intractable psychosis, catatonia, neuroleptic malignant syndrome, or delirium.[1,2] Worldwide, it has been estimated that approximately 1 million patients receive ECT each year.[3] As the incidence of major depressive disorder with psychotic features (an important indication for ECT) is about 4 in 1,000 individuals in the general population,[4] an incidence rate of about 64,000 patients might be expected in the Netherlands annually. This number contrasts greatly with the actual amount: in 1999 only 328 Dutch patients received ECT.[5] Nevertheless, ECT is a very effective biological treatment. Bilateral (BL) ECT is moderately more effective than right unilateral (RUL) ECT and high dosed ECT more effective than low dosed.[6] In adults with a major depressive disorder, ECT is probably more effective than pharmacotherapy.[6] It is also possible that certain depressed patients such as psychotic, catatonic, suicidal or otherwise life threatened patients may benefit even more from ECT than others.[1]

In the Netherlands, it is mostly general and university hospitals that provide ECT. The procedure follows the clinical guidelines of the Netherlands Association of Psychiatry ('NVvP') on the practice of ECT.[7,8] In 2010, references in the Dutch

national register for treatments ('Diagnose-Behandelcombinatie Informatie Systeem') revealed that ECT courses were given with a median of 9 sessions (interquartile range 4-15 sessions). The majority - female patients (75%) with an average age of 58 ± 15 years - were treated because of recurrent mood disorders (85%), often with psychotic features (33%).[9] Although most psychiatric patients are diagnosed and treated for their psychiatric illnesses in facilities for mental health care ('GGZ-instellingen'), only a minority of these institutions offer ECT. The annual use of ECT in the Netherlands had increased substantially from 1.8 per 10,000 inhabitants in 1999[5] to 8.5 per 10,000 inhabitants in 2008.[8] However, this rate is still low compared with the 14 treatments per 10,000 inhabitants in Scotland[10] and the approximately 27 per 10,000 inhabitants in the USA.[3]

1.2 Clinical practice of ECT

To be effective, ECT must induce generalized seizure activity in the brain of the patient by overcoming the ST.[11] Effectiveness of ECT not only depends on the administered electrical stimulus and the induced seizure, but is also related to electrode placement, level of seizure generalization and the extent to which the ST is exceeded.[1] Seizures are elicited by an electrical stimulus that is administered between two electrodes placed at the outside of the patient's head. In the Netherlands, ECT is usually given twice a week,[8] and takes place under general anesthesia in order to prevent awareness and distress. The patient also receives a muscle relaxant to prevent complications such as injuries and fractures.[1,7]

Generalized seizure activity occurs only when the electrical stimulus is strong enough to exceed a critical threshold (i.e., the ST).[12] The ST has several definitions in the literature. Normally, the smallest electrical stimulus dose that is necessary to produce a generalized seizure of at least 25-30 seconds on electroencephalogram (EEG)[1,13] is defined as the initial seizure threshold (IST). This definition seems arbitrary, however. Whether there are associations between the level of the ST and seizure duration on the one hand and the clinical effectiveness of ECT on the other hand is still a matter of debate. Moreover, experimental data to support the universally recommended 25-30 second minimum duration on EEG to define ST is lacking.[1,14] Although not studied extensively, for decades it has been clinically known that the level of IST varies substantially among patients.[14] Besides the anesthetic used, several other factors were described to affect the level of IST including gender,[15] age,[15,16] previous ECT treatment and concomitant medication use.[1,17] Additionally, ST seems to increase during the course of ECT, at least in some patients.[15,18] Recently however, this finding was not confirmed in BL ECT.[19] Underlying mechanisms explaining the initial ST level and its possible increase are hypothetical and need further study.

1.3 Optimal exceeding of the ST

For the individual patient, knowledge of the IST level seems crucial for estimating the proper electrical dose.[20,21] It is well-known that in RUL ECT the electrical dose should exceed the IST substantially (e.g., 6-12 times) to be as effective as BL ECT, with the advantage that RUL ECT results in fewer cognitive adverse effects than BL ECT.[22] Among ECT practitioners however, controversy exists about the optimal suprathreshold electrical stimulus dose and its proper determination.[14,23] Furthermore, it has been reported that the extent of the electrical dose above the individual IST, rather than the absolute electrical dose, was associated with short-term cognitive adverse effects.[20] Conversely, attempting to administer the lowest possible dose bears the risk of a subconvulsive stimulus and consequently of severe bradycardia and asystole.[24]

To decide on the proper electrical dose for a patient, the 'empirical dose-titration method' is used to calculate individualized stimulation above ST.[25] This means that, under proper anesthesia and muscle relaxation, the brain is initially stimulated with a low electrical stimulus; if consequently no seizure of a certain duration occurs, re-stimulation of the brain follows according to the steps of a predefined titration protocol. Also, in clinical practice, 'age-based' methods are often used to estimate the electrical dose that exceeds the ST sufficiently,[14,26] based on the assumption that increasing age raises the ST.[2] Furthermore, a 'fixed-high dose' strategy has been described in which a high dose (i.e., 400 milliCoulombs) is always administered regardless of other factors. This procedure may probably lead to overdosing in a substantial number of patients and a higher rate of cognitive adverse effects.[1]

In the literature, discussion exists about the accuracy of determining the IST using titration protocols.[27] It was suggested that only one single pulse of electrical current can decrease the ST, which may lead to underestimation of the IST with each additional stimulus administered during the titration procedure itself.[28] Also, most titration protocols vary regarding the used pulse widths, charge rates and increments of stimulus dosage causing internal inconsistency of the titration methods.[27] Therefore, studying the various factors that may determine the individual ST and its relation to the effectiveness and adverse effects of ECT in more detail is warranted.

Before focusing on the possible determinants of the ST, some understanding of the basic mechanisms of normal brain functioning, as described below, is helpful.

2. Normal human brain functioning

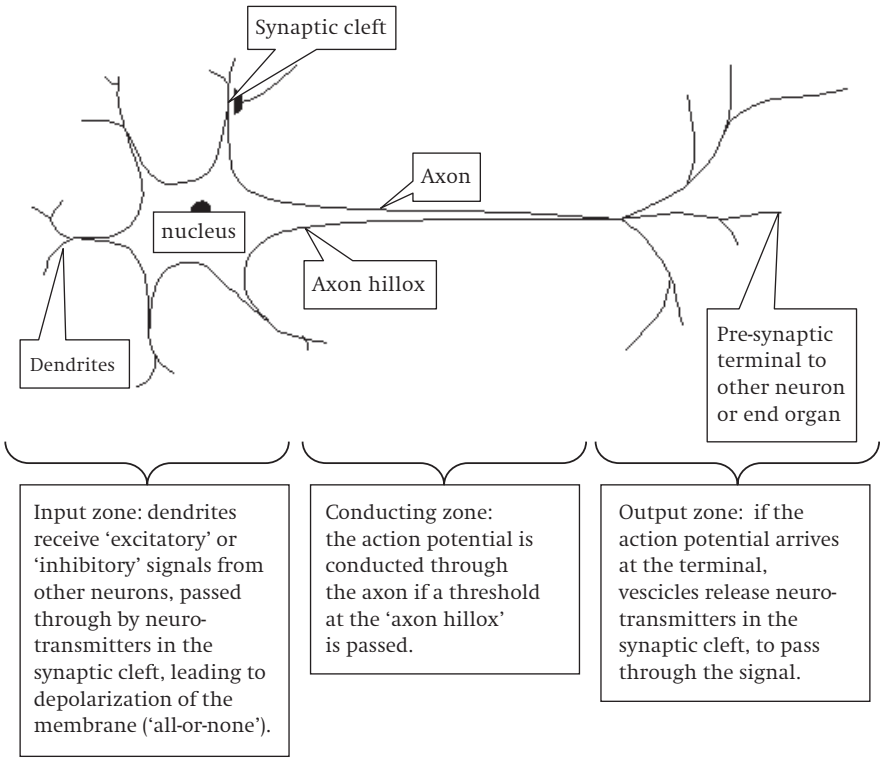
2.1 Communication systems and signaling in the brain

Most of the human brain's functions are based on the coordinated electrical and chemical interactions of large numbers of neurons that are distributed within and across different specialized brain areas (neuronal networks).[29] Ordinarily, using their sodium-potassium exchange pump, neurons generate a negative resting membrane potential and employ several different types of electrical signals to encode and transfer information. Neurons have cell bodies ('the soma') with dendrites and an axon (see Figure 1). Neuronal membranes may become more depolarized (becoming less negatively charged) by the influx of positively charged sodium ions. This depolarization occurs locally and propagates. Consequently, excitation of the membrane spreads from dendrites (input zone of the neuron), through the membrane of the cell body, towards the axon hillox. If at the hillox a critical threshold of sufficient depolarization has been reached, an action potential, following an 'all-or-none' excitatory process, is sent down the axon (conducting zone) and passed on to the dendrites of other neurons or end organs (output zone). All together, around 100 billion neurons communicate with each other through electrical and chemical signals.

When the action potential reaches the terminals of the neurons, calcium channels are opened leading to the release of neurotransmitters from the presynaptic neuron into the synaptic cleft (chemical synapse). These neurotransmitters (such as the excitatory glutamate or inhibitory gamma-aminobutyric acid [GABA]) attach to receptors at the dendrites of postsynaptic neurons. This causes the opening of sodium and other channels, which results in either continued depolarization of these dendrites or termination of the signal. As a result, the chemical signals may be excitatory (leading to depolarization of receiving neurons) or inhibitory (leading to hyperpolarization). Besides this chemical synaptic signaling, gap junctions (places of intimate contact between neurons) serve as electrical synapses passing through the current directly between neurons.[30] This direct electrical signaling is extraordinarily fast and such synapses may interconnect many neurons, facilitating synchronization among populations of neurons.

Glia cells, known as 'white matter' (astrocytes, microglia cells, oligodendrocytes), which surround the neuronal axons, seem to be particularly important in maintaining electrical and chemical balance as well as setting the general tone of excitability in the brain.[31] Glia cells can release or absorb glutamate and therefore excite or depress neurons.[31] Glia cells cannot generate electrical impulses themselves and seem to communicate with each other through calcium signaling.

Figure 1 The neuron consists of a cell body with nucleus (soma), dendrites and an axon (which starts with the 'axon hillox')



Glia cells do sense, affect and respond to changes in voltage as they absorb potassium ions released by neurons, drain these ions away into the bloodstream, and maintain proper potassium concentrations outside the neurons. These processes also lead to electrical charging and discharging throughout the brain.

All together, very efficient and huge communication systems within the brain exist, which are disrupted when a patient has a seizure. Knowledge about the generation of seizure activity, its spreading through the brain and its termination is important for our understanding of how ECT may work.

2.2 Network dynamics in the brain

In seizure activity, as provoked by ECT, the normal network dynamics of the brain are disturbed. Normal activity of large populations of neurons, working together in huge neuronal networks, is essential for optimal brain functioning. Even in the

absence of environmental and body-derived stimuli (resting state), the brain is perpetually active. In the human brain, most of the 100 billion (10^{11}) neurons are connected locally and approximately 100-200 million axons serve to interconnect symmetric and asymmetric neuronal groups in the two hemispheres, forming the corpus callosum and the somewhat larger numbers of long-range fibers connect areas within the same hemispheres.[32] Because of this tremendous connectivity and in order to generate a harmonious interplay between cortical circuits, excitation of neurons must be balanced with an equally effective inhibition so that neuronal homeostasis can be reached. Therefore, a stabilizing internal negative feedback control system is needed.[32,33] This neuronal homeostasis is often accomplished by oscillations, maintained by connected interneurons which use GABA-ergic neurotransmission and electrical gap junctions to stabilize the (local) networks.[32,34] Phenomena of neural network destabilization during seizure occurrence and propagation, as well as the network stabilization mechanisms, are most likely important in ECT and may partly determine the ST.

3. Technical aspects of ECT

3.1 Seizure generation and propagation

In the case of generalized seizure activity, overly large populations of neurons become excited simultaneously (known as synchronization) and are insufficiently compensated by inhibitory interneuron systems. As neurons are anatomically connected in neuronal networks (e.g., through cortico-cortical and cortico-thalamo-cortical feedback loops), during the process of synchronization, progressive recruitment (known as coupling) of different connected brain areas precedes complete system destabilization, clinically known as generalized seizure activity.[33,35] Seizures then result from large neuronal firing in pathological synchrony superimposed on the background activity, which disrupts normal brain function.[33,34,36,37] Seizure activity appears not only to be a neuronal process and glia cells also seem to play an important role.[31] During seizure activity, glia cells may release glutamate and other substances which may intensify the excitability of neurons, like pouring fuel on a fire.[31] Furthermore, glia cells may stimulate synapses connecting neurons into circuits by releasing growth factors in response to seizure activity.[31]

Seizure activity does not spread diffusely throughout the brain, but propagates along specific anatomic pathways.[38] For example, the hippocampus is often one of the first regions to exhibit seizure activity because of its apparently low ST, and basal ganglia circuits are suggested to control cortical excitability and to regulate

synchronization of neuronal discharge in widespread regions of the cortex.[38] Cortico-cortical seizure propagation between the frontal and parietal association cortex, with little effect on the intervening cortical regions, may occur through long association fiber pathways such as the superior longitudinal fasciculus.[39]

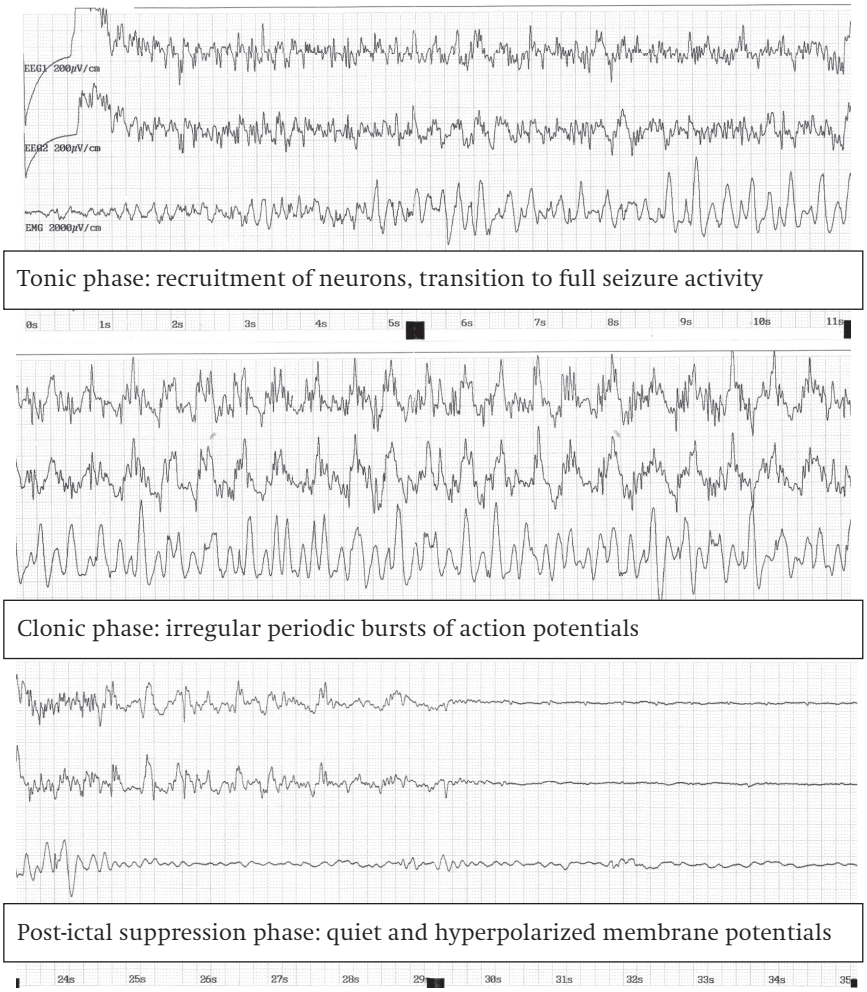
It can be hypothesized that, on the one hand, the amount of neuronal and glial connections will (at least partly) determine whether or not seizure activity will propagate through certain parts of the brain. On the other hand, a certain amount of connections would contribute to negative feedback systems and inhibition of (locally induced) seizure activity. In ECT, eliciting widespread seizure activity by exceeding the ST is intended. Therefore, externally administered electrical stimuli must induce a critical amount of synchronization in both large and connected brain areas, and must also overcome the inhibitory feed-back systems.

3.2 Seizure induction and termination in ECT

Traditionally, direct electrical depolarization of large groups of neurons by the flow of negatively charged electrons between two ECT electrodes has been described as the mechanism for seizure generation in ECT. Recently, it was proposed that electrical stimulus pulses pass through neuronal cell membranes and interact with the operation of the sodium-potassium exchange pump across it. Presumably, with each ECT stimulus pulse the intracellular sodium levels increase, leading to neuronal depolarization. As these depolarized neurons depolarize adjacent neurons, a wave of depolarization consequently sweeps through the brain, known as seizure activity.[28,30] In ECT, the transition to a fully generalized seizure is associated with maintained depolarization of the membrane potential and repetitive generation of action potentials (resulting in the clinically visible muscle spasm known as the tonic phase), followed by a period of irregular periodic bursts of action potentials (resulting in the clinically visible muscle contractions known as the clonic phase). With the final phase, the seizure ends with a relatively quiet and hyperpolarized membrane potential corresponding to a period known as post-ictal suppression.[36] These three phases can be identified on the EEG during ECT (Figure 2).

Passing through the scalp, skull, meninges and cerebrospinal fluid (CSF) space, electrical stimulation leads to a local sphere of depolarized neurons beneath the ECT electrodes, which increases in size with more electrical current. The pattern of propagation of activated neurons is likely to reflect the pattern in which axons project through the cortex, i.e., the cortico-(thalamo-)cortical networks.[40] Old cadaver studies using intracranial probes estimated that only 10% of the electrical current applied to the head reaches the brain tissue. Furthermore, the current did

Figure 2 Electroencephalographic registration of seizure activity during electroconvulsive therapy



not concentrate in one area or pathway, although with BL electrode placement the voltage was higher in the frontal lobes. Also, the current traversed the gray matter (soma and dendrites of neurons) relatively freely, but in white matter (axons surrounded by glia cells) the current generally followed the direction of the axons, concentrating in structures such as the corpus callosum, and traversing both sides of the brain, even when one electrode was applied to the vertex and the other to the parietal region (in clinical practice: placement according to d'Elia).[41,42]

More recently, single-photon emission computed tomography (SPECT) showed that BL electrode placement focally and bilaterally activated the frontotemporal and parietal association cortex, without affecting other brain regions; whereas in RUL ECT the left frontotemporal region remained relatively unaffected.[43] In another SPECT study, increase of cerebral blood flow at induction of the ECT seizure was shown near the electrodes as well as in some thalamic and basal ganglia regions. During the seizure, thirty seconds later an increase of blood flow occurred mainly in the parietal and occipital lobes. These phenomena were suggested to reflect seizure propagation through cortico-cortical (between the frontal and parietal association cortex) and cortico-thalamo-cortical (descending connections from frontal cortex to thalamus) networks.[39]

After seizure induction and propagation, ECT or the seizure itself activates mechanisms to terminate seizure activity and to create a period of post-ictal suppression. Seizure termination is unlikely to be caused by neuronal exhaustion or lack of metabolic substrate, but is probably the result of enhancement of the GABA-ergic neurotransmission during the ECT course.[12] Ten minutes after one single ECT-session, a huge increase in serum GABA levels was shown, suggesting an acute inhibitory GABA-ergic response to ECT and/or seizure activity,[44] although another small study found the opposite.[45] Based on results from human and animal studies, in the literature, a "network inhibition hypothesis" for epilepsy was proposed. An increased cortical activity in one region might inhibit subcortical arousal systems, which might lead to widespread decreased cortical activity.[46] In the post-ictal period, it was further observed that activity in the cerebellum continued to increase before returning to baseline. This might suggest inhibitory outputs from cerebellar Purkinje cells, influencing thalamico-cortical circuits that might contribute to seizure termination and/or post-ictal suppression in epilepsy,[46] and possibly also in ECT.

It is suggested that generalized and repeated seizures that terminate themselves and affect, in particular, prefrontal regions and thalamic structures, are essential for the efficacy of ECT.[28] It is likely that the mechanisms through which seizures cure patients involve structural and functional changes at different levels of complexity in the human brain. A course of ECT may restore more balanced neuronal activity and may reorganize preexisting brain homeostasis.[28] It is still a mystery as to which mechanisms are specifically responsible for the therapeutic effectiveness of ECT. For clinicians however, it is very important to apply an optimal beneficial electrical stimulus that will elicit a therapeutic and self-limiting seizure in the patient. In daily practice, there are some factors that have been supposed to obstruct optimal seizure induction, propagation and termination, and these determinants are subject to further studies.

4. Challenges for ECT

4.1 Obstacles in seizure induction

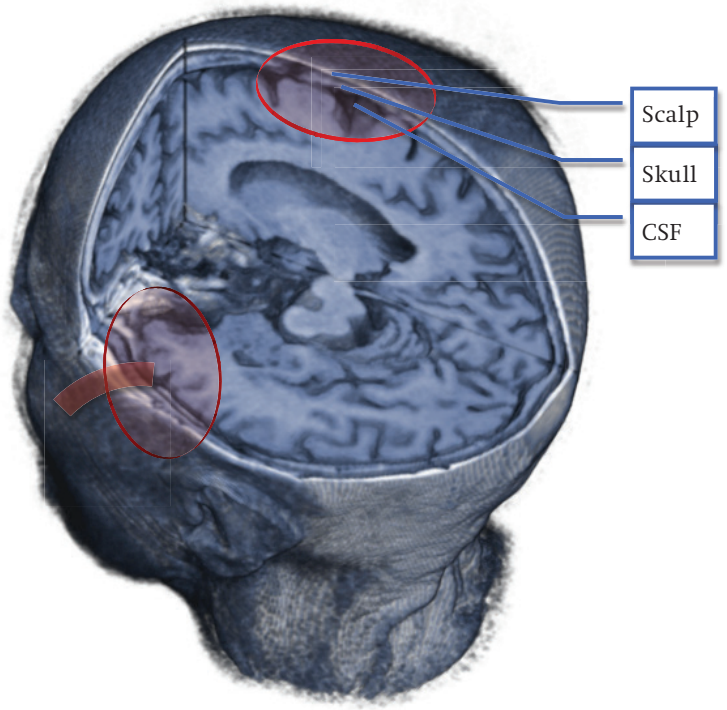
To reach the brain tissue effectively, the electrical stimulus must successively pass scalp tissue, skull, meninges, and cerebrospinal fluid (CSF), with each compartment (Figure 3) having a typical resistance to the passage of the stimulus.[47] Because the human skull is highly resistant to the passage of electrical current, large-voltage electrical stimulation must be applied to the scalp. Most of the flow of electrons is lost even before it reaches the brain tissue. After passage through scalp, skull and dura mater, the next layer consisting of CSF (an excellent conductor) also shunts current away from the brain tissue. A recent computerized simulation study of ECT in spherical head models estimated large effects of the variations in scalp and skull thickness as well as in brain volume, on the levels of stimulation strength and excited brain volume underneath the electrodes.[47] The amount of bone tissue and CSF in an individual patient, therefore, determines the amount of current reaching the brain tissue.[48] Moreover, the amount of shunting of the current depends on the distance between the two electrodes and the use of conducting substances (gel, saline, but also hairspray). The clinician modulates this distance between the two electrodes by choosing the electrode placement (BL[2], bifrontal[1] or RUL placement according to d'Elia[49]).

Interestingly, it is not common practice to evaluate skull and brain anatomy in patients undergoing ECT in order to decide on optimal electrode placement and electrical dosage. In older literature it was shown that the current density in the cortex immediately underneath sutures (places where the bony plates of the skull attach) may be three times higher than predicted.[50] This suggests the possible importance of assessing at least some of these anatomical features in the patient.

4.2 Obstacles in seizure propagation and termination

In ECT, seizure activity propagates through different parts of the brain following neuronal circuitry.[39] This process is followed by seizure termination probably induced by inhibitory thalamico-cortical feedback circuits and GABA-ergic enhancement.[44,46] Disease-related alterations of these anatomical connections and neurotransmitter systems may also interfere directly with mechanisms that support neuronal synchronization, seizure spreading and termination. For example, ischemic injuries of brain tissue, such as white matter hyperintensities, might cause certain cortico-(thalamo-)cortical circuits to be disconnected.[51] In the literature, ECT has been described to be less effective in older patients who showed more subcortical gray matter hyperintensities on MRI and medial temporal lobe atrophy.[52,53] Therefore, more destruction of connected neuronal circuits may lead

Figure 3 A T_1-weighted magnetic resonance imaging of the head to illustrate that the electrical stimulus must successively pass scalp tissue, skull, meninges, and cerebrospinal fluid (CSF), with each compartment having a typical resistance to the passage of the stimulus*



*Electrodes are shown in red and placed according to d' Elia and bifrontotemporal left. During electrical stimulation, the most electrons will flow between the two electrodes through the scalp without crossing the skull. Electrons that pass the highly resistant skull will reach the meninges and CSF space and will then be shunted between the electrodes due to the very low resistance of CSF. Therefore, only a small portion of the electrical current will excite the brain tissues and will be able to elicit seizure activity. Moreover, in right unilateral electrode placement, most current will excite the anterior two-third of the cortex ipsilateral to the electrodes, and in bifrontotemporal electrode placement the anterior frontal part of the brain tissue will be excited.

to less seizure propagation and/or less integrity of terminating negative feedback circuits. This may have implications for the level of the ST.

5. Aims and outline of this thesis

In summary, during the procedure of ECT, progressively large enough groups of cortico-(thalamo-)cortical connected neurons, embedded in supportive glia cells, fire synchronously, which leads to generalized seizure activity in (certain parts of) the brain. Scalp, skull, blood vessels, CSF, glia cells, damaged connections between brain tissue and inhibitory feed-back systems have all been suggested to hamper this process. To our knowledge, studies are lacking, which relate ST and effectiveness of ECT to anatomical factors (e.g., thickness of scalp and skull, volumes of gray matter, white matter, and CSF), as barriers for the current to reach the brain effectively. Also, studies relating ST and effectiveness of ECT to cerebral pathology (e.g., white matter hyperintensities, cortical atrophy), as determinants of the integrity of neuronal networks, which may hamper seizure propagation and/or termination, are not yet available. This thesis outlines studies that explore predictors of ST and its increase during the course in patients undergoing ECT.

The aims of our study in **Part 1** are to explore levels of IST in patients undergoing ECT and to examine clinical and anatomical determinants of the ST. In *Chapter 2* we describe the results of a meta-analysis of studies providing IST levels to determine common levels of IST in patients and to summarize its reported determinants. In *Chapter 3*, we study a patient with an exceptionally high IST and we systematically review the literature on this phenomenon, paying special attention to clinical and treatment characteristics as determinants of the IST. We also describe strategies for the management of high IST. *Chapter 4* contains a systematic literature review on hypotheses regarding clinical, morphological and functional determinants of changes in ST in older patients.

In **Part 2**, we examine in a prospective, explorative cohort study the hypothesized determinants of IST as described in Part 1 of this thesis. *Chapter 5* reports on the clinical characteristics influencing IST and ST change during the course of ECT. Correcting for the clinical variables influencing IST independently, *Chapter 6* examines the relation between scalp and skull thickness and structural brain characteristics (volumes of CSF, gray matter, white matter and white matter hyperintensities) related to IST and ST change during the course.

Part 3 of this thesis deals with the patients themselves. *Chapter 7* reports on our prospective study regarding clinical, treatment and morphological predictors of outcome in ECT. Furthermore, catatonic patients are retrospectively examined regarding ECT characteristics (seizure length, used electrical dosage and post-ictal suppression of the EEG) and outcome (*Chapter 8*). In *Chapter 9*, we study retrospectively

the relationship between time-interval between sessions, electrical dose and seizure duration, in patients treated with continuation ECT because of treatment-resistant mood disorder.

In conclusion, *Chapter 10* presents a summary and general discussion of the overall results, limitations, and the implications of our studies for clinical practice and further research.

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1

1 PART

Exciting matters regarding determinants of seizure thresholds: *reviews of literature*

2

Meta-analysis of initial seizure thresholds in Electroconvulsive Therapy

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Abstract

Background: In electroconvulsive therapy (ECT), electrical dosage is determined using 'fixed-dose', 'age-based' dose, or empirical titration methods. Estimation of initial seizure threshold (IST) has been claimed to be imperative for suprathreshold dosing. This systematic review aimed to determine common levels of IST, to define cut-off values for high IST, and to summarize reported IST associated factors.

Methods: Medline and PsycINFO were searched from 1966 to January 2008 and relevant references were cross-checked. Subject headings including ECT, seizure threshold, dosage, and dosing were used. All articles reporting on levels of IST and/or associated factors were included.

Results: Of 395 potentially relevant reports, 46 studies on 70 samples concerning 3,023 patients were selected. Nine samples (n=306 patients) without available standard deviation and four samples (n=275 patients) treated with mixed electrode placement were excluded. Meta-analysis was done on 30 unilaterally treated samples (n=1,326 patients) and 27 bilaterally treated samples (n=1,116 patients). In unilateral ECT, weighted mean of IST was 68.2 milliCoulombs (mC; 95% CI: 63.2-73.3 mC), and in bilateral ECT 111.6 mC (95% CI: 103.7-119.4 mC). Calculated cut-off values for high IST were 121 mC for unilateral ECT and 221 mC for bilateral ECT. According to the literature, male gender and use of bilateral electrode placement appeared to increase IST most prominently.

Conclusions: Calculated electrical doses for 'suprathreshold' right unilateral ECT and for 'moderate above threshold' bilateral ECT, using commonly reported IST levels, were in the same though narrower ranges as provided in 'fixed-dose' and 'half-age' based strategies, respectively.

2

Introduction

Electroconvulsive therapy (ECT) is an important treatment option for patients with severe, psychotic, or pharmacotherapy-resistant mood disorders.[1,2] To be effective, seizure activity has to be elicited, and the minimal electrical stimulus in the first treatment session that provokes a generalized seizure of sufficient duration indicates the initial seizure threshold (IST).[1,2] In the literature, different seizure durations define seizure adequacy and no systematic association has been shown between seizure duration and clinical improvement.[1,3,4] Clinicians use different methods to choose the initial stimulus dose, of which 'age-based',[4] 'half-age based',[5] 'fixed-high',[1,6] and 'empirical titration based' dosing strategies are common.

Controversy, however, exists about the ability of these different methods to determine the optimal stimulus dose and their risk-benefit ratios.[4,7-10] For example, in unilateral ECT it has been claimed that the electrical stimulus has to exceed the IST substantially for optimal effectiveness (e.g., 6-12 times above IST).[6,11] Moreover, seizure thresholds appear to vary substantially among patients,[4] and factors as gender,[12] age,[13] previous ECT treatment and concomitant medication usage[1,14] may influence seizure thresholds. Some patients show exceptionally high IST being associated with an increased risk of subconvulsive stimulation and unilateral ECT failure.[15]

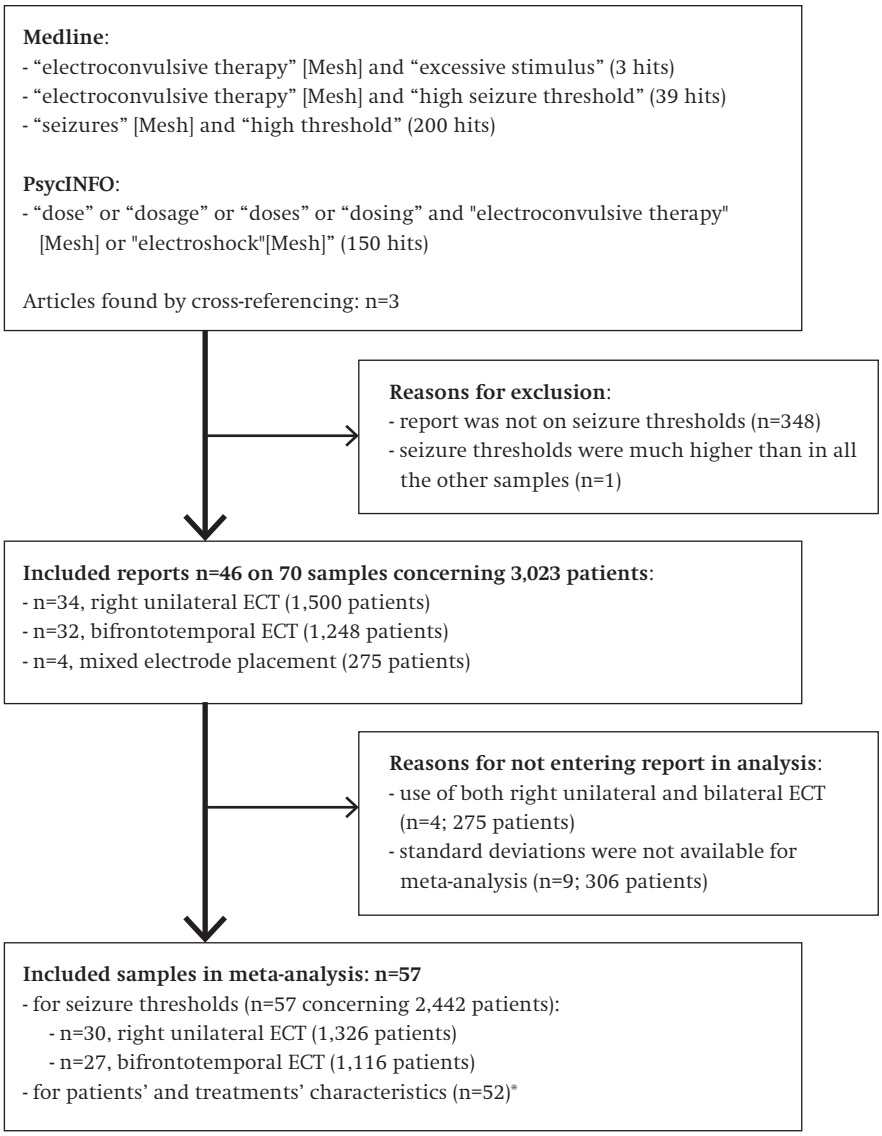
These findings may imply that basic measurement of the IST by titration protocols would be favorable above other methods. Others, though, stated that in the vast majority of patients the distribution of IST would be tightly clustered in the 50-200 milliCoulombs (mC) range, and therefore the proper electrical dose should be accomplished without dose titration.[4,16] Thus for clinicians, knowledge about the common IST level in average patients may be useful to decide on the preferred stimulus dosing method. Therefore, the aim of our study was to analyze studies on IST and to determine whether common IST levels for both unilateral and bilateral ECT could be possibly deduced from these data. We also wanted to define cut-off values for high IST, since these patients may pose a special problem for clinicians. Additionally, we aimed to summarize reported factors that may be associated with IST levels.

Method

This review aimed to include all published articles on IST in ECT. Medline (Pubmed, National Library of Medicine, http://www.ncbi.nlm.nih.gov) and PsycINFO (American Psychological Association 2008) were searched for articles that were published from 1966 to January 2008. The abstracts of the 395 retrieved articles were

examined for information on IST (Figure 1). Of these articles, 348 were excluded because they did not report on IST and one because the reported mean IST was extraordinarily high compared to those reported in the other studies.[17] References

Figure 1 Flow diagram of selection of reports on initial seizure threshold in ECT



* For 5 samples the characteristics of patients and treatments were not reported.

of the remaining 46 articles were cross-checked, and three standard works on ECT were examined as well.[1-3] The 46 studies that were selected for further investigation consisted of 70 patient samples; 34 patient samples were treated with unilateral ECT, 32 with bilateral ECT and 4 with mixed electrode placement. Because electrode placement is known to have a substantial influence on seizure thresholds,[13] mixed samples were excluded (n=4; 275 patients). Furthermore, nine samples (306 patients) could not be used in the meta-analysis because standard deviations of the mean IST were lacking. Therefore, 57 samples containing 2,442 patients were available for further investigation. These studies were scrutinized for: (1) patient characteristics such as age, gender, psychiatric diagnosis, use of anticonvulsants and previous ECT; (2) treatment characteristics such as electrode placement, settings of the device (constant-current and pulse width), titration process including seizure duration and definition of an adequate seizure, and the anaesthetic drugs used; and (3) data on IST [mean and standard deviation (SD), or median and range in mC] in both unilateral and bilateral ECT.

Statistics

Data are presented as numbers and percentages, and means and SD or medians and interquartile ranges (IQR) when appropriate, using SPSS for Windows (version 13.0). After meta-analysis of the data on mean IST with the statistical package of Comprehensive Meta-Analysis (version 2.0), forest plots were generated. Because the included studies proved to be substantially heterogeneous, random effect models were used. Furthermore, we defined high IST level as the upper high 95% bound of the mean IST, which was calculated by adding two times the SD to the mean IST of each patient sample. For both unilaterally and bilaterally treated samples the medians and IQR of these cut-off values were calculated.

Results

Patient and treatment characteristics of the samples

Table 1 summarizes the patient and treatment characteristics of the samples included in the meta-analysis. Mean age of the 57 samples (n=2,442 patients) ranged from 29.8 to 73.8 years, and 36.9% of the patients were male. Most samples concerned patients with major depression (n=37; 64.9%). In 22 (38.6%) samples, also patients with bipolar depression were included. In most studies, seizure adequacy was defined as visible motor activity (35.1%) or EEG seizure activity (22.8%) with a duration ≥ 25 s. All studies, except one,[18] described the use of ECT devices with constant-current and brief pulse properties. In most cases (52 samples; 91.2%), a barbiturate (methohexital or thiopental) was administered as anesthetic.

Table 1 Characteristics of patients and treatment in all the study samples (n=57 concerning 2,442 patients)

Mean age (± SD, range) in years	51.7 (± 9.1, 29.8-73.8)
Male*	971 (36.9%)
Psychiatric diagnosis*	
Major depression	37 (64.9%)
Bipolar depression as well	22 (38.6%)
Psychosis	3 (5.3%)
Various diagnoses	13 (22.8%)
Not described	4 (7%)
Exclusion criterion used*	
Use of anticonvulsants	42 (73.7%)
ECT in previous 6 months	41 (71.9%)
Definition of seizure adequacy in seconds (s)*	
Visible motor seizure activity ≥ 25 s	20 (35.1 %)
EEG seizure activity ≥ 25 s	13 (22.8 %)
Visible motor seizure activity ≥ 15 s	11 (19.3 %)
Visible motor seizure activity ≥ 30 s	3 (5.3 %)
Other description	2 (3.5 %)
Not described	8 (14 %)
Settings of ECT device*	
Constant current 0.8 Ampere (A)	27 (47.4%)
Range of used currents in studies	0.55-0.9 A
Brief pulse 1.0 milliseconds (ms)	20 (35.1%)
Range used pulse width in studies	0.5-2.0 ms
Anaesthetic used*	
Methohexital	36 (63.2 %)
Thiopental	16 (28.1 %)
Other anaesthetic (etomidate; propofol; or not specified)	2 (3.5%)
Not described	3 (5.3%)
Values of IST in unilateral treated patient samples (n=30):	
Range of IST values	42.7-138.9 mC
Median IST	66.6 mC (IQR: 58.4-78.1 mC)
Weighted mean in meta-analysis	68.2 mC (95% CI: 63.2-73.3 mC)
Cut-off values for high IST in unilateral treated patient samples (n=30)	
Range of high IST values	59.3-281.5 mC
Median of high IST values	120.9 mC (IQR: 104.1-163.5 mC)
Values of IST in bilateral treated patient samples (n=27)	
Range of IST values	63.8-192.3 mC
Median IST	107.5 mC (IQR: 94.8-130.0 mC)
Weighted mean in meta-analysis	111.6 mC (95% CI: 103.7-119.4 mC)

Table 1 Continued

Cut-off values for high IST in bilateral treated patient samples (n=27)	
Range of high IST values	119.9-499.9 mC
Median of high IST values	221.0 mC (IQR: 161.8-285.5 mC)

* Data are in numbers and percentages unless otherwise indicated; SD=standard deviation; EEG= electroencephalogram; IST=initial seizure threshold; IQR=interquartile ranges; mC=milliCoulombs.

Levels of IST (Table 1)

The means and ranges of reported IST were analyzed in two ways. Using Comprehensive Meta-Analysis software (random effects model), the weighted overall mean IST in right unilateral ECT was 68.2 mC (standard error 2.59; 95% confidence interval [CI] 63.2-73.3 mC), and in bilateral ECT 111.6 mC (standard error 4.02; 95% CI 103.7-119.4 mC). Figure 2 presents these findings in a forest plot.

In the unilaterally treated samples, the means of IST ranged from 42.7 to 138.9 mC (median of all means 66.6 mC; IQR: 58.4-78.1 mC), and in bilaterally treated samples from 63.8 to 192.3 mC (median of all means 107.5 mC; IQR: 94.8-130.0 mC). The cut-off values for high IST in the unilaterally treated samples ranged from 59.3 to 281.5 mC (median 120.9 mC, IQR 104.1-163.5 mC); and in the samples treated with bilateral ECT from 119.9 to 499.9 mC (median 221.0 mC; IQR: 161.8-285.5 mC).

Determinants of IST

In the reviewed literature, several patient-related, treatment-related and some miscellaneous factors were shown or mentioned to be possibly associated with the level of IST (Table 2). When taking into account prospective studies only, levels of IST were significantly related to the following factors: gender,[12] age,[12] number of cumulative treatments,[12,19] electrode placement,[20] dynamic impedance,[21] current characteristics such as stimulus train duration, frequency, pulse width, and amperage,[22,23] and sleep deprivation.[24] Male gender [12] and bilateral electrode placement [20] were reported to increase IST most prominently.

Figure 2 Forest plot of meta-analysis of initial seizure thresholds (IST) in electroconvulsive therapy (n=30 right unilaterally treated samples concerning 1,326 patients, and n=27 bilaterally treated samples concerning 1,116 patients)

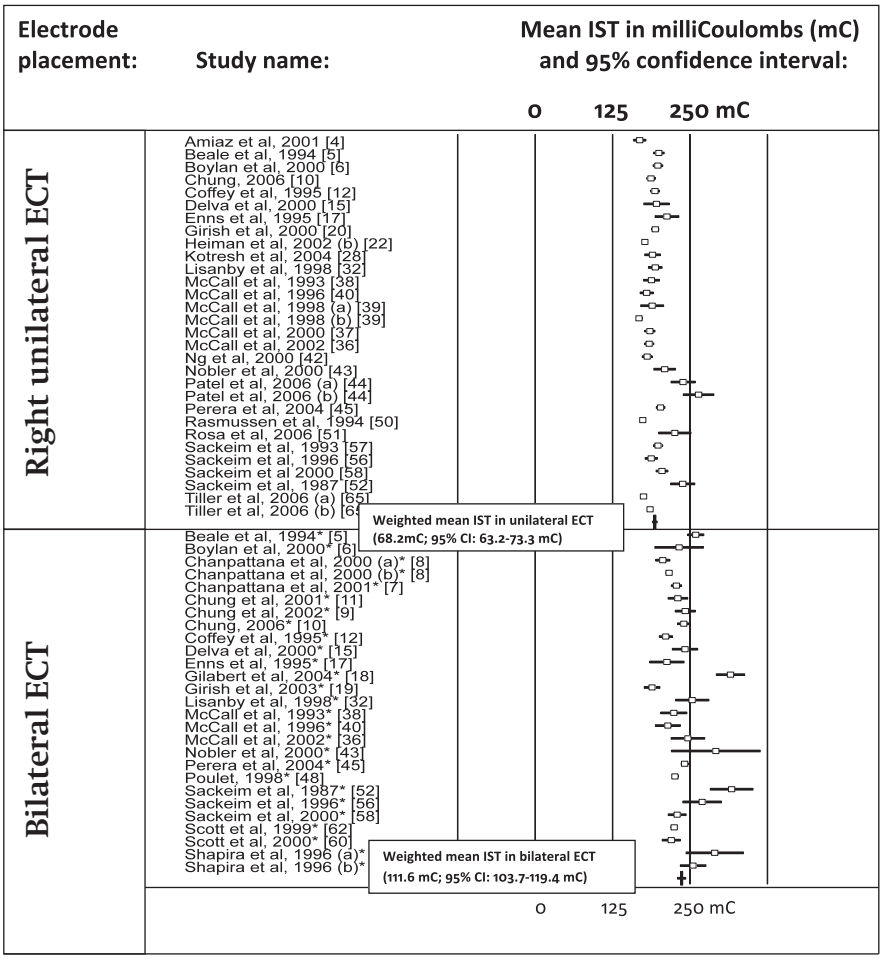


Table 2 Possible determinants for initial seizure thresholds (IST) in electroconvulsive therapy (ECT)

Determinant	Type of influence
Patient characteristics	
Gender*	Men have much higher IST (approximately 70%) than women.[12]
Age*	Moderate association, somewhat sex dependent: elderly men have highest IST.[12]
Racial diversity	African-Americans may have higher IST.[29]
Some morphological characteristics	Thickness of skin and scalp bone, and higher brain density may raise the IST, probably due to a raise of static impedance.[30]
Longer inion-nasion distances	Wider interelectrode (inion-nasion) distance may be associated with higher IST, especially in women.[29,31]
Body-mass index (BMI)	In Chinese patients, higher BMI was associated with higher IST.[32]
Presence of neurodegenerative disorder	In dementia, there may be an additional decrease in neuronal excitability associated with higher IST.[33]
Greater medical burden	Modest association with higher IST, especially in patients with cardiovascular diseases.[25]
Psychiatric diagnosis	Manic patients may have lower IST than depressed patients.[26]
Use of psychotropic drugs	
Anaesthetic drugs	Thiopental may have a disadvantage over etomidate in producing seizures of adequate duration.[34]
Anticonvulsants	Higher stimulus doses are required to overcome IST.[1]
Benzodiazepines	Average lorazepam dosage in 48 hours before ECT was not associated with higher IST, but with decreased seizure duration.[25]
Barbiturates	Have anticonvulsant properties.[25]
Neuroleptics	May have an inverse effect and be associated with a lower IST.[35]
Beta-blockers	May raise IST; atenolol does not pass the blood-brain barrier, but metoprolol and propranolol do.[36]
Calcium-antagonists	May raise IST.[37]
Lidocaine	Shortens seizures and may raise IST.[3]

Table 2 Continued

Determinant	Type of influence
ECT characteristics	
Cumulative number of treatments*	Average of 65% increase in IST from first to final session of ECT course.[12,19]
Electrode placement*	IST is higher in bilateral than in right unilateral ECT, and increased on average by 87% during bilateral treatment, and only 40% during right unilateral ECT.[12]
Dynamic impedance*	Lower dynamic impedance increased IST.[38]
Current*	Shorter stimulus train duration with same dose increased IST.[22]
	Higher stimulus frequency (pulses per second) increased IST.[22]
	Longer pulse width increased IST.[23,39]
	Stimuli of 0.8 A gave higher IST than stimuli of 0.9 A.[40]
Miscellaneous factors	
Sleep deprivation*	Decreased IST.[24]
Drinking alcohol	May increase IST.[41]

* Results of prospective study

Discussion

We found that the overall mean of IST in the 30 patient samples treated with right unilateral ECT was 68.2 mC (95% CI 63.2-73.3 mC), whereas in the 27 patient samples that received bilateral ECT the overall mean was 111.6 mC (95% CI 103.7-119.4 mC). IST might be considered as high when the electrical stimulus has to exceed 121 mC in unilateral ECT or 221 mC in bilateral ECT to induce a generalized seizure of at least 25-30 s on EEG. Of reported factors associated with IST levels, male gender and bilateral electrode placement predicted higher IST most explicitly.

Clinical relevance of these findings

Although in the literature, IST levels were suggested to vary substantially between individual patients justifying the empirical titration as a more accurate dosing method (e.g., a 35-fold range [25]), this meta-analysis showed a more narrow range of mean IST. The IST levels, as found in this meta-analysis, bring together the concepts of 'dose-titration', 'fixed-dose' and 'half-age' methods, which was suggested before by rough clinical estimations.[16] After all, a calculated dose for suprathreshold

unilateral ECT [11] using our calculated weighted mean IST (e.g., 6 x 68.2 mC ≈ 409 mC) corresponds to the stimulus dose range as advocated in 'fixed-dose' methods (378-504 mC) for both unilateral and bilateral ECT.[4] On the other hand, the found IST level of 111.6 mC used in 'moderate above IST bilateral stimulus dose' calculations (e.g., 1.5-2.5 x 111.6 mC ≈ 167-279 mC) suggests that the use of 'fixed-dose' methods (378-504 mC [4]) may result in overstimulation, and corresponds more to the 'half-age' method stimulus dose range (50-252 mC) in bilateral ECT.[5]

Strengths and limitations

Although our systematic literature review is relatively complete, only cautious conclusions may be drawn. IST levels were collected from studies that did not primarily aim to examine IST and its associated factors, and the selected samples could not be stratified for gender or for other presumed influencing factors as many data on the 2,442 individuals studied were lacking. This may have influenced our results. For example, if samples would contain relatively more males, or more subjects with lower dynamic impedances, or if IST increasing current characteristics (shorter stimulus train duration, higher stimulus frequency, longer pulse width, lower amperage) were used, the weighted mean would be higher than real. Furthermore, in 22 samples (38.6%) seizure thresholds were analyzed in patients with unipolar as well as bipolar depressive disorders together. Since it has been suggested that patients with bipolar disorder may have a lower seizure threshold,[26] inclusion of these patients may have decreased the overall means of IST. Also, patients who could not reach adequate seizure durations most probably have been excluded, leading to underestimation of the seizure threshold. In only one study, however, this was mentioned as an exclusion criterium.[27]

Moreover, the lack of a standardized definition of adequate seizure duration in titration protocols hampered appropriate comparison of studies. In 40% of the studies, minimal duration of 25-30 s of 'visible motor seizure activity' was assumed to be adequate, which is rather arbitrary.[1,4] In more than 19% of the studies, a shorter seizure duration was regarded as adequate. Limiting our meta-analysis though to the studies that defined an adequate seizure duration as ≥ 25 s of 'visible motor seizure activity' revealed, however, comparable weighted means of IST (unilateral ECT n=27; mean 68.2 mC; 95% CI 62.8-73.6 mC; bilateral ECT n=19; mean 107.1 mC; 95% CI 97.8-116.3 mC). Seizure duration monitoring was sometimes performed with the cuff method only, which is probably unreliable and might lead to higher estimation of IST as the seizure duration would sometimes be incorrectly regarded as insufficient.[28] Further research on IST could be optimized by using standardized procedures for seizure duration monitoring and an agreed definition for seizure adequacy in the titration protocols.

Finally, the calculated levels of mean IST will probably be applicable in most patients, but some individuals will have lower or higher IST, which in unilateral ECT might result in over- or understimulation. Although some factors are known to influence IST, it is uncertain in what manner these must be taken into account in determining IST for the individual patient.

In conclusion, based on this meta-analysis, an IST of 68.2 mC for calculation of suprathreshold unilateral ECT is within the stimulus dose range of 'fixed-dose' methods. A 'moderate above IST bilateral ECT stimulus' dose, calculated with an IST of 111.6 mC, is substantially lower than the stimulus dose range of 'fixed-dose' methods but is within the 'half-age method' based dose range. Given the discussion in the literature about optimal dosing strategies, these findings support use of 'fixed' and 'half-age' methods. Male gender and bilateral electrode placement were reported to increase IST most prominently, and IST exceeding 121 mC in unilateral ECT and 221 mC in bilateral ECT may be regarded as high. More research is needed to determine the relevance of factors influencing IST.

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3

Exceptionally high initial seizure threshold in a catatonic patient treated with electroconvulsive therapy

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Abstract

Background: Seizure threshold in electroconvulsive therapy (ECT) is generally defined as the smallest electrical stimulus dose that produces a generalized seizure of at least 25 to 30 seconds on electroencephalogram. Seizure thresholds vary considerably among patients, and some patients have an exceptionally high initial seizure threshold. We describe a patient with catatonia who showed an initial seizure threshold exceeding 500 milliCoulombs (mC). The literature was searched for other reports on this phenomenon.

Methods: A systematic review was conducted using MedLine from 1966 to January 2008 and PsychINFO (2007), cross-referencing ECT and (excessively high) seizure threshold, as well as standard works on ECT. The literature was scrutinized for reports on high initial seizure threshold and associated demographic and clinical characteristics.

Results: Besides our patient, 6 articles were found reporting on 9 severely depressed, mostly elderly patients (aged 45-85 years; 5 males, 2 females, 2 persons with unknown sex) with excessive initial seizure thresholds ranging from 335 to 896 mC, and most with cardiovascular compromise. Strategies to lower seizure thresholds in ECT included manipulation of stimulus parameters, adjustment of anesthetics, and augmentation with proconvulsant agents.

Conclusions: Because reports on exceptionally high initial seizure thresholds in ECT are rare, no definite conclusions can be drawn regarding its possible risk factors and management. However, since high initial seizure thresholds can complicate ECT, it is clinically important to further investigate this phenomenon.

Introduction

In clinical practice, some patients treated with electroconvulsive therapy (ECT) show exceptionally high initial seizure thresholds. At the first ECT session, a high stimulus dose is then needed to induce a seizure of sufficient length in case a stimulus titration method [1] is used, or a subconvulsive stimulus is the result of the initial "age-based estimated dose method". Seizure threshold in ECT is generally defined as the smallest electrical stimulus dose that results in a generalised seizure of at least 25 to 30 seconds on electroencephalogram (EEG).[2,3] Seizure thresholds vary greatly among patients, and no consistent relationship has been found with the antidepressant response, except in unilateral ECT.[4,5] Induction of any seizure activity is thought to be imperative for effectiveness of ECT,[2] whereas it has also been reported that subconvulsive stimulation can be dangerous for the patient because of harmful bradycardia or asystole.[6] Exceptionally high seizure thresholds may therefore complicate ECT, due to the increased risk of inadequate treatment, especially in countries where the maximum stimulus dose of ECT devices is limited.[7]

In this report we describe ECT in a catatonic patient who needed an exceptionally high initial stimulus dose to induce an adequate seizure. The literature was searched for other reports on this phenomenon paying special attention to clinical and treatment characteristics and to strategies for management of high initial seizure threshold.

Case report

A 76-year-old patient with a history of recurrent depressive disorder with psychotic features and personality disorder for more than 20 years was referred for ECT because of catatonia during the last two months. She had a history of diabetes mellitus type 2, myocardial infarction, and ischemic cerebral infarction; in addition a moderate to severe aortic stenosis and aortic insufficiency had recently been diagnosed. During the previous year symptoms of cognitive impairment had emerged, probably due to cerebral cardiovascular disease. At admission, she almost exclusively showed severe muscle rigidity and mutism. On the Bush-Francis Catatonia Rating Scale (CRS), a score of 18 (from a maximum of 69 points) was rated.[8] The patient's clinical condition deteriorated quickly because she could not eat or drink. ECT was considered to be the treatment with the least risks and the highest probability to achieve improvement of her condition. In line with the clinical diagnosis of catatonia, apart from dehydration with uremia and masked

anemia, no abnormalities were found in blood tests. Cerebral MRI showed generalized atrophy with central and peripheral liquor spaces and bilateral periventricular white matter lesions. No signs of infarction were found.

At the first ECT session, anesthesia was induced with 10 mg etomidate intravenously (IV). Because the patient had been immobile for a prolonged period muscle relaxation was initiated with 8 mg mivacurium IV, instead of succinylcholine, to inhibit release of large amounts of potassium. In addition, 0.5 mg methylatropine IV was given to prevent bradycardia. Metoprolol was administered to prevent tachycardia and hypertension; in patients with aorta stenoses the latter conditions are potentially fatal. Standard bilateral (bifrontotemporal) ECT was administrated with the Thymatron IV (constant current, 0.9 Ampère; brief pulse; Somatics, Lake Bluff, Ill., USA). Seizure duration was monitored by EEG and motor activity by electromyography using the cuff method.

At the first stimulus, a dose of 223.2 milliCoulombs (mC; frequency, 70 Hz; pulse width, 0.25 milliseconds; stimulus duration, 7.2 seconds; static impedance, 1620 Ω; dynamic impedance, 270 Ω) was administered. This dosage was considered to be well above the age-based estimated seizure threshold. However, no muscle contractions occurred, and no seizure activity was registered on the EEG; the patient continued to have a regular heart rate and normal blood pressure. After 30 seconds, a second dose of 497.8 mC (frequency, 140 Hz; pulse width, 0.25 milliseconds; stimulus duration, 8 seconds; static impedance, 1460 Ω; dynamic impedance, 270 Ω) was given, again without any motor or EEG convulsive activity. While the patient was still adequately paralyzed and anesthesia was maintained, a third stimulus of 760.8 mC (frequency, 70 Hz; pulse width, 0.75 milliseconds; stimulus duration, 8 seconds; static impedance, 1350 Ω; dynamic impedance, 260 Ω) could be given. This stimulus resulted in 22 seconds of motor activity, and 29 seconds of EEG seizure activity.

Because of the patient's clinical condition, ECT was administered daily. During treatments, the stimulus doses and etomidate doses were kept identical resulting in adequate seizures with duration of motor activity ranging from 20 to 38 seconds. After 6 ECT sessions, the Catatonia Rating Scale score declined to 6 points, and after the 10th ECT session, the score was only 1 point. Clinically, the patient could speak, eat and drink again, and the catatonic features were no longer present. Unfortunately, after the 10th session, the patient suddenly developed paralysis of the left side of her face and mouth for several hours. After 3 days, the CT scan did not show infarction of the brain. However, ECT was discontinued because a transient ischemic attack was suspected, and it was considered that there was a

substantial risk of inducing more (severe) vascular incidents. The catatonia did not recur, and the patient was transferred back to the long-stay facility where she lived before admission to the hospital.

Literature search

We made a systematic search of the literature for other reports on patients with this phenomenon using Medline from 1966 to January 2008 and PsychINFO (2007), cross-referencing ECT and (excessively high) seizure threshold. The references of the articles found were hand searched for any additional reports. Furthermore, standard works on ECT were consulted.[2,3,9] We were especially interested in demographic and clinical factors that might enhance the initial seizure threshold and in strategies for its prevention. The abstracts of the articles found were scrutinized for reports on patients with high initial seizure thresholds in ECT, associated demographic and clinical characteristics, and recommendations for its management. Articles that did not describe any patient characteristics or descriptions of initial seizure thresholds were excluded.

Only 6 articles reporting on 10 patients with excessive initial seizure thresholds were found (Table 1).[7,10-14] The highest seizure threshold (3,226 mC) was described in a patient treated with ECT for status epilepticus,[14] although ECT is normally not indicated in such a condition. The other 5 case reports described high initial seizure thresholds (ranging from 335 to 896 mC) in severely depressed, mostly elderly patients (age range, 45-85 years; 5 males, 2 females; in 2 patients, data on age and sex were lacking). In 5 patients, comorbid somatic diseases were described, mostly of cardiovascular origin. In the literature, several factors influencing the seizure threshold could be identified, of which many were present in our patient (see Discussion). Some of the methods reported to lower seizure thresholds are given in Table 2.[2,12,15-24]

Table 1 Characteristics of patients (n= 10) with exceptionally high initial seizure thresholds, reported in the literature

Reference	Sex	Age (years)	Indication for ECT	Comorbidity	Initial seizure threshold*
[10]	Female	45	Major depression	Hypertension; diabetes mellitus type 2; dialysis-dependent renal failure; cardiomegaly; peripheral neuropathy; retinopathy	576 mC
	Female	74	Major depression	Dementia due to small-vessel cerebrovascular disease; hypertension; urinary incontinence; organic heart disease	RUL: 576 mC
[11]	Male	'elderly'	Psychotic depression	-	BL: 672 mC
[7]	Male	70	Bipolar depression	Renal insufficiency; hypertension; diabetes mellitus; atrial fibrillation	BL: 840 mC
	Male	85	Recurrent major depression	Cardiovascular diseases	RUL: 896 mC
[13]	-	-	Major depression	-	BL: 428 mC (n=1)
	-	-	Major depression	-	BL: 335 mC (n=2)
[12]	Male	54	Major depression	-	RUL: 840 mC
	Male	80	Major depression	-	BL: 576 mC
[14]	Male	36	Status epilepticus	Partial left posterior frontal resection	Modified (right frontotemporal + left anterior-frontal): 3,226 mC

*In milliCoulombs (mC); RUL: right unilateral electrode placement (d'Elia); BL: bifrontotemporal placement.

Table 2 Methods used to overcome high seizure threshold in patients undergoing ECT

Manipulation of stimulus parameters	**Reference**
(Switch to, or provide) unilateral ECT d'Elia.	[27]
Raise the stimulus dose Provide longer stimulus duration with same dosage Lower stimulus frequency Lower the frequency of treatments	[2,17,18]
Adjustments made by the anesthesiologist	
Switching anesthetic (administration of etomidate is advised as first-line in patients with high seizure thresholds; administrating ketamine or combining methohexital with alfentanil may prolong seizure duration)	[15]
Hyperventilation before stimulation, which lowers the carbon oxide level thereby raising neuroexcitability	[2,19]
Administer antagonist (flumazenil) if concomitant benzodiazepines are used	[12,20]
Augmentation strategies during ECT	
Caffeine augmentation significantly increases seizure duration, but does not decrease the seizure threshold	[19]
Theophiline augmentation	[19]
Concomitant use of an antipsychotic (chlorpromazine and clozapine have a relatively high seizurogenic potential).	[21]
Concomitant use of an antidepressant use (maprotiline, clomipramine, bupropion) is inconclusive	[21]
Augmentation strategies during ECT	
If possible, advise the patient to stop using or lower the use of anticonvulsants, benzodiazepines (also hypnotics), and antihypertensive medication (e.g. beta-blockers and calcium antagonists)	[2,16]
Advise sleep deprivation the night before ECT	[22]
Advise the patient to stop drinking alcohol	[23]
Encourage weight loss in an obese Chinese patient	[24]

Discussion

We have described bilateral ECT in a 76-year-old female catatonic patient with an exceptionally high initial seizure threshold. Because 2 preceding subconvulsive stimuli may have lowered the seizure threshold, her initial threshold might have been even higher.[25] A literature search revealed only 10 other cases with excessively high initial seizure thresholds. Compared with our patient, in most other cases, even higher seizure thresholds had to be overcome in order to elicit an adequate seizure. Several factors might have played a role in the occurrence of the exceptionally high seizure threshold in our patient, including, higher age, pre-existent dementia, large medical burden (in particular of cardiovascular origin), dehydration, use of metoprolol before ECT, bilateral electrode placement, lower dynamic impedance (260-270 Ω), and higher pulse frequency (70-140 Hz). Malnutrition for several months may have further contributed to the excessively high seizure threshold of our patient. It has been shown in young rats that a low-carbohydrate diet produces a significant increase of the seizure threshold.[26] On the other hand, female patients generally have a lower seizure threshold than males,[27] and the stimulus parameters used in our patient (i.e., long stimulus duration and short pulse width) may have contributed to lowering her seizure threshold.[18] Etomidate has been recommended as the first-line anesthetic for patients with very high seizure thresholds.[15] Because we routinely administer etomidate, lowering the seizure threshold by switching to another anesthetic was not an option with our patient. The cardiovascular condition of our patient was severely compromised as shown by the transient ischemic attack during the treatment period. Earlier, higher severity scores for cardiac illness and other forms of vascular diseases have been associated with higher seizure thresholds.[12] Concomitant use of antihypertensives and antiarrhythmics may have raised the seizure threshold in our patient who was given metoprolol before the first ECT because of aortic stenosis to prevent severe tachycardia and hypertension.[16,28]

In conclusion, patients with an exceptionally high seizure threshold at their first ECT are rare. Until now, besides our patient, very few have been reported in the literature. Several factors are known to raise the seizure threshold, thereby complicating ECT. Some of these factors might be managed clinically, with the aim to improve treatment and hopefully the outcome in individual patients. Further research may help to identify patients with exceptionally high seizure thresholds, to better understand their underlying causes, and to better deal with such phenomena.

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4

Seizure thresholds in elderly patients treated with electroconvulsive therapy for major depressive disorder. *A review*

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Abstract

Background: Electroconvulsive therapy (ECT) is effective and generally safe in depression. Its effectiveness and side effects are suggested to be related to the electrical stimulus administered relative to the seizure threshold. Since aging seems to raise the seizure threshold in ECT, we reviewed the literature for evidence correlating advanced age and seizure threshold, and for hypotheses explaining why seizure thresholds might raise with age.

Methods: Pubmed, PsychINFO, three standard works on ECT, and cross-references were searched for studies investigating seizure thresholds and/or associated factors in elderly depressed patients.

Results: A total of 406 possibly relevant articles were found, of which 27 studies could be included. One very recently published study was included afterwards because of its significance. Aging was moderately associated with a raised initial seizure threshold with correlation coefficients ranging from 0.30 to 0.64 ($P<0.05$). Also, seizure thresholds in elderly patients were more likely to raise during the ECT course. Reported hypotheses for these clinical phenomena include a decrease of neuroexcitability, changes in morphologic and functional characteristics of the brain, somatic comorbidity, and concomitant medication use.

Conclusions: To optimize ECT in elderly patients, hypotheses and suggestions for further research are proposed regarding the moderate correlation between advanced age and initial seizure threshold and the rise in seizure threshold during the ECT course.

Introduction

Electroconvulsive therapy (ECT) is an effective treatment for late life depression.[1] Also in other severe psychiatric conditions (e.g., catatonia, malignant neuroleptic syndrome, intractable psychosis, mania and delirium) ECT can be worthwhile and even lifesaving in elderly patients.[2] In old age, treatment of depression is often complicated by somatic comorbidity and polypharmacy, whereas transient post-ictal confusion, cardiovascular problems and falls are the most serious side-effects of ECT.[3,4] Even in patients aged >75 years, ECT is generally safe when carefully monitored and when its side-effects are balanced against the risks of untreated depression and complications of psycho-pharmacotherapy.[3]

Effectiveness and side-effects of ECT seem to be related to the administered electrical stimulus dose and electrode placement.[2] The electrical stimulus must exceed the seizure threshold to elicit a sufficient seizure,[5] whereas subconvulsive stimulation may cause bradycardia and asystole.[6] Seizure threshold has been defined as the smallest electrical stimulus dose that is necessary to produce a generalized seizure of at least a 25-30 seconds on EEG.[2] In addition, the extent of the electrical dose above the individual seizure threshold, rather than the absolute electrical dose, was suggested to be associated with short-term cognitive side-effects.[7] For example, patients aged > 50 years who fail to respond to moderate-charge right unilateral ECT, may benefit from high-charge right unilateral stimulation rather than from bilateral ECT, with less cognitive side-effects.[8]

Although not studied extensively, it is established that seizure thresholds vary substantially between patients. Several factors are known to increase seizure threshold and in clinical practice higher seizure thresholds seem to occur more often in elderly patients, especially in elderly men.[9-11]

To decide on the proper electrical dose for a patient, the empirical dose-titration method that determines the actual initial seizure threshold may be used to calculate individualized 'moderate' or 'high above' seizure threshold stimulation. In clinical practice, an 'age-based' method is often used to estimate the electrical dose that sufficiently exceeds the seizure threshold, based on the assumption that increasing age raises the seizure threshold.[12] However, the precise relationship between age and age-associated factors on the one hand and seizure threshold on the other hand is unknown. Therefore, we reviewed the literature for evidence correlating advanced age and seizure threshold in depressed patients, and for hypotheses explaining why seizure thresholds might raise with age.

Method

Medline (Pubmed, National Library of Medicine, http://www.ncbi.nlm.nih.gov) and PsychINFO (American Psychological Association, 2007) were searched for articles that were published from 1966 through March 2008 (see Figure 1 for the search strategy). All retrieved titles and abstracts (n=406) were investigated. Studies exploring seizure thresholds and/or associated factors in elderly patients were included in this review. In addition, one important, more recently published study was included afterwards,[13] three standard works on ECT were consulted [2,12,14] and their references were cross-checked to reveal relevant additional articles.

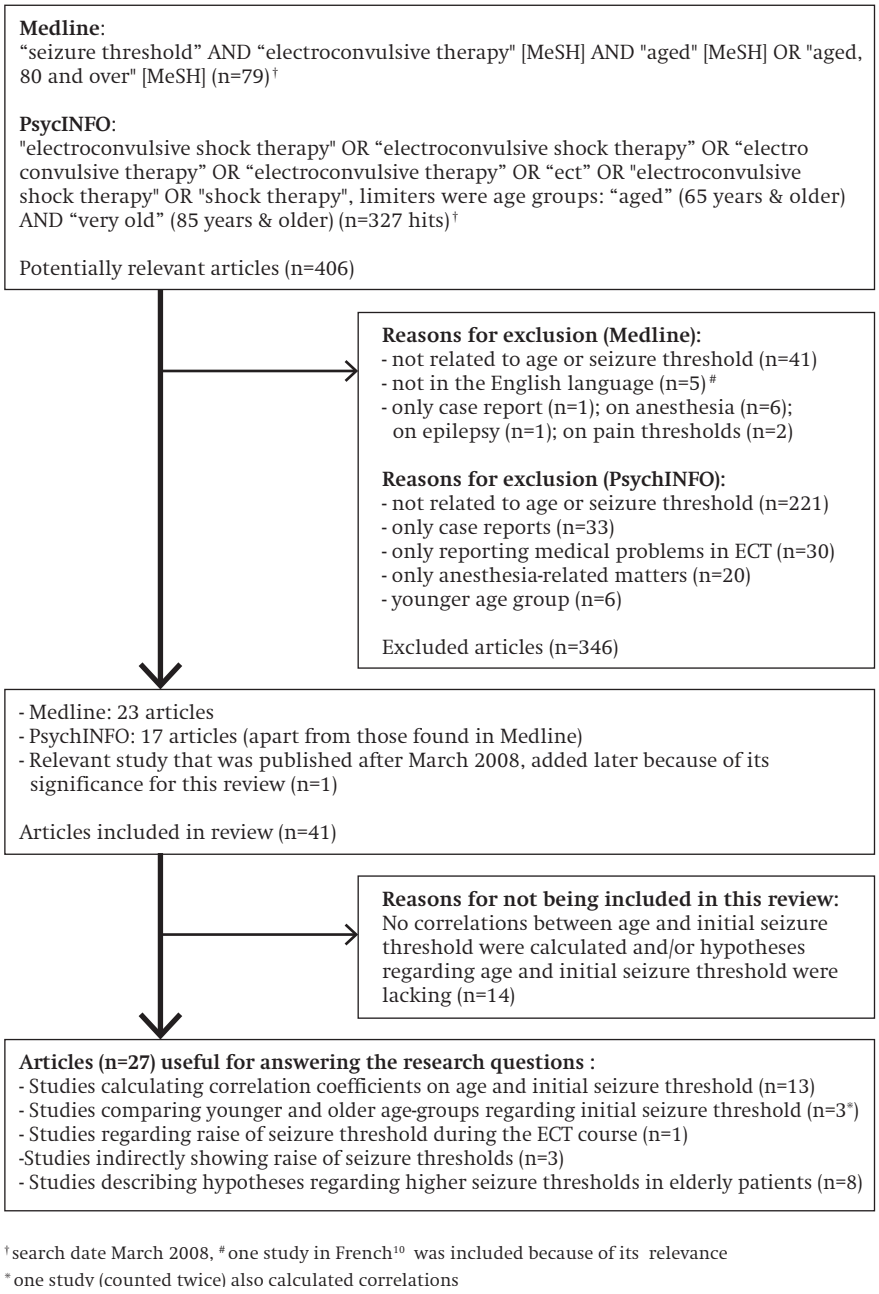
Results

For the present review, 27 studies appeared to be relevant. Of these, 13 studies presented data on correlations between seizure threshold and age, 3 studies compared younger and older age groups (of which 1 also calculated correlations), 1 study examined changes in seizure thresholds during the ECT course, 3 studies indirectly showed an increase of seizure threshold in elderly patients, and 8 studies presented hypotheses for an increased seizure threshold in elderly patients.

Initial seizure threshold in relation to age

In the 13 studies investigating the correlation between seizure threshold and age, a total of 1,481 subjects were included. The mean age of these samples ranged from 43.6 to 67.1 years and the absolute age from 18 to 93 years (Table 1). In all studies moderate significant overall correlations (r=0.30-0.64, P<0.05) between initial seizure thresholds and age were found,[9,10,15-25] except for one unilaterally treated female sample (r=0.098; P>0.05),[22] a bilaterally treated male sample (r=-0.47, P=0.17) [22] and a bilaterally treated female sample (r=-0.06; P>0.05).[23] After Z-transformation, sample size weighted average correlation coefficients were 0.42 ± 0.12 in right unilateral treated samples, 0.48 ± 0.07 in bilateral treated samples and 0.37 ± 0.06 in samples treated with both electrode placements, which are moderate correlations. Three studies reported that the initial seizure threshold, as measured at the first ECT session, was almost twice as high in patients aged ≥ 65 years than in younger patients aged < 55 years.[13,18,26] Further, being an elderly man appeared to be positively correlated with initial seizure threshold in right unilateral ECT [22] and bilateral ECT.[10,23]

Figure 1 Flow diagram of articles on ECT and initial and/or raise of seizure threshold in elderly patients



† search date March 2008, # one study in French[10] was included because of its relevance

* one study (counted twice) also calculated correlations

Table 1 Studies describing correlations between age and initial seizure thresholds (IST) in patients treated with electroconvulsive therapy (ECT)

Study	Psychiatric diagnosis; length of disease, or age at onset	% of female in sample	Prior ECT	Mean age (years ± SD; range*)	Electrode placement	Sample size	Correlations	P-value	Remarks
[14]	MDD**, schizophrenia; nd***	2%	-	53.0 ± 11.8	RUL****	27	r=0.36	P<0.001	Using sine wave and brief stimulus in almost only male patients.
				47.7 ± 12.6	BL****	40			
[9]	MDD; nd	68%	Excluded < 6 months	61.9 ± 15.3	RUL	25	r=0.32	P<0.05	No somatic comorbidity or use of somatic drugs mentioned.
		63%		60.8 ± 10.7	BL	27			
[15]	MDD, bipolar depression; nd	63%	n=66 (44.6%) had prior ECT	58.1 ± 14.3	RUL and BL	148	r=0.30	P=0.0001	No somatic comorbidity or use of somatic drugs mentioned.
[16]	MDD, mania, schizophrenia; nd	57%	-	47.1 ± 16.5; 19-83	RUL	14	r=0.49	P<0.01	No somatic comorbidity or use of somatic drugs mentioned.
					BL	14	r=0.58	P<0.001	
[17]	-; nd	49%	-	-	RUL	52	r=0.43	P<0.001	No somatic comorbidity or use of somatic drugs mentioned.
					BL	82			
[18]	-; nd	73%	Prior ECT excluded	55.2 ± 17.9	RUL	52	r=0.36	P=0.009	Occasionally patients received beta-blockers, and received their regular cardiovascular medications.
[19]	MDD, bipolar depression; nd	64%	Excluded < 6 months	57.5 ± 17.7	RUL	86	r=0.35	P<0.0001	Subjects using beta-blockers were excluded.
					BL	25			

[20]	MDD, schizoaffective disorder, mania; nd	62%	-	52.1 ± 19.5; 18-86	RUL BL	43 23	*r*=0.52	*P*<0.001	No somatic comorbidity or use of somatic drugs mentioned.
[10]	MDD, bipolar depression, psychotic disorder; nd	71%	Excluded < 6 months	56.4 ± 19.1	BL	147	*r*=0.44 *r*=0.58 (♂) *r*=0.39 (♀)	*P*<0.0001 *P*<0.0001 *P*<0.0001	No somatic comorbidity or use of somatic drugs mentioned.
[22]	MDD, bipolar depression; nd	67%	Excluded < 3 months	49.8; 28-69	RUL	50	*r*=0.31 *r*=0.64 (♂) *r*=0.098 (♀)	*P*=0.027 *P*=0.0061 *P*>0.05	Somatic medications were held constant during the ECT course.
				47.3; 24-77	BL	30	*r*=0.35 *r*=-0.47 (♂) *r*=0.59 (♀)	*P*=0.054 *P*=0.17 *P*=0.0064	
[23]	MDD, bipolar depression; nd	73%	Excluded < 6 months	52 ( ) 48 ( )	BL	137	*r*=0.06 *r*=0.46(♂) *r*=-0.06 (♀)	*P*>0.05 *P*<0.01 *P*>0.05	No prescribed treatment was relevant to this study.
[24]	MDD, bipolar depression; length of disease 18.3 ± 16.4 (range 0-78) years	65%	Excluded < 6 months	58.7 ± 18.2; 18-93	RUL BL	267 27	*r*=0.36	*P*<0.001	Use of beta-blocker in 5 patients.
[25]	MDD, schizophrenia, bipolar depression; age at onset 35.6 ± 14.8 years	63%	Excluded < 12 months	43.6 ± 15.4; 15-82	RUL BL	60 105	*r*=0.55 *r*=0.55	*P*<0.01 *P*<0.01	No somatic comorbidity or use of somatic drugs mentioned.

*age range was not always available; ** MDD=major depressive disorder; ***not described in study; ***RUL=right unilateral ECT, BL= bilateral ECT

Seizure threshold during the course of ECT

Increasing age was associated with a greater likelihood that seizure threshold would raise during the ECT course, independently of electrode placement. For example, of 15 patients aged 70-89 years, 12 (80%) showed an increase in seizure threshold from the first to the sixth treatment session compared to 26 of 52 patients (50%) aged < 70 years (Chi-square=8.78;*df*=1; *P*<0.003).[27] More recently, however, age was reported not to be associated with a raise in seizure threshold measured after an index ECT course, comparing only bilaterally treated patients aged > 50 years (n=55) and ≤ 50 years (n=20).[28]

There are also indirect indications for the clinical phenomenon of a raise in seizure threshold in elderly patients. Older age was a predictor of requiring the maximum possible stimulus intensity during the course of ECT;[29] in older patients more failures to elicit an adequate seizure occurred.[30] Although seizure duration does not necessary reflect seizure threshold, in a stepwise regression analysis of mostly bilaterally treated subjects (n=334), higher age was found to predict failure or short duration of the seizure in both women and men, but only if the number of medical diagnoses was not taken into account.[31]

Discussion

In the present review, advanced age showed a moderate correlation with initial seizure threshold in ECT, which is in line with studies reporting that age accounted for only 8-25% of the variance in initial seizure threshold.[9,13,20,24,25] In addition, only a few studies showed seizure failure and a greater likelihood of seizure threshold raise during the ECT course in elderly patients. Although the use of the commonly practiced 'age-based' dosage methods, assuming increased seizure threshold in older patients, seems rational,[32-34] the upper limit of the reviewed study samples' mean age was only 67.1 years. This raises questions about the generalizability of these findings to the ECT practice in (very) old patients, especially taking into account their vulnerability for side-effects.[3,4] Also, in elderly patients without increased seizure threshold 'age-based' methods may lead to overestimation of the seizure threshold, leading to overstimulation and possibly increased risk of cognitive dysfunction. On the other hand, underestimation of the seizure threshold may increase the risk of subconvulsive stimulation associated with cardiac arrhythmia (bradycardia or even asystole).[6] Furthermore, a suboptimal treatment response may be the result in case of underestimation of the seizure threshold. Therefore, in right unilateral ECT electrical dosage 6-12 times above seizure threshold is advised for optimal effectiveness.[12] Only with the 'dose-titration'

method, however, the individualized initial seizure threshold is determined at the first ECT session.[2,12] Therewith, an optimal suprathreshold dosage may be chosen, and the expected effectiveness can be weighted against the risk of cognitive side-effects and cardiac arrhythmia.[6,12] It remains unclear why increasing age affects seizure threshold, especially because other factors (e.g., electrode placement, pulse width, stimulus frequency) have been suggested to influence seizure threshold more than age.[2] Therefore, based on the reviewed literature, hypotheses on the relation between increased seizure threshold in elderly patients and morphological, functional and clinical factors of aging are discussed below (see also Table 2).

Morphological factors and decreased neuroexcitability

The aging brain undergoes several morphological changes which may contribute to decreased neuronal excitability and consequently higher seizure threshold in ECT.[15,29,35] Elderly subjects show reduced brain volumes primarily affecting the prefrontal cortex, angulus gyrus, superior parietal gyri and hippocampus. Also, a general reduction of neural density (disproportionally more so in the frontal white matter) as well as a reduction in neuronal complexity are part of the aging process, thereby compromising cerebral synaptic communication.[36-39] The age-related atrophy and decreased complexity of the brain network may increase the distance between ECT electrodes and cortex, which may lead to both decreased and less synchronous stimulation of the neurons resulting in reduced neuroexcitability.[39,40]

Because of the cerebral atrophy, the brain's volume of cerebrospinal fluid (CSF) also increases with age.[37] Furthermore, brain vessel changes and breakdown of the ventricular lining in old age can cause leakage of CSF into the white matter.[41] It has been shown that, compared to controls, patients with late-life major depression have even larger volumes of CSF on magnetic resonance imaging (MRI).[42] Electrical current flows easier through CSF than brain tissue.[43] Consequently, increased volumes of CSF in elderly patients will result in more shunting of electrical current, also explaining higher seizure thresholds.[43] The finding that elderly men show a more pronounced increase in CSF volumes than elderly women,[44] is in line with the finding that elderly men have higher seizure thresholds compared to women.[2,9]

The interelectrode distance and scalp, skull and brain tissue characteristics are important determinants of the seizure threshold, probably also in elderly patients,[27,43] Scalp impedance was hypothesized to increase with age which can imply higher seizure thresholds,[45] although others did not find evidence for this factor.[15] Anthropometric research regarding the forehead width showed a decrease

Table 2 Suggested hypotheses for morphological, functional and clinical factors explaining the relation between higher seizure threshold in electroconvulsive therapy (ECT) and aging

Morphological factors:	
Atrophy	- Age-related atrophy increases the distance between ECT electrodes and cortex. - Age-related atrophy decreases the number of neurons that are stimulated or less synchronously activated. - Age-based decrease of neuronal density and complexity results in less synaptic communication.
Cerebrospinal fluid (CSF)	- Increase of CSF volume results in more shunting of electrical current. - Elderly men have increased CSF volumes compared to women, therefore men have higher seizure thresholds.
Scalp impedance	- Scalp impedance increases with age.
Interelectrode distances	- Shorter interelectrode distances gives more shunting of the current through the scalp. - Decrease of interelectrode distance and the skin-electrode interface in elderly women results in lower seizure threshold, compared to men.
Functional factors:	
Cerebral metabolism	- Decreased metabolism in the prefrontal brain areas results in lower neuroexcitability.
White matter hyperintensities (WMH)	- Increased rates of subcortical WMH are associated with lower coherence on the quantitative electroencephalogram (a measure of neuronal connectivity) resulting in poorer neuroexcitability.
Neurotransmitters	- More GABA-A receptors in the hippocampus. - Reduction in the brain's concentration of glutamate.
Clinical factors:	
Medical illness	- Higher prevalence of medical illnesses predicts higher seizure threshold.
Pharmacotherapy	- Concomitant medication use predicts higher seizure threshold.

of the bony and skin surface in old women (aged 81-90 years) but not in men, compared to youngsters.[46] As a consequence, interelectrode distance as well as the skin-electrode interface may be relatively smaller in elderly women and thus contribute to lower seizure thresholds compared to elderly men.[17] This is, however, not consistent with the fact that reduced interelectrode distances have been associated with increased shunting of the current through the scalp, thus requiring a higher stimulus intensity to elicit a seizure.[43,47]

Functional factors and decreased neuroexcitability

Functional brain research in normal aging reveals a decrease of frontal metabolism [48] and of activation in the prefrontal areas,[36] which are especially stimulated in bilateral ECT [43] and may result in reduced neuronal excitability.[9,35,40] Furthermore, synthesis, release and reuptake of different neurotransmitters change with aging, and inhibitory responses are increased.[39,49] For example, surviving hippocampal neurons in aging possibly cause increased synthesis of GABA-A receptors in order to maintain inhibitory hippocampal circuitry,[50] which may also raise the seizure threshold. Age-related reduction in the brain's concentration of glutamate (an excitatory neurotransmitter) [36] may also result in reduced neuroexcitability. Nowadays, cortical excitability can be measured noninvasively using transcranial magnetic stimulation (TMS),[51,52] but studies relating TMS to seizure threshold in ECT are lacking.

Late-onset depression has been associated with disruptions of fronto-striatal neuronal pathways due to ischemic microvascular lesions, associated with white matter hyperintensities (WMH) on MRI.[53] These WMH are associated with low quantitative electroencephalographic (EEG) coherence, a measure of functional cerebral connectivity between brain regions and dependent upon integrity of white matter tracts and gray matter structures.[54] Interestingly, lower interhemispheric coherence in the delta frequency band on EEG measures of depressed patients treated with ECT has been associated with poorer treatment response.[55] It may be hypothesized that decreased functional neuronal connectivity results in higher seizure threshold because a decreased number of neurons is less, or less synchronously, activated.[40]

Clinical factors and increased seizure threshold

Greater burden of medical illness, especially of cardiovascular origin, has been associated with higher initial seizure thresholds.[24] As elderly depressed patients are at higher risk of serious medical comorbidity, including cardiovascular diseases,[42] this clinical factor may contribute to the higher chance of increased seizure thresholds in older patients. Furthermore, such comorbidity often leads to pharmacotherapeutic treatments of which several are known to increase the seizure threshold, in particular anticonvulsants, benzodiazepines, beta-blockers, and calcium antagonists.[56] Although in most studies on the relation of seizure threshold and age the use of psychopharmacological drugs was an exclusion criterion, concomitant use of non-psychotropic drugs was hardly mentioned. To what extent higher seizure threshold in elderly patients may be explained by higher prevalence of medical illnesses (e.g., cardiovascular diseases accompanied by white matter abnormalities) and/or concomitant medication use is not clear.

Conclusion

The present review revealed that increasing age is moderately associated with an increased initial seizure threshold in ECT. Especially elderly men seem to require higher electrical doses, and their seizure thresholds are more likely to be raised during the ECT course compared to elderly women and younger patients. The question why aging affects seizure thresholds has received little attention. Reported hypotheses for the influence of increasing age on seizure threshold include decreased neuronal excitability, changes in morphologic (cerebral atrophy, increase of CSF, and of the scalp and skull thickness) and functional characteristics of the brain (frontal hypometabolism, increased inhibitory responses, reduced EEG coherence), as well as somatic comorbidity and concomitant medication use. These hypotheses need to be further investigated which may lead to new strategies for optimizing ECT dosing, especially among frail elderly patients.

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2 PART

EXCITING MATTERS ABOUT PREDICTING SEIZURE THRESHOLD: *A PROSPECTIVE, OBSERVATIONAL COHORT STUDY*

5

Clinical predictors of seizure threshold in electroconvulsive therapy: *A prospective study*

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Abstract

Background: At the start and during the course of electroconvulsive therapy (ECT), estimation of the seizure threshold (ST) is useful in weighing the expected effectiveness against the risks of side effects. Therefore, this study explores clinical factors predicting initial ST (IST) and levels of ST during the ECT course.

Methods: This prospective observational study included patients aged ≥ 18 years receiving ECT without contraindications for dosage titration. At the first and every sixth consecutive ECT session, ST level was measured. Using multivariate linear regression and multilevel models, predictors for IST and change in ST levels were examined.

Results: A total of 91 patients (mean age, 59.1±15.0 years; 37% male; 97% diagnosis of depression) were included. In multivariable analysis, higher age (β=0.24; *P*=0.03) and bifrontotemporal (BL) electrode placement (β=0.42; *P*<0.001) were independent predictors for higher IST, explaining 49% of its variation. Also, these two variables independently predicted higher ST levels at different time points during the course. Using multilevel models, absence of a previous ECT course(s) predicted a steeper rise in ST during the course (*P*=0.03 for the interaction term time*previous ECT).

Limitations: The age-adjusted dose-titration method is somewhat crude, resulting in some measurement error. Concomitant medication use could have influenced ST levels.

Conclusion: Increasing age and BL electrode placement predicted higher (I)ST, which should be taken into account when selecting ECT dosage. Previous ECT course(s) may avoid an increase in ST during the course of ECT.

Introduction

Electroconvulsive therapy (ECT) is an effective and safe treatment for depression as well as for other severe psychiatric conditions, such as catatonia, malignant neuroleptic syndrome, intractable psychosis, mania and some specific forms of delirium.[1,2] To be effective, ECT must elicit generalized seizure activity in the brain by using an electrical stimulus that exceeds the seizure threshold (ST).[3] Although controversy exists about the optimal electrical stimulus dosing strategy,[4,5] there is some consensus that, especially in right unilateral (RUL), the stimulus should substantially exceed the ST.[1,6,7] The initial ST (IST) has been defined as the smallest electrical dose needed to produce a generalized seizure of at least 25-30 s on an electroencephalogram (EEG) at the first session.[1,8] IST is reported to vary substantially between patients,[4] although prospective studies are sparse.[9,10]

Higher IST is associated with male gender,[9,11] advanced age,[9,11,12] bifrontotemporal (BL) electrode placement,[9,13,14] lower dynamic impedance,[13,15] a greater burden of medical illness,[9] higher body mass index (BMI),[9,16] and with previous ECT course(s) and concomitant medication use.[1,9]

Because, on the one hand, the extent of the electrical dose above the IST is associated with more short-term cognitive side effects [17] and, on the other, subconvulsive stimulus administration is related to cardiac arrhythmia,[18] better knowledge of the factors determining the individual IST would be clinically useful in weighing the expected effectiveness against the risks of side effects of ECT.

Over a complete treatment course, 40-100% of patients are reported to show a rise in ST, and failure to reach a substantial ST increase may be a marker of lack of efficacy.[19, 20] Moreover, in RUL ECT, a rise in ST during the course is associated with a significantly lower likelihood of therapeutic response; in addition, older patients are more likely to show ST increase and to be a non-responder.[21] Apart from age, seizure intensity on EEG, total course duration and electrode placement, are suggested to determine a rise in ST.[19-21] However, those disagreeing with these findings estimate that only 20-46% of patients would show a rise in ST during the course without negative consequences for the effectiveness of the treatment.[1,22,23] Hypotheses to explain the variation of IST and the change of ST during the ECT course in relation to clinical characteristics are sparse.[24] Clinically, it will be helpful if patient characteristics could guide an optimal decision regarding the electrical stimulus, both at the start and during the course of ECT. Therefore, this study is a prospective investigation of clinical factors predicting IST and change of ST during the course of ECT.

Methods

Participants

All consecutive patients (from December 1, 2009, to November 15, 2011) with an indication for ECT at the Rijnstate Hospital (a 36-bed psychiatric facility in Arnhem, with a catchment area of 600,000 inhabitants) were asked to participate in this prospective observational study. Patients were excluded if age was < 18 years (n=0), no written informed consent was provided (n=5), and contraindications existed for dose titration (e.g., life-threatening condition of the patient, severe cardiovascular comorbidity; n=18). The local medical ethical committee approved the research protocol (trial registration number: NL24697.091.09). Written informed consent was obtained from all participants.

Age, gender, psychiatric disorder(s) classified according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) by at least two experienced psychiatrists, somatic comorbidity, BMI (weight/[height]^2), previous ECT treatment (including time interval between last ECT session and current titration session), and concomitant medication use were documented in a standardized way. Of those patients who did not agree to participate or who were excluded, age, gender, psychiatric diagnoses (DSM-IV-TR, axis 1 and 2), and somatic comorbidity were registered. Only patients who were diagnosed with a well-documented personality disorder or who were clinically suspected to suffer from comorbid personality disorder were classified according to the DSM-IV-TR, axis 2.

Instruments

In the week before the first ECT (baseline), severity of the mood disorder was assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS), a validated observer-rated scale that contains 10 items (scored 1-6 per item). Maximum score is 60, with higher scores indicating more and a higher severity of depressive symptoms.[25]

Cognitive functioning in the week before the first ECT (baseline) was measured using the Mini-Mental State Examination (MMSE). This validated instrument is commonly used to evaluate cognitive functioning in patients (maximum score is 30, with lower scores indicating more cognitive dysfunction).[26]

Amount and severity of somatic comorbidity was rated using a modified Cumulative Illness Rating Scale (CIRS),[27] consisting of 14 aspects of possible pathology and impairment of major organ systems, which are rated from 1 (no impairment to that organ/system) to 5 (impairment is life threatening; treatment is urgent or of

no avail; prognosis is grave), whose sum score ranges from 14 through 70 points.[27] The item 'Psychiatric/Behavioral (includes depression, anxiety, agitation, psychosis, not dementia)' was set at 5.

Electroconvulsive therapy and measurement seizure thresholds

ECT was administered using a constant-current (0.9 Ampère), brief-pulse (0.25 milliseconds [ms] in RUL ECT; 0.5 ms in BL ECT) device (Thymatron IV; Somatics Incorporation, Lake Bluff, Illinois, USA), after intravenous induction of anesthesia with etomidate (1.5 mg/kg body mass), muscle paralysis with succinylcholine (0.5-1 mg/kg body mass), and with appropriate oxygenation (100% oxygen, positive pressure) until the resumption of spontaneous respiration. Electrode placement was initially RUL, except in patients at high risk for suicidality and/or somatic complications, or if previous ECT had successfully been administered bilaterally. The decision as to whether a patient should be switched to BL during the course was based on the clinical judgment of the treating psychiatrist (mostly when less/no clinical response had been reached after six RUL sessions). Treatment parameters (electrode placement, dynamic impedance, etomidate and succinylcholine dose, switch from RUL to BL during the course, and total ECT sessions of the index ECT course) were documented.

ST was measured by an internationally accepted, empirical, age-adjusted, titration method at the 1st (IST), 6th, 12th, 18th and 24th ($ST_{6\text{-}12\text{-}18\text{-}24}$, respectively) ECT session.[7] Consecutive measurements of ST depended on the duration of the ECT course. Index ECT was terminated if the patient had recovered, showed no (further) clinical improvement over a period of 2 weeks, or had shown no improvement at all after 10 BL sessions, based on the judgment of at least two experienced psychiatrists. If the starting stimulus dose failed to elicit a seizure of at least 20 s of motor activity measured with the cuff method and/or ≥ 25 s on EEG, stimulus charge was increased according to the titration schedule (for patients aged < 50 years: 25.2 mC, 50.4 mC, 100.8 mC, 201.6 mC, and 403.2 mC; for patients aged ≥ 50 years: 50.4 mC, 100.8 mC, 201.6 mC, and 403.2 mC), and the patient was restimulated after 30 s. After the titration session, dosage was set at 2.5 times ST for BL, and at six times ST for RUL treatment. Patients were treated twice weekly. During the titration session, if the ST was reached, and muscle relaxation and anesthesia were still sufficient, the patient was restimulated at a therapeutic dose in that same session.

Statistical analyses

Data are presented as means, standard deviations (SD) or standard errors (SE), medians and interquartile ranges (IQR), or numbers and percentages, when appropriate.

The excluded patients were compared to the study group using t-tests for age, MADRS score, and CIRS score, with the X^2-test for gender, and the Mann-Whitney U test for the skewed MMSE score. First, descriptive statistics were applied on patient and treatment parameters. Differences between levels of IST and $ST_{6\text{-}12\text{-}18\text{-}24}$ were calculated, and the median change in ST value per ST measurement was compared in the RUL and BL treated groups, using Mann-Whitney U tests. Second, to detect independent clinical factors predicting IST, univariate regression analyses were performed for all variables, followed by multivariate regression analyses selecting those variables that were associated with *P*-values < 0.10 in the univariate analyses. Finally, multivariate multilevel regression analyses (i.e., linear mixed models, adjusted for gender, age, CIRS score, MMSE score, previous ECT, electrode placement, dynamic impedance and succinylcholine dose) were performed to detect predictors of ST levels during the ECT course. Multilevel regression analysis was also used to analyze the association between baseline predictors and changes over time in ST (using appropriate interaction terms of the predictor*time; in which time was used as a continuous variable). In multilevel analyses, we used a compound symmetry covariance model with a two-level structure consisting of up to five observations in time (lower level) and the subject (higher level).

All tests were two-sided with *P*<0.05 denoting statistical significance. SPSS for Windows version 17.0 (SPSS Inc., Chicago, Illinois, USA) was used for all analyses.

Results

Patient and treatment characteristics

Of the initial 114 patients, 91 indicated for ECT were included in this study. Excluded patients (no informed consent [n=5], contraindications for dose titration [n=18]) did not differ from the study group regarding mean age (t=-1.436; *df*=112; *P*=0.15), gender (Fisher's exact test=0.053; *df*=1; *P*=0.51), mean MADRS score (t=0.445; *df*=99; *P*=0.66), median MMSE score (Mann-Whitney U test=344.5; Z=-1.88; *P*=0.06), and mean CIRS score (t=1.671; *df*=112; *P*=0.10). In the excluded group, there were more patients with a diagnosis of catatonia (X^2=12.48; *df*=3; *P*=0.006).

Table 1 shows the patient and treatment characteristics. Mean age was 59.1±15.0 years, 37% (n=34) was male, nearly all patients (97%; n=88) were depressed, and 26% (n=24) of them also had psychotic features. At baseline, mean MADRS score was 36.2±8.6 and median MMSE score was 28 (IQR: 25-29). The CIRS showed a mean score of 22.2±3.8, and higher CIRS scores were significantly related to higher age (*r*=0.48; *P*<0.001). Of all patients, 31% (n=28) had undergone previous ECT course(s),

Table 1 Patient and treatment characteristics (n=91)

Patient characteristics	**n (%); or mean ±SD*; or median; IQR****
Male gender	34 (37.4)
Age, in years	59.1±15.0
Body Mass Index, in kg/m^2	24.7; 22.7-27.3
CIRS score^	22.0±3.8
Diagnostic category, according to axis 1 of DSM-IV-TR$^{\$}$:	
Depressive disorder without psychotic features	50 (54.9)
Depressive disorder with psychotic features	24 (26.4)
Bipolar disorder, depressive episode	14 (15.4)
Other disorders^^	3 (3.3)
Documented or clinically suspected personality disorder present, according to axis 2 of DSM-IV-TR	27 (29.7)
MADRS*** score at baseline (n=88)	36.2±8.6
MMSE**** score at baseline (n=86)	28; 25-29
Treatment characteristics	
Had previous course(s) of ECT	28 (30.8)
Days between last ECT and index ECT (n=28)	646; 202-1393
Use of seizure threshold influencing concomitant pharmacotherapy:	
Benzodiazepines	54 (59.3)
Anti-epileptics	7 (7.7)
Antidepressants	52 (57.1)
Antipsychotics	58 (63.7)
Electrode placement is bifrontotemporal at first titration session	28 (30.8)
Initial seizure threshold, in milliCoulombs	60.9±42.3
Dynamic impedance at first titration session, in Ω	275.5±59.5
Etomidate dose at first titration session, in mg	20; 18-22
Succinylcholine dose at first titration session, in mg	80; 75-100
Total number of ECT sessions$^{\#}$ (n=86)	17.9±7.4
Switch from right unilateral to bifrontotemporal electrode placement during course$^{\#\#}$ (n=63)	33 (52.4)

*Standard deviation; **Interquartile range; ^Cumulative Illness Rating Scale (modified version); $^{\$}$Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; ^^Schizophrenia (n=2) and malignant neuroleptic syndrome (n=1); ***Montgomery-Åsberg Depression Rating Scale; ****Mini-Mental State Examination; $^{\#}$Dropouts of treatment (suicide n=1; terminal illness n=1; wanted to stop n=3) excluded from analysis; $^{\#\#}$Only patients started with right unilateral electrode placement were analyzed.

with a median of 646 (IQR: 202-1,393) days between the last previous ECT session and the IST session.

Mean level of IST was 60.9±42.3 mC. In patients treated with BL electrode placement, mean IST was on average 50 mC higher than in RUL (95.4±59.5 mC vs. 45.6±16.8 mC; t-test=-4.35; *df*=28.9; *P*<0.001). During the ECT course, concomitant pharmacological drugs that might influence ST were commonly used, mostly antipsychotics (64%; n=58). Of all patients, 69% (n=63) were initially treated with RUL ECT, of whom 52% (n=33) switched to BL electrode placement during the ECT course. A mean of 17.9±7.4 treatments were administered during the index ECT course.

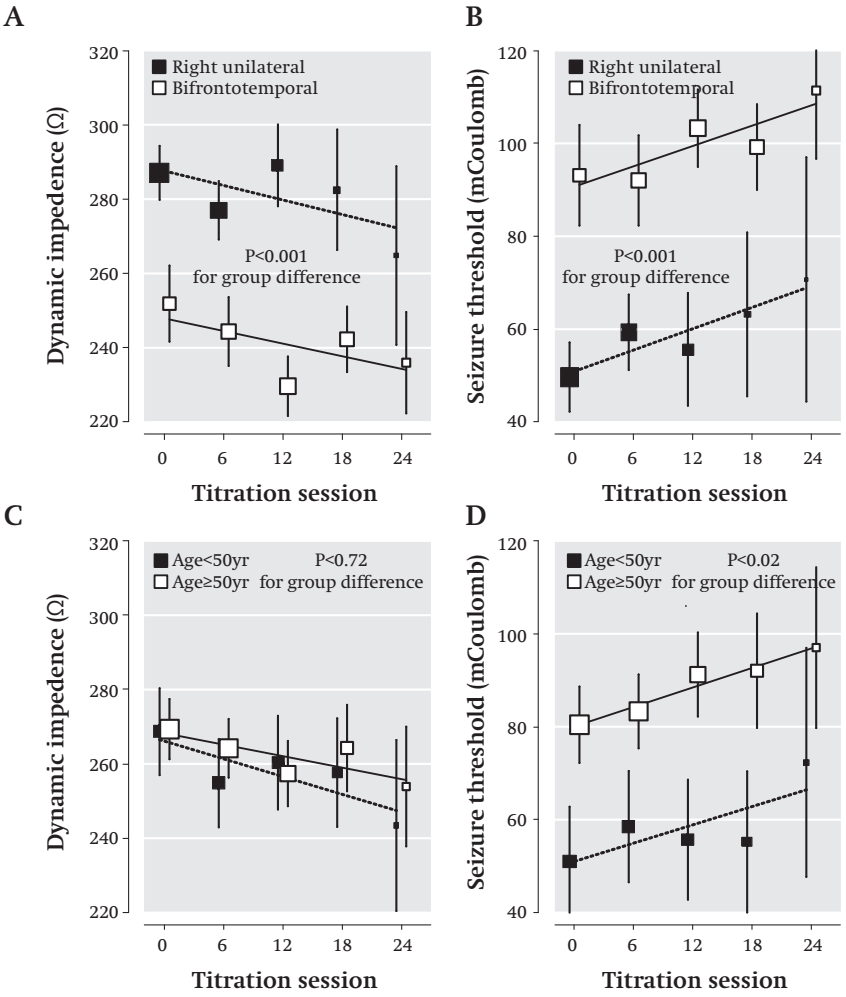
Predictors for IST

Univariate regression analyses showed significant associations with higher IST of higher age (*P*<0.001), higher CIRS score (*P*<0.001), lower MMSE score at baseline (*P*=0.002), having had previous ECT (*P*=0.001), treatment with BL electrode placement (*P*<0.001), lower dynamic impedance (*P*=0.02), and lower dose of succinylcholine (*P*=0.005) (Table 2). Multivariable regression analysis yielded higher age (β=0.24; *P*=0.03) and BL electrode placement (β=0.42; *P*<0.001) as independent predictors for higher IST. This model explained 49% (R^2=0.493) of the variation in IST.

Predicting for ST change during the ECT course

ST values were similar to IST in 78% (n=67 of 86) of the patients at the ST_6 measurement, in 60% (n=40 of 67) at ST_{12}, in 44% (n=19 of 43) at ST_{18}, and in 33% (n=5 of 15) at ST_{24}. Table 3 presents the changes in ST over time in the RUL- and BL-treated groups. Mean ST levels increased during the course (t=4.797; *df*=231; *P*<0.001; see also Figure 1B), in patients undergoing RUL and BL ECT. Six (of 86; 7%) patients showed a lower ST_6 than IST, as well as five (of 67; 7%) at the ST_{12} measurement, three (of 43; 7%) at ST_{18}, and one (of 15; 7%) at ST_{24}. At the 12th session, a rise in ST with respect to IST occurred 40% more often in BL than in RUL electrode placement (53% [n=24] vs. 14% [n=3]; Fisher's exact test=9.68; *df*=1; *P*=0.03), with a median change of 25.2 (IQR: 0-50.4) mC in BL-treated patients and of zero (IQR: 0-0) mC in RUL-treated patients (*P*=0.02; Table 3). At the ST_{18} measurement, the median value of ST change was also higher with BL electrode placement, but with borderline significance (*P*=0.06); at ST_{24}, the median value of ST change in BL treated patients was higher than in the RUL group, but the difference was not significant (*P*=0.34; Table 3).

Figure 1 Adjusted mean values* of dynamic impedance and seizure threshold during the course of electroconvulsive therapy in patients treated with right unilateral or bifrontotemporal electrode placement [**A**, **B**], and in patients aged < 50 years (n=29) and ≥ 50 years (n=62) [**C**, **D**]



*Error bars represent standard errors and black (dotted) lines are regression lines. The size of each square is proportional to the number of patients. Adjusted mean values and *P*-values were calculated by multivariable regression analysis adjusted for age [for A and B], CIRS score, MMSE score at baseline, previous ECT and electrode placement [for C and D], dynamic impedance, and succinylcholine dose.

Table 2 Univariate and multivariate regression analyses to detect independent patient and treatment characteristics to predict initial seizure threshold (IST), and mixed analyses to detect independent predictors of the variation in seizure threshold (ST) during the course of electroconvulsive therapy (ECT)

	Univariate correlates of IST at baseline		Multivariate correlates of IST* at baseline		Multivariate correlates of ST* during follow-up	
Patient characteristics	**β-coefficient**	**P-value**	**β-coefficient**	**P-value**	**β-coefficient**	**P-value**
Male gender	-0.043	0.682				
Age, in years	0.466	**<0.001**	0.238	**0.033**	0.279	**0.009**
Body Mass Index, in kg/m^2	-0.156	0.143				
CIRS score^	0.385	**<0.001**	0.154	0.131	0.127	0.227
Diagnostic category, according to axis 1 of DSM-IV-TR§						
Depressive disorder without psychotic features	-0.064	0.544				
Depressive disorder with psychotic features	0.030	0.781				
Bipolar disorder, depressive episode	0.076	0.476				
Other disorders^^	-0.046	0.664				
Documented or clinically suspected personality disorder present, according to axis 2 of DSM-IV-TR	-0.134	0.207				
MADRS** score at baseline	0.082	0.450				
MMSE *** score at baseline	-0.331	**0.002**	-0.045	0.641	0.058	0.549
Treatment characteristics						
Had previous course(s) of ECT	0.346	**0.001**	0.059	0.579	-0.052	0.564
Days between last ECT and index ECT	-0.064	0.746				

Use of seizure threshold influencing concomitant pharmacotherapy							
Benzodiazepines	0.033	0.758					
Anti-epileptics	0.027	0.803					
Antidepressants	0.084	0.431					
Antipsychotics	-0.112	0.289					
Electrode placement is bifrontotemporal	0.546	**<0.001**	0.424	**<0.001**	0.348	**<0.001**	
Dynamic impedance	-0.248	**0.018**	-0.082	0.344	-0.107	0.062	
Etomidate dose	-0.084	0.427					
Succinylcholine dose	-0.295	**0.005**	-0.071	0.452	-0.056	0.376	

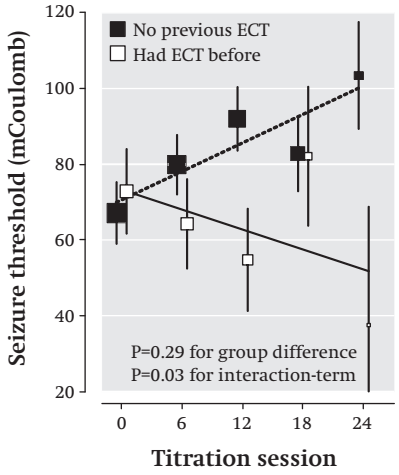
*Multivariate regression analysis and mixed analysis only for variables showing *P*<0.10 at univariate analysis; ^Cumulative Illness Rating Scale (modified version); $Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; **Montgomery-Åsberg Depression Rating Scale; ***Mini-Mental State Examination

Using multilevel linear models, higher age (β=0.28; *P*=0.009) and BL electrode placement (β=0.35; *P*<0.001) were independent predictors for higher ST during the course (Table 2). Mean dynamic impedance decreased during the course (t=-5.031; *df*=217; *P*<0.001), and lower dynamic impedance showed borderline significance (β=-0.11; *P*=0.06) for being a predictor of higher ST during the course. Figure 1 shows that, during the ECT course, adjusted mean values of dynamic impedance decreased and were significantly lower in BL-treated compared with RUL-treated patients (*P*<0.001; Figure 1A) and also that adjusted mean values of ST increased for both electrode placements and were significantly higher in patients treated with BL electrode placement compared with those treated with RUL (*P*<0.001; Figure 1B). Comparing patients aged < 50 years and ≥ 50 years, no difference was found regarding adjusted mean values of dynamic impedance during the course (Figure 1C). In patients aged ≥ 50 years, adjusted mean values of ST (Figure 1D) showed a steeper increase during the ECT course than in patients aged < 50 years (*P*=0.02), illustrating the strong linear association with age as a continuous variable (Table 2).

Multivariate multilevel models in which age, CIRS score at baseline, MMSE score at baseline, electrode placement, dynamic impedance and succinylcholine dose were entered showed an independent interaction term only for having had previous ECT course(s) predicting the

value of ST (t=2.188; *df*=217; *P*=0.03). Figure 2 shows that patients with previous ECT course(s) had less/no rise in ST during the course and that the absence of previous ECT treatment predicted a steeper rise in ST.

Figure 2 Adjusted mean values* of seizure threshold during the course of electroconvulsive therapy (ECT) in patients with no previous ECT (n=63), and in patients with previous ECT course(s) (n=28)



* Error bars represent standard errors and the black (dotted) line is the regression line. The size of each square is proportional to the number of patients. Adjusted mean values and the *P*-value for interaction (i.e. time*previous ECT) was calculated by multivariable regression analysis adjusted for age, CIRS score, MMSE score at baseline, previous ECT, electrode placement, dynamic impedance, and succinylcholine dose.

Table 3 Mean values of seizure thresholds (ST), the number of patients with increased ST with respect to initial ST, and median change of ST values, during a course of electroconvulsive therapy, in patients treated with right unilateral (RUL) and bifrontotemporal (BL) electrode placement

Characteristic	RUL placement				BL placement				P-value for comparing median ST change in RUL versus BL**
	n	Mean ±SD	ST increase present (%)	Median ST change versus baseline; IQR	n	Mean ±SD	ST increase present (%)	Median ST change versus baseline; IQR	
ST* at initial session	63	45.6±16.8			28	95.4±59.5			
ST at 6th session	49	53.0±25.3	9 (18.4)	0; 0-0	37	98.1±77.9	11 (29.7)	0; 0-25.2	0.953
ST at 12th session	22	52.7±25.7	3 (13.6)	0; 0-0	45	98.6±103.0	24 (53.3)	25.2; 0-50.4	**0.019**
ST at 18th session	8	47.3±25.0	2 (25.0)	0; 0-18.9	35	94.9±55.2	22 (62.9)	25.2; 0-75.6	0.055
ST at 24th session	3	50.4±0.0	2 (66.7)	25.2; 0-25.2	12	100.8±52.6	8 (66.7)	50.4; 0-75.6	0.339

SD = standard deviation; IQR = interquartile range; * in milliCoulombs; ** Mann-Whitney U-test.

Discussion

In this prospective, observational study in patients treated with ECT, higher IST was predicted by a higher age and BL electrode placement. During the ECT course there was a rise in ST, but not in all patients. A rise in ST occurred more often in patients treated with BL electrode placement and in those having had more ECT sessions. During the course, higher age and BL electrode placement also predicted higher ST levels. At the same time, having had previous ECT course(s) was associated with an absence of ST increase and, therefore, seems to avoid any rise in ST.

Predictors of IST and ST levels during the course

In internationally accepted guidelines, beside dosage-titration methods, age-based dosing strategies are being mentioned for use in clinical practice.[7] Our study seems to justify the use of these age-based strategies, because age was an important predictor of IST and rise in ST during the course of ECT. CIRS score, dynamic impedance, lower MMSE at baseline, and succinylcholine dose were no longer independently associated with (I)ST, as they may all be critically dependent on age. Although it remains unclear why higher age is associated with higher (I)ST, several factors of morphological brain maturation related to age are hypothesized to influence ST.[24] For example, advanced age was related to both increased scalp impedance and cerebral atrophy. Furthermore, in elderly patients less functional connectivity between brain areas (due to neuronal damage) was suggested to result in less seizure propagation.[33] Also, an ECT-induced shift of the brains inhibitory (GABA) versus excitatory (glutamate) potency has been suggested to explain ST increase during the course.[22,33] Therefore, it is important to study these possible morphological and functional determinants prospectively.[24]

In accordance with other studies,[9,11,13-15,20,21,28] we also found that BL electrode placement predicted higher ST levels during the ECT course and more often showed a rise in ST compared to RUL-treated patients. The higher ST in case of BL electrode placement might be related to differences in current pathways; that is, in BL ECT, there is a greater interelectrode distance than in RUL ECT, probably resulting in more shunting of current through the scalp which might require a higher electrical dosage to elicit seizure activity.[29] Moreover, due to the presence of hair and the difficulty of keeping two electrodes coupled to the scalp, the impedance to the passage of current might be higher and more variable with RUL than with BL electrode placement, probably resulting in a higher ST.[29]

Dynamic impedance is the resistance observed between the electrodes, during the passage of the electrical stimulus, and mainly depends on electrode-skin interface (e.g., hair, conductive gel), skull thickness and electrode placement.[29] A lower dynamic impedance is associated with BL electrode placement and with a higher IST, and the dynamic impedance was found to decrease during the ECT course.[13,20] It has been hypothesized that dynamic impedance would decrease due to electrochemical changes of the electrode-scalp interface during the ECT course.[20] However, it is more likely that the higher electrical stimulation, due to ST increase later in the ECT course, would have resulted in lower dynamic impedance, that is, because the passage of relatively high intensity electrical stimuli resulted in much lower impedance values than the passage of lower intensity stimuli.[29] Our study supports these earlier findings, since lower dynamic impedance was associated with higher IST in univariate regression analysis, and the adjusted mean dynamic impedance values decreased during the ECT course. Also, lower dynamic impedance proved to be an independent predictor for higher ST levels during the ECT course, and dynamic impedance was lower in BL-treated compared with that in RUL-treated patients.

The use of concomitant pharmacological drugs may have both increased (e.g., anti-epileptics and benzodiazepines) and decreased (e.g., tricyclic antidepressants and antipsychotics) the level of IST. However, our univariate regression analyses showed no significant effect of the use of medication on IST level. This might be because, in most of our patients, medications with both ST increasing (benzodiazepines, anti-epileptics) and ST decreasing (antidepressants, antipsychotics) properties were administered simultaneously, so that no specific influence could be established. Also, the anticonvulsive properties of the anesthetics may have had a stronger influence on ST, thereby masking the influence of concomitant medication, as also reported by others.[30]

Predictors of ST increase during the course

ST is reported to increase in ≤ 20-90% of patients during a course of ECT, probably due to an induced shift of the brain's inhibitory versus excitatory potency.[19-22,31] Accordingly, in the present study, mean ST levels increased during the course in ≤ 67% of our patients. Although the median change of ST at the consecutive ST measurement points was higher with BL than with RUL electrode placement, in the multilevel models the interaction term of time*electrode placement was not significant.

Having undergone a previous course of ECT a considerable time before the index ECT (median: 646 days; IQR: 202-1395 days) was independently associated with the

absence of ST increase during the treatment course. Although the mean IST level of patients who underwent ECT for the first time was similar to that of patients having undergone previous ECT, first-time patients showed a rise in ST during the further ECT course, as also reported by others.[28] However, another study suggested that prior ECT course(s) resulted in higher IST in future ECT, but only in male patients.[32] In summary, previous ECT might preclude an increase of ST during the ECT course, suggesting long-term adaptation of the brain after earlier ECT. Alternatively, the association may have been confounded by the characteristic of suffering from chronic or remitting depression, being reflected in the previous ECT course; these latter patients might have a lower tendency for a rise in ST during the ECT course.

Clinical implications

In the present study, a rise in ST occurred in a substantial proportion of patients underpinning the rationale to take age into account in ECT dosing strategies. Also, because comparison of BL and RUL ECT revealed that on average 50 mC higher IST can be expected with BL ECT, and ST increase during ECT might occur up to 40% more often, electrode placement should be taken into account when selecting the dose of the first and subsequent ECT sessions. Furthermore, patients treated earlier with ECT might be a specific clinical group. Clinicians should be aware of the fact that previous ECT course(s) might predict ST stability during the course. This might imply that, in these patients, less electrical dose adjustments are required during the ECT course, which might also prevent cognitive side effects.

Study limitations

Several potential limitations need to be addressed. First, for ECT, ST is determined by several physical stimulus characteristics (e.g., pulse width, frequency, current strength) and by the minimum seizure duration selected to be sufficient in the titration procedure. In earlier studies, different settings and definitions have been used,[1,33] thus hampering comparison of our estimated ST levels with those of others. Furthermore, our ECT device controls charge delivery by frequency, stimulus train duration and setting of the pulse width, resulting in changes of these parameters when delivering higher charges.[1] This might have influenced the measurements of IST and ST levels, although the changes were the same for those patients who needed higher charges. Second, our ST levels were determined by a somewhat crude method, because the titration protocol consisted of steps of ≥ 25 mC. Using an ECT device that offers the possibility to increase the dose with (very low) steps might have refined the titration procedure, but this method would probably be limited due to the maximum length of anesthesia and muscle paralysis. Furthermore, we used an age-based adjustment in our titration protocol,[13] which

may have led to some bias and circularity, as such adjustment may explain (in part) the higher ST levels in older patients. Finally, almost all of our patients used concomitant medication during the ECT procedure.

In conclusion, in 91 prospectively examined, mostly depressed and older patients treated with ECT, age and electrode placement independently predicted IST and ST levels during the course. Some patients showed a persistent rise in ST at the consecutive measurement points. However, having had previous ECT course(s) predicted an absence of ST increase during the ECT course, independent of age and electrode placement. Future studies should explore whether or not these factors adversely affect treatment response.

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MRI characteristics predicting seizure threshold in patients undergoing electroconvulsive therapy: *A prospective study*

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Abstract

Background: In electroconvulsive therapy (ECT), the electrical current must pass the scalp, skull, cerebrospinal fluid (CSF) and brain tissues, to sufficiently exceed the seizure threshold (ST).

Objective: To investigate the relationship between these anatomical strata of the head and the level of the ST, in both right unilateral (RUL) and bifrontotemporal (BL) ECT.

Methods: Observational prospective study among 74 mainly depressed patients. STs were measured at the 1st (initial ST), 6th, 12th, 18th and 24th session. MRI scans were acquired before the 1st session. Scalp and skull thickness at electrode sites were measured on T_2-weighted images. Volumes of intracranial space (ICV), CSF, gray and white matter, and white matter hyperintensities were estimated using whole brain isovoxel T_1-weighted images. Separate multivariate regression analyses for RUL (n=55) and BL (n=19) treated groups were used to estimate the predictive values of the MRI variables.

Results: The patients had a mean age of 57.7±14.8 years, and 39% were men. After adjustment for age, gender and ICV, CSF volume strongly and independently predicted initial ST in both RUL (β=0.31; *P*=0.049) and BL ECT (β=0.64; *P*=0.007). Using multilevel regression analysis, CSF volume was associated with ST during the remaining RUL ECT course (β=0.20; *P*=0.02).

Conclusions: Taking into account the limitations in the titration method and MRI analysis, volume of CSF strongly and independently predicted initial ST. Therefore, the exclusive use of age-based ECT dosing methods may result in suboptimal electrical stimulus dosage in patients with CSF volumes that are not within the average range.

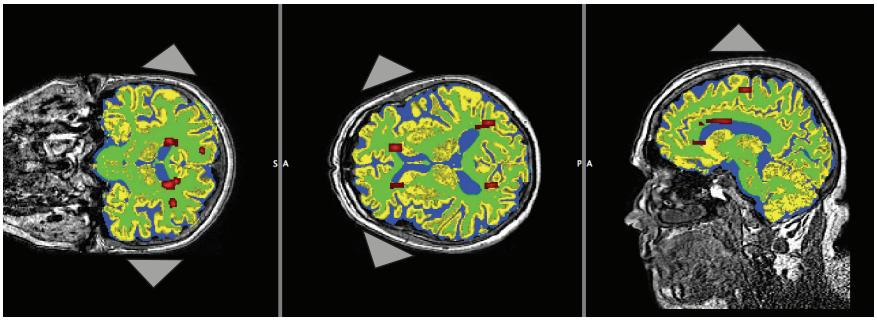
Introduction

Electroconvulsive therapy (ECT) is a fast, effective and safe treatment with remission rates up to 80% in cases of severe depression.[1-3] Generalized seizure activity is elicited at several consecutive ECT sessions.[4] Seizure activity will only be achieved when the patient's seizure threshold (ST) is exceeded by a flow of electrical current.[5] The initial ST (IST), as measured at the first ECT session, varies among patients over a forty-fold range,[6] with higher age and bifrontotemporal (BL) electrode placement as reported predictors of higher IST.[7-9] Also, ST has been shown to change during the course, at least in some patients.[10-12] For optimal ECT effectiveness, the electrical dosage must be substantially increased above the ST, especially in right unilateral (RUL) ECT.[13,14] Because of the presumed increase in ST, consecutive adjustment of electrical dosage during the ECT course has been advised.[12,15] In daily clinical practice, age-based dosing methods are frequently used to determine the proper initial electrical dose.[15,16] Alternatively, a stimulus titration method is advised to estimate an individualized electrical dose.[6,17]

The electrical stimulus must excite sufficient volumes of brain tissue to elicit seizure activity, and is determined by several parameters, e.g., pulse amplitude, shape, pulse width, train frequency, directionality, polarity and stimulus duration.[18] Higher electrical dosages (i.e., a higher number of pulses) activate larger brain regions.[5,19,20] Moreover, electrical currents will not move in a straight line between the electrodes, but traverse the tissues proportional to its resistances.[5,19] To reach brain tissue effectively, the electrical stimulus must successively pass through scalp, skull, meninges, and cerebrospinal fluid (CSF), with each compartment (Figure 1) having a typical resistance to the passage of the electrical stimulus.[5,19] The skull has a high electrical resistance and gray matter has less resistance, whereas CSF conducts current very well due to the high concentration of free ions in this aqueous solution,[5,19] Consequently, the stimulus dose determines whether the power of the electrical current is sufficient to pass through the different compartments to reach the essential brain tissue.

Electrode placement and head anatomy determine the electric field distribution in the brain.[18] The pathway of the electrical current depends on the electrode proximity to skull foramina, sutures and eye cavities, as well as on brain surface morphology with varying amounts of surrounding CSF.[21,22] In RUL application, the distance between the electrodes is much shorter than in BL, resulting in a more evenly distributed electrical stimulus across the anterior cortex and increased shunting of current.[5,21,23] Therefore, electrode placement plays an important role in determining the spatial distribution of the ECT-induced electric field and, consequently, the ST

Figure 1 Magnetic resonance imaging (MRI)* of scalp, skull, cerebrospinal fluid (CSF), gray matter, white matter and white matter hyperintensities related to right unilateral (RUL) and bifrontotemporal (BL) electrode placement in electroconvulsive therapy



*T_1-weighted MRI of the head in gray colors of a patient showing the highest volume of CSF. Voxels representing CSF are colored blue, gray matter voxels are yellow, white matter is green, and areas underneath the voxels that might be detected as white matter hyperintensities are colored red. Gray triangles represent electrode placement sites. RUL means 3 cm right of the sagittal midline on the vertex and 3 cm above the midline between the right meatus acusticus externa and lateral angle of the right orbita. BL means 3 cm above the midline between the meatus acusticus externa and lateral angle of the orbita, right and left frontotemporal, respectively.

level. RUL electrodes (positioned more closely together) cause more shunting in the scalp and produce more focal and weaker electric fields within the brain. Therefore, in RUL ECT, more electrical pulses are needed to elicit seizure activity than in BL ECT,[18,19] Additionally, after local seizure induction in areas directly beneath the electrodes, cortico-(thalamico-)cortical propagation is required to further spread the seizure.[24] This propagation may be hampered by interruption of these circuits, for instance, due to cerebral lesions such as white matter hyperintensities (WMH). In clinical studies, subcortico-frontal lesions predicted less effective ECT.[25-27] Therefore, information on the relevance of each barrier for the electrical stimulus to excite brain tissue effectively, as well as for the seizure to propagate sufficiently, seems important in order to optimize ECT in an individual patient.

However, prospective studies on the relationship between anatomical characteristics on magnetic resonance imaging (MRI) of the head on the one hand, and IST and ST change on the other, are sparse.[28] Therefore, this prospective study explores the influence of head anatomy on IST and ST during the ECT course.

Methods and materials

Participants and clinical data acquisition

In this observational prospective study, all consecutive patients indicated for ECT in Rijnstate Hospital (Arnhem, the Netherlands, a 36-bed psychiatric facility with a catchment area of 600,000 inhabitants), from December 1 2009 until November 15 2011, were asked to participate. Patients were excluded in case of age < 18 years, absence of written informed consent, and a contraindication for dose titration (e.g., life-threatening condition, severe cardiovascular comorbidity) or for MRI. Within two weeks before the first ECT session, an MRI of the head was made. Patient characteristics were extracted from the medical chart. At baseline, severity of depression was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) [29] and cognitive functioning using the Mini-Mental State Examination (MMSE) [30], both within one week before the start of ECT. Amount and severity of somatic comorbidity was rated using a modified Cumulative Illness Rating Scale (CIRS) [31]. The Medical Ethical committee approved the study protocol, and written informed consent was obtained from all participants.

Patient and clinical characteristics of the study population are described in detail elsewhere.[7] In short, higher age (β=0.24; *P*=0.03) and BL electrode placement (β=0.42; *P*<0.001) independently predicted higher IST.[7] During the ECT course, concomitant medications, including psychopharmacological agents, were continued in a similar dosage, and did not predict the level of IST.[7]

Electroconvulsive therapy and measurement of ST

ECT was administered using a constant-current (0.9 Ampère), brief-pulse (0.25 milliseconds [ms] in RUL and 0.5 ms in BL electrode placement) device (Thymatron IV; Somatics Incorporation, Lake Bluff, Illinois, USA), after induction of anesthesia with intravenous etomidate (1.5 mg/kg body mass), muscle paralysis with intravenous succinylcholine (0.5-1 mg/kg body mass), and with appropriate oxygenation until the resumption of spontaneous respiration. Electrode placement was initially RUL, except in patients at high risk for suicidality and/or somatic complications, or if previous ECT had successfully been administered bilaterally. STs were measured at the 1st, 6th, 12th, 18th and 24th ECT session, in which the latter measurements depended on the duration of the course. The same age-adjusted titration schedule was used at each titration session;[15] patients aged < 50 years started with 25.2 milliCoulombs (mC) and older patients with 50.4 mC. If the first stimulus dose failed to elicit a seizure of at least 20 s of motor activity measured with the cuff method and/or ≥ 25 s on the electroencephalogram, the stimulus charge was doubled according to the titration schedule (see Appendix 1 for the

independent stimulus parameters), and the patient was re-stimulated after 30 s. To become therapeutic, the consecutive electrical dosage was set at 6 times ST in RUL ECT and at 2.5 times ST in BL ECT. Patients were treated twice weekly. At the titration session, if the ST was reached and the levels of muscle relaxation and sedation were still appropriate, the patient was re-stimulated at a therapeutic dose also in this session.

MRI data acquisition

Imaging was performed on a 1.5 Tesla Philips Medical Instruments (Best, the Netherlands) MRI scanner, using a 16-channel SENSE receive head coil. The scanning protocol included a high resolution T_1-weighted (T_1W) turbo field echo MRI (sequence parameters: repetition time = 7.6 ms; echo time = 3.5 ms; flip angle = 15°; 145 sagittal slices; voxel size = 1.1 mm isotropic), a T_2-weighted (T_2W) turbo spin echo MRI (sequence parameters: repetition time = 4803 ms; echo time = 100 ms; flip angle = 90°; 24 transverse slices; in plane voxel resolution = 0.60x0.76 mm; slice thickness = 5 mm; slice gap = 1 mm), and a FLuid Attenuated Inverse Recovery (FLAIR) image (sequence parameters: repetition time = 8000 ms; echo time = 140 ms; flip angle = 90°; 26 coronal slices; in plane voxel resolution = 0.9x1.1 mm; slice thickness = 5 mm; slice gap = 1 mm).

Measurement of scalp and skull thickness

Since the flow of current through the skull is mostly normal to the surface and occurs in the vicinity of the electrodes due to the low conductivity of the skull,[5,18] skull thickness was measured at the electrode placement sites. Furthermore, it was considered that scalp thickness measured under the electrodes was representative for individual scalp thickness around the head. On T_2W images, two independent raters (BART, TWFP) measured the thicknesses in millimetres (mm) at the RUL (i.e., 3 cm right of the sagittal midline on the vertex according to d'Elia [32] and 3 cm above the midline between the right meatus acusticus externa and lateral angle of the right orbita) and at the BL electrode placement sites (i.e., 3 cm above the midline between the meatus acusticus externa and lateral angle of the orbita, right and left frontotemporal, respectively). Interclass coefficients (ICCs) between the raters ranged from 0.6-0.7. Means of the scalp and skull thickness, as measured by the two raters, were calculated for the three localisations (vertex, right and left frontotemporal).

Structural MRI analysis

All analyses were performed using the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL) tools (http://www.fmrib.ox.ac.uk/fsl/). Prior to analysis, all raw data were visually checked for the presence of (motion) artifacts.

Brain extraction.

For each subject, T_1W and FLAIR volumes were brain-extracted (BETv2.1, manually selected individual fractional intensity thresholds).

Mask.

For each subject, a FLAIR-based mask of WMH was created by manually delineating WMH on all coronal slices in FSL view.

Registration.

For each subject, linear transformation parameters from FLAIR native space to T_1W native space were estimated (FLIRTv5.5) and applied to the FLAIR-based mask of WMH, resulting in one T_1W-compatible probability mask that was then thresholded and binarized (automatically calculated individual thresholds to preserve total mask volume). All registrations were visually inspected.

Segmentation.

Each brain-extracted T_1W was segmented into partial volume maps of total CSF, total gray matter and total white matter (FASTv4.1). White matter that was erroneously classified as gray matter due to the presence of WMH (as WMH appear hypo-intense on T_1W) was identified using the T_1W-compatible WMH mask, subtracted from the total gray matter segmentation and added to the total white matter segmentation. All segmentations were visually inspected; no problems occurred during the analysis.

Volumes.

Volumes of total CSF, total gray and white matter, total WMH, and total intracranial volume (ICV) were calculated by multiplying the number of voxels within each partial volume map by the mean value of all voxels within each partial volume map, then multiplied by the voxel volume (1.1x1.1x1.1 mm) and, finally, divided by 1000 to obtain volumes in milliliters (mL).

Analysis of data

Data are presented as means ± standard deviations (SD) and ranges, medians and interquartile ranges (IQR), or numbers and percentages when appropriate. Normally distributed continuous variables (age and MADRS score) between the included/excluded groups were compared using t-tests, non-normally distributed continuous variables (CIRS score and MMSE score) using Mann-Whitney U tests, and categorical variables (gender and diagnosis) were compared using Chi-square tests. Descriptive statistics were used to describe the clinical and MRI characteristics. Mean composite scores for the three localizations of scalp and skull thickness

were calculated. Z-scores were obtained for all appropriate variables. Continuous clinical and MRI variables for RUL and BL electrode placement were compared using t-tests, non-normally distributed continuous variables using Mann-Whitney U tests, and categorical variables using Chi-square tests.

Because of the assumed differences between RUL and BL current distributions and used pulse widths,[5,33] preliminary analyses were performed, showing a significant interaction term (CSF*RUL/BL; $P<0.001$). Therefore, regression analyses were performed for RUL and BL groups separately. First, multivariate regression analyses, adjusted for age, gender and ICV, were done using the z-scores of the six compartments (composite mean scalp and skull thickness, and total volumes of CSF, gray matter, white matter and WMH, respectively) as separate independent variables, to find variables showing $P<0.10$ as possible predictor of the dependent variable IST. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Hence, because of collinearity between both gray and white matter volumes and ICV (tolerance<0.1 and variance inflation factor [VIF] value>10), the latter was excluded in the next multivariate analyses. Then, multivariate regression analyses were done with IST as dependent variable and age, gender and all MRI variables showing $P<0.10$ as independent factors. Finally, multivariate regression analyses were repeated for the $ST_{6\text{-}12\text{-}18\text{-}24}$ measured during the ECT course (if available), and combined in a multilevel regression analysis (i.e., mixed linear analysis) entering only the previously identified independent predictors of IST, as well as age, gender and ICV. All tests were two-sided with $P<0.05$ denoting statistical significance; SPSS for Windows (version 18.0) was used for all analyses.

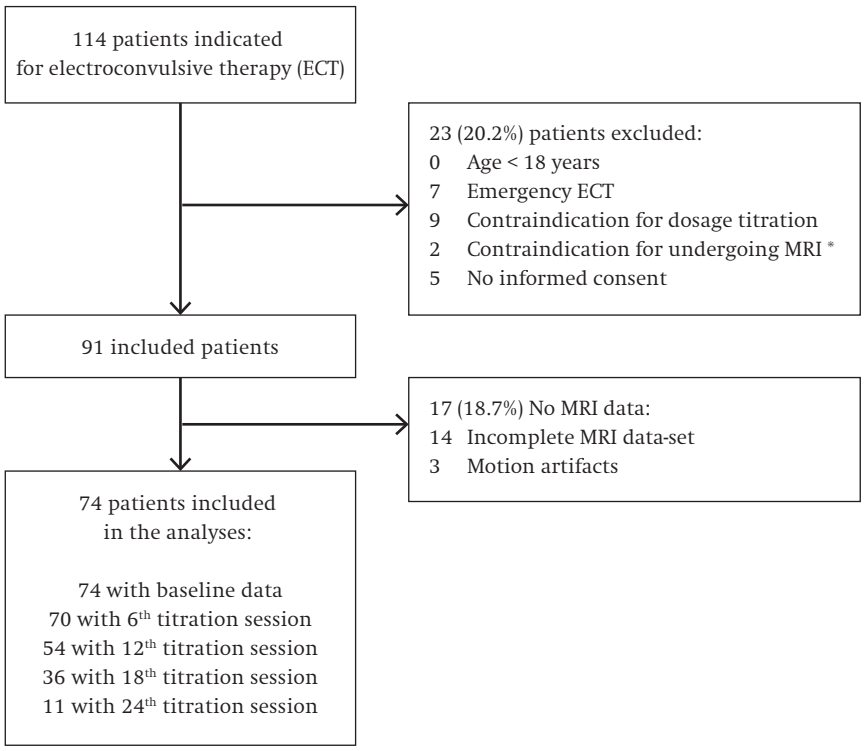
Results

Participants, clinical and anatomical MRI characteristics

Complete MRI datasets were obtained for 77 patients. Due to excessive motion artifacts on the T_1W images, another three subjects had to be excluded, yielding a final sample of 74 patients from the 114 patients indicated for ECT (Figure 2). The excluded patients did not differ from the study group regarding mean age ($P=0.82$), gender ($P=0.56$) and mean MADRS score ($P=0.55$), but excluded patients had a higher median CIRS score ($P=0.003$), a lower median MMSE score ($P=0.02$), and more often had psychotic depression ($P=0.03$) and catatonia ($P=0.003$).

Mean age of the study population was 57.7±14.8 (range: 22-93) years, with 39% men (n=29) (Table 1). The median CIRS score was 21 (IQR: 19-23). Of all patients, 99%

Figure 2 Flow diagram showing the patient selection process



*Magnetic Resonance Imaging

(n=73) suffered from a mood disorder and most patients used a constant dose of concomitant medication. During the index ECT course, an average of 18.1±7.2 (range: 6-38) ECT sessions was administered to 69 patients who completed the course. Anatomical characteristics of the patients are also summarized in Table 1. Patients treated with RUL (n=55) and BL (n=19) electrode placement did not differ from each other, except for their mean level of IST (45.4±17.8 mC in RUL and 87.5±52.0 mC in BL; $P<0.001$), as was expected.

Table 1 Clinical and anatomical characteristics on magnetic resonance imaging (MRI) of patients (n=74) with measured seizure thresholds (ST) during electroconvulsive therapy (ECT), and for right unilateral (RUL; n=55) and bifrontotemporal (BL; n=19) electrode placement

Patient and treatment characteristics	Mean ±SD*, range; n (%); or median; IQR** in all (n=74)	Mean ±SD, range; n (%); or median; IQR in RUL (n=55)	Mean ±SD, range; n (%); or median; IQR in BL (n=19)	P-value for comparison RUL and BL***
Male gender	29 (39.2)	22 (40)	7 (36.8)	1.0
Age, in years	57.7±14.8, 22-93	57.1±13.4, 22-80	59.7±18.5, 27-93	0.24
Diagnostic category, according to axis 1 of DSM-IV-TR****:				
Depressive disorder without psychotic features	45 (60.8)	35 (63.6)	10 (52.6)	0.43
Depressive disorder with psychotic features	16 (21.6)	11 (20)	5 (26.3)	0.54
Bipolar disorder, depressive episode	12 (16.2)	9 (16.4)	3 (15.8)	1.0
Other disorders (i.c. catatonia)	1 (1.4)	0 (0)	1 (5.3)	0.26
Use of seizure threshold influencing concomittant pharmacotherapy:				
Benzodiazepines	46 (62.2)	35 (63.6)	11 (57.9)	0.79
Anti-epileptics	6 (8.1)	4 (7.3)	2 (10.5)	0.64
Antidepressants	44 (59.5)	35 (63.6)	9 (47.4)	0.28
Antipsychotics	49 (66.2)	39 (70.9)	10 (52.6)	0.17
MADRS score$ at baseline	36.0±8.6, 17-54	35.4±8.9, 17-54	37.7±7.5, 23-49	0.18
MMSE score$$ at baseline	28 (26-29.8)	28 (26-29.3)	27 (25-30)	0.10
CIRS score$$$ at baseline	21 (19-23)	21 (19-23)	21 (18-24)	0.43
Electrode placement is bifrontotemporal at first titration session	19 (25.7)			
Total amount of ECT sessions during the course (n=69; 51; 18)	18.1±7.2, 6-38	18.6±7.6, 6-38	16.7±5.7, 10-28	0.44
Initial ST, in milliCoulombs (mC)	56.2±35.3, 25.2-201.6	45.4±17.8, 25.2-100.8	87.5±52.0, 25.2-201.6	<0.001

Thickness scalp, in mm^				
At d'Elia	4.9±1.9, 1.0-9.5	4.8±1.7, 2-9.5	5.2±2.4, 1-8.5	0.15
Right frontotemporal	7.9±2.7, 2.5-15.5	7.9±2.4, 2.5-14	7.5±3.5, 3-15.5	0.51
Left frontotemporal	8.5±3.3, 2.5-18.0	8.6±3.0, 2.5-16.0	8.4±3.9, 2.5-18.0	0.87
Mean composite scalp thickness	7.1±2.4, 2.5-13.3	7.2±2.2, 2.5-11.5	7.1±3.1, 2.7-13.3	0.99
Thickness skull, in mm				
At d'Elia	5.7±1.9, 2.5-10.0	5.9±1.9, 2.5-10.0	5.8±1.9, 2.5-8.5	0.65
Right frontotemporal	4.5±1.5, 1.5-8.0	4.3±1.5, 1.5-8.0	4.5±1.5, 2-7	0.27
Left frontotemporal	4.5±1.4, 1.5-7.5	4.5±1.5, 1.5-7.5	4.5±1.3, 2.5-7	0.24
Mean composite skull thickness	4.9±1.4, 2.2-7.3	4.9±1.5, 2.2-7	4.9±1.4, 2.3-7.3	0.31
Total volumes, in mL^^				
Intracranial volume	1456±140, 1182-1789	1454±143, 1208-1789	1464±139, 1182-1680	0.79
Cerebrospinal fluid	376±45, 302-528	372±42, 302-469	386±54, 315-528	0.25
Gray matter	537±60, 405-697	541±56, 434-697	526±70, 405-635	0.33
White matter	543±63, 420-697	540±66, 420-679	552±54, 436-640	0.49
White matter hyperintensities	3.1; 1.1-9.8	3.0; 1.1-6.5	4.3; 0.8-34.6	0.40

*standard deviation; **interquartile range; ***continuous variables tested with t-tests, categorical variables tested with Chi-square tests, and not-normally distributed continuous variables tested with Mann-Whitney U tests; ****Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; §Montgomery-Åsberg Depression Rating Scale; §§Mini-Mental State Examination; §§§Cumulative Illness Rating Scale (modified version); ^millimetres, measured by two independent raters; ^^milliliters.

Anatomical characteristics and ST

Table 2 shows the results of the regression analyses. Because total ICV may confound volumes of CSF and brain structures measured, the influence of ICV on the level of IST was analyzed first with univariate regression analysis and showed no association (in RUL β=-0.14, *P*=0.31; in BL β=0.08, *P*=0.73). In both RUL and BL groups, the volume of CSF was positively associated with IST (Table 2). Because of

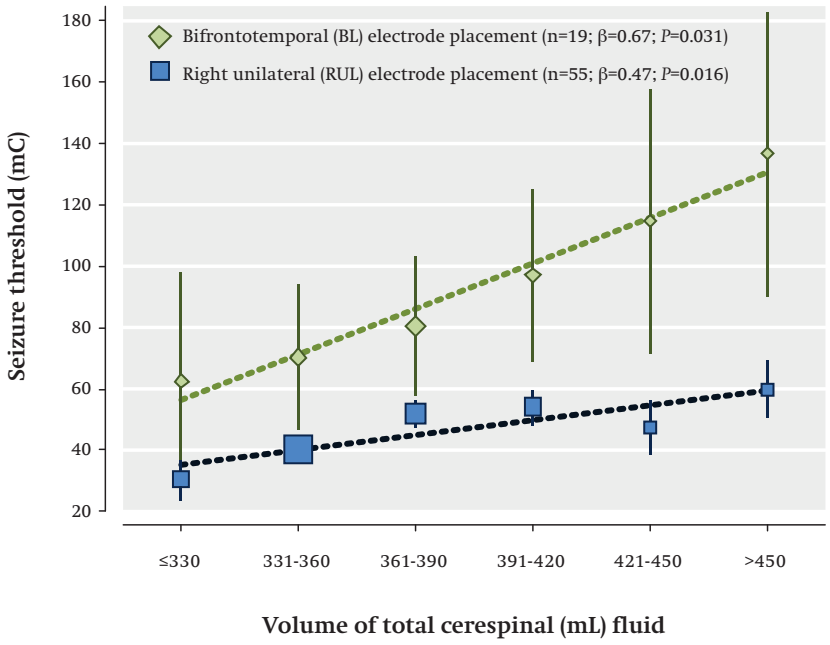
Table 2 Data on regression analyses to detect independent anatomical characteristics on magnetic resonance imaging predicting the variation of seizure threshold (ST) in 74 patients undergoing right unilateral (RUL) and bifrontotemporal (BL) electroconvulsive therapy (ECT).

Index-scores in RUL ECT	**Correlates of initial ST (n=55)***		**Multivariate correlates of initial ST** (n=55)**	
	β-coefficient	*P*-value	β-coefficient	*P*-value
Age	0.41	0.002	0.29	0.03
Gender	-0.03	0.82	-0.07	0.69
Thickness of the scalp	0.24	0.08	0.19	0.14
Thickness of the skull	0.21	0.11		
Volume of total cerebrospinal fluid	0.47	0.02	0.31	0.049
Volume of total gray matter	-0.56	0.15		
Volume of total white matter	-0.74	0.07	-0.30	0.10
Volume of total white matter hyperintensities	0.11	0.50		
Index-scores in BL ECT	**Correlates of initial ST (n=19)***		**Multivariate correlates of initial ST** (n=19)**	
	β-coefficient	*P*-value	β-coefficient	*P*-value
Age	0.64	0.003	0.33	0.24
Gender	-0.02	0.94	-0.14	0.49
Thickness of the scalp	0.02	0.94		
Thickness of the skull	-0.08	0.71		
Volume of total cerebrospinal fluid	0.67	0.03	0.64	0.007
Volume of total gray matter	-0.89	0.08	-0.05	0.84
Volume of total white matter	-0.66	0.26		
Volume of total white matter hyperintensities	-0.02	0.96		

*All six anatomical structures were adjusted for age, gender and intracranial volume (ICV). **Multivariate regression analysis only for variables showing *P*<0.10 at first regression analysis, adjusted for age and gender, and not for ICV due to multicollinearity.

multicollinearity with gray and white matter volumes, ICV was not entered into the multivariate analyses. After entering all variables showing $P<0.10$ in the first step of our regression analyses, only the volume of CSF was an independent predictor of the level of IST, in both RUL and BL treated patients (β=0.31; $P=0.049$ and β=0.64; $P=0.007$, respectively; see Table 2). In an additional confirmatory analysis, in which age, gender and ICV were entered into the model, the strong predictive value of CSF volume persisted in RUL and BL ECT (β=0.47, $P=0.02$ and β=0.67, $P=0.03$, respectively) (Figure 3).

Figure 3 Mean values of initial seizure threshold in milliCoulombs (mC; with error bars representing standard errors) according to categories of volumes of cerebrospinal fluid in milliliters (mL) in patients undergoing either bifrontotemporal (BL) or right unilateral (RUL) electroconvulsive therapy *



* The dotted lines represent the regression lines. The size of each square is proportional to the number of patients. Mean values are adjusted for age, gender and volume of intracranial space. Beta-coefficients and *P*-values by multivariable regression analyses. The *P*-value for interaction (i.e., CSF*RUL/BL) was statistically significant ($P<0.001$).

Subsequently, entering the CSF volume into the linear mixed model and using $ST_{6\text{-}12\text{-}18\text{-}24}$ as dependent variables, thereby adjusting for age, gender and ICV, a significant association was found with the consecutive ST levels during the RUL ECT course (β=0.20; *P*=0.02). In the BL treated group, the positive association appeared to be similar in strength, although not significant (β=0.23; *P*=0.24).

Discussion

In this observational prospective study, the total volume of CSF appeared to be the only independent and strong morphological predictor of IST in both RUL and BL ECT. This relationship persisted after adjustment for age, gender and ICV, and showed an even stronger association with BL than with RUL electrode placement. Although this relation has previously been hypothesized [28] and was estimated in computer models,[19] this prospective study is (to our knowledge) the first to demonstrate an important role for CSF volume on the level of IST.

The fact that CSF volume predicted the IST can be explained by its biophysical properties. CSF is a relatively cell-free, low-protein ultrafiltrate of blood, and contains an abundant amount of ions.[34] As a good electric conductor[19], CSF may serve as a spherical conducting shell (as a Faraday cage) that reduces the size of the ECT-induced electric field inside the brain. A weaker and more focal electrical field, in case of more surrounding CSF, has to be pulsed more times to trigger a seizure.[18,19] Therefore, in our patients with a relatively increased CSF volume, during titration with fixed current amplitude and pulse width, the number of electrical pulses probably had to be increased.
Different electrical shunting patterns were expected in RUL and BL electrode placement,[5,21] as was confirmed by the significant interaction term CSF*RUL/BL. In BL ECT, the relationship between CSF volume and IST was much stronger than in RUL ECT. Possibly, a larger distance between BL placed electrodes, and enhanced electrical shunting through more CSF, resulted in higher IST levels than in RUL placement. On the other hand, the larger 0.5 ms pulse width used in BL placement, which may show higher ST than with 0.25 ms used in RUL,[33] may have confounded the results.

Anatomical differences and disruptions of current pathways are suggested to explain variations of ST in patients.[23,28,35-37] In a recent computerized simulation study of ECT in spherical head models, a 15% decrease in volume of gray and white matter (corresponding to an increase of CSF volume of 116% and 113%, in the male and female model, respectively), led to a 55% decrease of stimulated gray matter

volume and about a 36% decrease of the stimulation strength and, thereby, to a higher ST.[19] Our clinical results seem to be in accordance with these computer model calculations, as higher volumes of CSF predicted higher IST. Furthermore, large effects of scalp and skull thickness on stimulation strength and excited brain volume were estimated in the computer models.[19] In detail, the RUL ECT model showed that lower scalp thickness resulted in stronger stimulation strength and larger stimulated brain volume with, consequently, lower ST. At the same time, higher skull thickness resulted in weaker stimulation strength, smaller excited brain volume and higher ST.[19] However, in our clinical study, these modeled influences on IST could not be confirmed, probably because in the computer model thicknesses were used derived from the literature, which probably did not exactly match ours at the electrode placement sites. Also, due to the sites that we selected for thickness measurement, the influence of the inferior portions of the head was not taken into account, which may explain the very weak univariate correlations between ST and scalp and skull thickness for BL electrode placement compared to RUL. Moreover, our MRI estimates of scalp and skull thicknesses were hampered by measurement differences between the raters, which could have weakened the influence of these variables in the regression models. Furthermore, we hypothesized that a higher IST is due to more white matter disruptions in neuronal circuitry; however, no predictive value of the total WMH volume on IST could be determined, possibly due to some important methodological limitations, which we discuss below.

It is remarkable that, in our study, the influence of CSF volume on IST was independent of age and gender, because older people often show increased CSF volume due to cortical atrophy,[38] especially men.[39] In our data, age is indeed correlated with CSF volume (r=0.26; P=0.03), and men show higher mean CSF volumes than women (P<0.001; data not shown), supporting the clinical experience of higher ST in older men.[2] It is noteworthy that age and gender did not limit the strong associations between CSF volume and IST. However, increased CSF volume, due to cortical atrophy, is not determined exclusively by age and gender. Cortical atrophy has also been associated with (amongst other parameters) hereditary factors, starvation, neurodegenerative and cerebrovascular diseases, alcohol abuse and the use of certain medications (e.g., lithium).[40] Moreover, compared to normal controls, larger CSF volumes have been demonstrated in patients suffering from major depression.[41] These risk factors for increased atrophy and increased CSF volume were present in our study patients.

During the ECT course, in 18-67% of our patients the ST levels increased with a median of 25-50 mC versus IST, mostly with BL treatment.[7] The CSF volume also

predicted the consecutive ST levels during the ECT course, although only reached significance in RUL ECT, most likely due to the limited sample size of the BL treated group. However, the estimated standardized associations were lower (βs were 0.2 [$ST_{6\text{-}12\text{-}18\text{-}24}$] instead of 0.3 and 0.6 [IST], in RUL and BL ECT, respectively). Since it is very unlikely that the CSF volume changed significantly during the ECT course, other ECT-related factors may have emerged as more dominant determinants of the consecutive ST levels.[7] For instance, consecutive ECT sessions may have decreased neuroexcitability through an increase of the inhibitory (e.g., gamma-aminobutyric acid) and/or a decrease of the excitatory (e.g., glutamate) neurotransmitter systems.[10,21]

Clinical implications

Our study provides new information for clinicians to estimate the proper ECT dose. Our results suggest that, in patients with higher CSF volumes on MRI scans, a higher electrical stimulus dose may be needed to elicit therapeutic seizures. Current age-based dosing methods do not take CSF volumes into account,[2] and age explained only 8-25% of the IST variance.[28] Therefore, with age-based methods, younger patients with increased CSF volumes may be treated with ineffectively low electrical doses, and older patients with less than average brain atrophy may be overdosed and, consequently, prone to more cognitive side-effects.

Study limitations

The most critical limitation in this study is probably our very crude and age-adjusted ST titration method. Substantial steps of 25-100 mC were used, which undoubtedly led to overestimation of ST in several patients.[7,33,42] Moreover, our pulse widths differed between the two electrode placements, which could have resulted in higher ST levels in the BL group, compared to the RUL treated patients.[33] Also, our dosage increments were accompanied by higher stimulus frequencies and durations (and change in pulse width at the final step in RUL ECT), which will have had considerable impact on the level of ST. Possibly, more discrete predictors of ST (e.g., anatomical factors) were not detected due to the crudeness of our measurements. Furthermore, age probably confounded the anatomical variables and choice of electrode placement, because of (severe) somatic comorbidity and/or pre-existing cognitive functioning. Despite these limitations, CSF volume was an important predictor of ST. Replication of this finding, using a more precise and age-neutral titration method, is definitely needed.

Another important limitation is the FSL program used to determine brain tissue volumes. The brain extraction tool limited outer-brain CSF estimates causing a systematic error with underestimation of the CSF volume.[43] Furthermore, the

segmentation process did not always adequately distinguish between CSF and brain tissue, and the registration processes had appointed some voxels to wrong structures, leading to erroneous calculations of the volumes. For example, Figure 1 shows that the CSF space between the superficial cortex and the skull was occasionally poorly segmented and that parts of the skull and CSF were assigned to white matter and gray matter. These errors most probably biased the effect estimates towards the null hypothesis implying that the predictive value of CSF volume on (I)ST may be even higher.

Several other potential limitations need to be addressed. Of the 114 potential participants, only 74 had complete head MRI datasets; moreover, compared with the study population, the excluded patients differed in clinical diagnosis, somatic comorbidity and cognitive functioning. Also, in the literature different titration methods are used, which limits comparison of our estimated ST levels with others. In our study, titration took place under anesthesia with etomidate, an anesthetic that has been associated with lower ST than propofol.[44] Therefore, our results can not be generalized to patients anesthetized with other anesthetics. Furthermore, usage of constant doses of concomitant medication during the ECT course could have influenced the ST. Although we did not show such association in our preliminary clinical study,[7] confounding of our results cannot be excluded. Finally, measurement of scalp and skull thickness by the two independent raters showed ICCs of only moderate strength (0.6-0.7), suggesting a measurement error which could have led to an underestimation of the true relationships in our regression analyses (type II error). Nevertheless, using the mean of these two raters reduced some of this measurement error (by a factor of 1.4) as compared to using one rating alone. Especially with RUL ECT, more shunting of current through the thicker layers of scalp tissue was expected to predict higher IST; however, in the multivariable model the effect was of moderate strength and only tended toward significance (β=0.24; P=0.08).

In conclusion, in this observational prospective study, taking into account the methodological limitations, CSF volume predicted the level of IST in ECT, besides the well-known predictors of age and electrode placement. Moreover, during the RUL ECT course, higher STs were predicted by higher CSF volume. Therefore, it is important to take into account that, when exclusively age-based dosing methods are used, less effective electrical stimuli may be administered in younger patients with increased CSF volumes and overdosing may occur in older patients with average CSF volumes. Additional studies relating CSF volume to IST and the clinical efficacy of ECT are needed before firm conclusions can be drawn.

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Appendix 1

Independent electrical stimulus parameters in the titration schedule using a constant current of 0.9 Ampère ECT device.

Electrode placement	% of maximum output charge of ECT device	Charge, in milliCoulombs	Pulse width, in milliseconds	Frequency	Stimulus duration, in seconds
Right unilateral	5*	25.2	0.25	10	5.60
	10	50.4	0.25	20	5.60
	20	100.8	0.25	30	7.47
	40	201.6	0.25	60	7.47
	80	403.2	0.5	60	7.47
Bifrontotemporal	5*	25.2	0.5	10	2.80
	10	50.4	0.5	10	5.60
	20	100.8	0.5	20	5.60
	40	201.6	0.5	30	7.47
	80	403.2	0.5	60	7.47

* Patients aged < 50 years started with 5%, older patients with 10%

3

PART

Exciting matters in patient populations treated with ECT

7

Patient, treatment and anatomical predictors of outcome in electroconvulsive therapy: *A prospective study*

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Abstract

Background: Baseline predictors of effectiveness and cognitive adverse effects of electroconvulsive therapy (ECT) were prospectively examined.

Methods: Before and after ECT, the Montgomery-Åsberg Depression Rating Scale (MADRS) and Mini-Mental State Examination (MMSE) were assessed. Before ECT, a magnetic resonance imaging of the head was performed. Outcome predictors were investigated using multivariable regression analyses.

Results: Of 83 patients (mean age ± SD, 59.2±15.3 years; 39% men), 28% had a psychotic depressive disorder, 16% had a bipolar depression, 30% had had previous ECT course(s), and 66% used concomitant antipsychotics. Presence of psychotic depression (β=-0.25; *P*=0.04) and having had previous ECT (β=-0.35; *P*=0.003) predicted lower post-ECT MADRS score. Baseline magnetic resonance imaging characteristics were not predictive of post-ECT MADRS and MMSE scores. The use of concomitant antipsychotics predicted a lower post-ECT MMSE score (β=-0.21; *P*=0.02), whereas presence of bipolar depression at baseline predicted higher post-ECT MMSE score (β=0.23; *P*=0.01). The post-ECT MADRS score seemed to be a confounder for the post-ECT MMSE score (β=-0.20; *P*=0.02).

Conclusions: Effectiveness of ECT was better in the patients with a baseline psychotic depression and those who had had ECT before. Cognitive outcome was better in patients with baseline bipolar depression but worse in those who used antipsychotics during ECT and those who showed more persistent depressive symptoms after ECT.

Introduction

Electroconvulsive therapy (ECT) is a fast, effective and safe treatment for severe pharmacotherapy-resistant depression and shows remission rates up to 80%.[1-3] Occurrence of particularly memory disturbances during and after a course of ECT is a main adverse effect and may limit acceptance and use of this treatment.[2] During a course of ECT, consecutive seizures are elicited by administering an electrical stimulus above the seizure threshold (ST) under generalized anaesthesia, muscle relaxation, and continuous oxygen supply.[2]

Many attempts have been made to determine whether certain patient, treatment and brain anatomical characteristics may predict effectiveness and cognitive adverse effects of ECT.[2,4,5] Effectiveness of ECT was studied in relation to the type and specific symptoms of depression. It was shown that depression with disturbances in vegetative functions, psychomotor retardation, psychotic features, and shorter duration of the current episode was associated with a more positive outcome of ECT.[4,6,7] In addition, older patients,[8,9] patients with catatonic symptoms,[4] and patients without a comorbid borderline personality disorder had a better outcome of ECT.[10] The presence of bipolar depression was examined as a factor of influence for effectiveness in ECT but has not been shown a consistent predictor of outcome,[7,11,12] Effectiveness of ECT has also been associated with certain (technical) aspects of the treatment itself. Having been treated with ECT before predicted better outcome of ECT,[7] as well as treatment with higher electrical stimulus dosage above the ST[3] and concomitant nortriptyline use during the ECT course.[13] Bifronto-temporal (BL) electrode placement was shown to be equally effective to right unilateral ECT (RUL), if appropriate attention was paid to the technical aspects of dosing.[2,14] Regarding brain anatomical predictors of ECT effectiveness, measured with the Montgomery-Åsberg Depression Rating Scale (MADRS), a poorer response was suggested by increased amounts of subcorticofrontal gray matter hyperintensities[15] and by the presence of medial temporal lobe atrophy.[16]

Predictors of post-ECT cognitive adverse effects have more scarcely been studied.[17,18] Poorer pre-treatment global cognitive functioning, assessed with the Mini-Mental State Examination (MMSE) [19], seemed to be a strong predictor of persistent retrograde amnesia after ECT.[17,20] Furthermore, advanced age showed a robust association with greater memory deficits after a course of ECT,[21] but on the other hand, several studies showed an improvement of cognitive functioning after ECT.[18,22] Regarding technical treatment characteristics, administering more BL ECT sessions (but not RUL) during the treatment course predicted more cognitive adverse effects, as well as electrical stimulation with longer pulse widths and

treating patients in higher frequencies (e.g., 3 times a week compared to 2 times).[21,23] From an anatomical point of view, less hippocampal volume on magnetic resonance imaging (MRI) of the head was associated with poorer ECT-related memory outcomes in one small study,[24] but this result has not been replicated in studies associating anatomical head MRI characteristics and possible cognitive adverse effects of ECT. In this prospective study, we investigated in 83 patients undergoing ECT whether certain patient, (technical) treatment, and anatomical head MRI characteristics were predictive of effectiveness and cognitive adverse effects of ECT.

Materials and methods

Patients, demographic and clinical data acquisition

All consecutive patients indicated for ECT in Rijnstate Hospital (Arnhem, the Netherlands, a 36-beds psychiatric facility with a catchment area of 600,000 inhabitants), from December 1, 2009, until November 15, 2011, were asked to participate in a prospective MRI study relating anatomical and functional parameters and seizure threshold (trail registration number: NL24697.091.09).[25] Patients were excluded if age was younger than 18 years, no written informed consent was provided, or contraindications existed for dose titration (e.g., life-threatening condition of the patient, severe cardiovascular comorbidity) or for MRI (e.g., metals in the body, claustrophobic reactions, patients' inability to lie still in the scanner). Within 2 weeks before the first ECT session, a head MRI was obtained. The medical ethical committee of the hospital approved the study protocol, and written informed consent was obtained from all participants. Patient and head MRI characteristics of the study population are described in more detail elsewhere.[26] In this present open observational study, the relation between baseline characteristics and prospectively obtained outcome measures were analyzed.

Psychometric instruments

Severity of depression was scored by a trained research nurse (O.B.H.) in the week before the first ECT (baseline) and within 1 week after the last ECT session using the MADRS, a validated observer-rated scale that contains 10 items (scored 1-6 per item), with the sum score ranging from 0 to 60 and higher scores indicating more and a higher severity of depressive symptoms.[27]

Cognitive functioning at baseline and within 1 week after the last ECT session was assessed using the MMSE, a commonly used validated instrument to evaluate

cognitive functioning, with the total score ranging from 0 to 30, and lower scores indicating more cognitive dysfunction.[19]

Amount and severity of somatic comorbidity at baseline were rated using a modified Cumulative Illness Rating Scale (CIRS), consisting of 14 aspects of possible pathology and impairment of major organ systems, which are rated from 1 (no impairment to that organ/system) to 5 (impairment is life-threatening; treatment is urgent or of no avail; prognosis is grave), ranging from 14 to 70. The item 'Psychiatric/Behavioral (includes depression, anxiety, agitation, psychosis, not dementia)' was set at 5.[28]

Electroconvulsive therapy and measurement of ST

Electroconvulsive therapy was administered using a constant-current (0.9 Ampère), brief-pulse (0.25 milliseconds [ms] in RUL and 0.5 ms in BL ECT) device (maximum output, 1008 milliCoulombs [mC]; Thymatron IV; Somatics Incorporation, Lake Bluff, Illinois, USA) after induction of anesthesia intravenously with etomidate (1.5 mg/kg body mass), muscle paralysis with succinylcholine (0.5-1 mg/kg body mass) intravenously, and with appropriate oxygenation (100% oxygen, positive pressure) until the resumption of spontaneous respiration. Electrode placement was started RUL, except in patients at high risk for suicidality and/or somatic complications, or if previous ECT had successfully been administered bilaterally. Initial ST (IST) was measured at the 1st ECT session by an empirical titration method.[4] If the starting stimulus dose failed to elicit a seizure of at least 20 seconds of motor activity measured with the cuff method and/or 25 seconds or longer on electroencephalogram, stimulus charge was increased according to the titration schedule (for patients younger than 50 years: 25.2 mC, 50.4 mC, 100.8 mC, 201.6 mC, and 403.2 mC; for patients aged 50 years and older: 50.4 mC, 100.8 mC, 201.6 mC, and 403.2 mC), and the patient was restimulated after 30 seconds. At the second session, dosage was set at 6 times the IST in RUL ECT and at 2.5 times the IST for BL treatment. The patients were treated twice weekly. Right unilateral electrode placement was changed into BL during the ECT course, based on the clinical decision of experienced psychiatrists, mostly if the patient did not show (enough) improvement after 6 RUL sessions. If at the titration session the ST was reached and there was still sufficient sedation and muscle relaxation, the patient was restimulated at a therapeutic dose also in this session.

Magnetic Resonance Imaging data acquisition to explore anatomical characteristics

More details of the MRI data acquisition and analyses are described elsewhere.[25] Imaging was performed on a 1.5 Tesla Philips Medical Instruments (Best, the

Netherlands) MRI scanner. The scanning protocol included a high-resolution T_1-weighted image and a FLuid Attenuated Inverse Recovery (FLAIR) image. Structural MRI analyses were performed using the Oxford Centre for Functional MRI of the Brain Software Library (FSL) tools (http://www.fmrib.ox.ac.uk/fsl/). After visually checking for the presence of (motion) artifacts, brains were extracted and masks for white matter hyperintensities (WMH) were created manually using FLAIR. Each brain-extracted T_1-weighted image was segmented into partial volume maps of total cerebrospinal fluid (CSF), total gray matter and total white matter, and total WMH. All segmentations were visually inspected and showed no problems during the analysis. Volumes of total CSF, total gray and white matter, and total WMH were obtained in milliliters (mL).

Analysis of data

Data are presented as means ± standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages when appropriate. Differences between the in- and excluded group were compared using t-tests for normally distributed variables (age and MADRS score), Mann-Whitney U tests for non-normally distributed continuous variables (CIRS score and baseline MMSE score), and chi-square tests for categorical variables (sex and diagnosis categories). Main outcome was effectiveness of ECT as determined by the post-ECT MADRS score. Response to ECT was defined as 50% or greater decrease of the MADRS score after the ECT course compared to baseline, and complete remission as the MADRS score 10 or less at endpoint. In addition, cognitive functioning as determined by the MMSE score after the ECT course was a main outcome variable.

Several groups were compared using (paired and unpaired) t-tests for continuous variables, and Wilcoxon signed ranks tests and Mann-Whitney U tests for nonnormally distributed variables. To explore whether patient, treatment and anatomical characteristics were predictive of ECT effectiveness and cognition after ECT, first univariate regression analyses, adjusted for the baseline MADRS scores and MMSE scores, respectively, were performed with the post-ECT MADRS and MMSE scores as dependent variables. Because the distribution of the MMSE scores were negatively skewed (because of the ceiling effect of 30), they were natural log transformed (i.e., -ln[31-MMSE score]) to obtain a near-normal distribution.[29] Patients' characteristics (sex, age, CIRS score, diagnostic categories), treatment characteristics (previous ECT course[s], use of concomitant pharmacotherapy and the level of IST), and anatomical characteristics (z-scores of total volumes of CSF, gray matter, white matter and WMH, respectively) were entered as independent variables. The variable 'level of IST' was adjusted for age and electrode placement because of their known associations.[26] Preliminary analyses were

conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Next, only variables showing $P<0.10$ in these univariate analyses were entered in an overall multivariate analysis, adjusted for age, sex and baseline MADRS and MMSE scores, to explore whether they were independent predictors for the post-ECT MADRS and MMSE scores. In the multivariable analysis of post-ECT MMSE score, adjustment for electrode placement at the first ECT session was performed as well because the level of IST was entered as independent variable and is confounded by electrode placement.[26] All tests were two-sided, with $P<0.05$ denoting statistical significance, and were analyzed using SPSS for Windows (version 18.0; SPSS Inc., Chicago, Illinous, USA).

Results

Patient, treatment and anatomical MRI characteristics

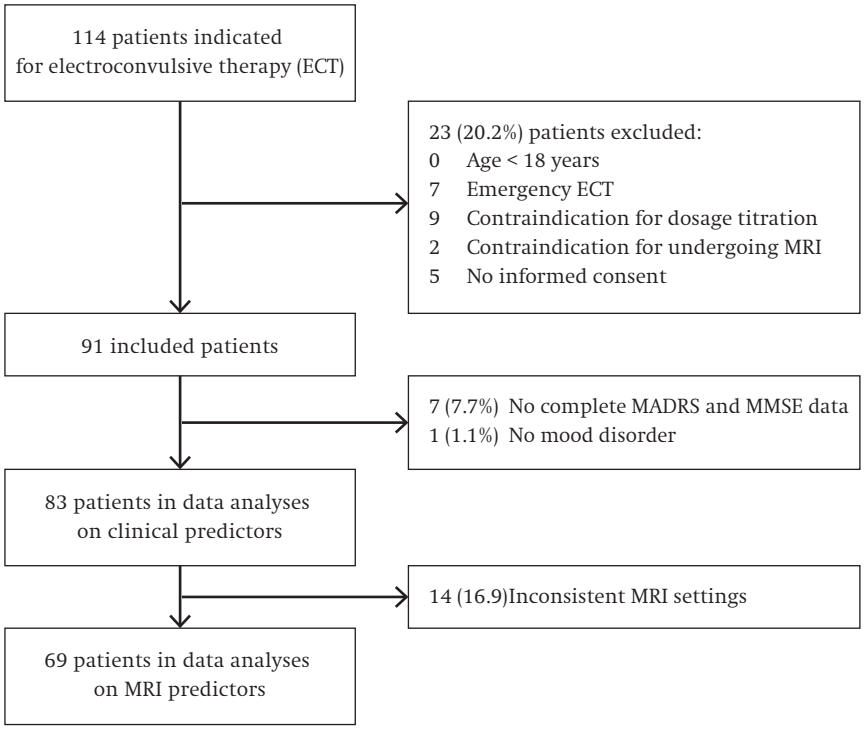
Of 114 patients indicated for ECT, 18 had to be excluded and 5 patients did not give written informed consent (Figure 1). Some baseline (n=2) and post-ECT measurements (n=5) of MADRS and MMSE scores were missing, one patient did not have a mood disorder, and in 14 head MRI scans, different settings of scanning parameters had been used. Therefore, of 83 (73%) patients, the patients' and treatment characteristics could be entered in the analyses, and of 69 (61%) patients, the anatomical MRI characteristics could be entered in the analyses. The excluded patients did not differ from the study group regarding mean age (P=0.20), sex (P=0.66), and mean MADRS score at baseline (P=0.56), although the excluded group of patients showed lower median MMSE score at baseline (P=0.03), higher median CIRS score (P=0.02), and comprised catatonic patients ($P<0.001$).

In Table 1, patient (n=83), treatment (n=83) and anatomical (n=69) characteristics are summarized. Mean age ± SD was 59.2±15.3 years, 39% was composed of men (n=32), and median CIRS score was 21 (IQR, 20-23). All patients were depressed (16% [n=13] bipolar depression), and most of them used concomitant medications (antipsychotics in 66% [n=55]). Thirty percent (n=25) had had ECT. Initial ST was 62.2±44.8 mC, 30% (n=25) of the patients started the ECT course with BL electrode placement, and 37% (n=31) switched electrode placement from initially RUL to BL during the course.

Outcome of ECT

In total, a mean ± SD of 17.4±7.4 ECT sessions was administered to the patients during a completed ECT course (Table 2). Patients who changed electrode placement (n=31) from RUL to BL during the ECT course were treated with more sessions

Figure 1 Flow diagram showing the patient selection process



MRI=magnetic resonance imaging

(*P*<0.001). After the ECT course, in the total group, the mean MADRS score was significantly lower than pre-ECT (*P*<0.001) and decreased with mean ± SD of 22.8±12.7 points. Patients who started ECT with RUL (n=27) and BL (n=25) electrode placement, as well as patients who changed from RUL in BL during the ECT course (n=31) showed significantly lower MADRS scores after ECT. Moreover, patients who changed electrode placement showed a significantly higher mean post-ECT MADRS score than those who did not change.

The bipolar depressed patients (n=13) showed a higher median post-ECT MMSE score (30; IQR, 28.5-30) than the unipolar patients (n=70; median 28; IQR, 26.8-29; Mann-Whitney U Test, 620.5; n=83; *P*=0.03), but did not differ regarding mean age (*P*=0.44), MADRS score at baseline (*P*=0.70) and after ECT (*P*=0.70), MMSE score at baseline (*P*=0.97), IST level (*P*=0.75), electrode placement (*P*=0.75), and mean total

Table 1 Patient, treatment and anatomical characteristics at baseline of patients (n=83) treated with electroconvulsive therapy (ECT)

Patients' characteristics	**Mean ±SD*; n (%); or median; IQR****
Male gender	32 (38.6)
Age, in years	59.2±15.3
Modified Cumulative Illness Rating Scale score	21; 20-23
Diagnostic category, according to axis 1 of DSM-IV-TR^:	
Depressive disorder without psychotic features	47 (56.6)
Depressive disorder with psychotic features	23 (27.7)
Bipolar disorder, depressive episode	13 (15.7)
MADRS*** score at baseline	36.1±8.6
MMSE**** score at baseline	28; 26-29
Treatment characteristics	
Had ECT before	25 (30.1)
Use of seizure threshold influencing concomitant pharmacotherapy:	
Benzodiazepines	51 (61.4)
Anti-epileptics	7 (8.4)
Antidepressants	50 (60.2)
Antipsychotics	55 (66.3)
Electrode placement is bifrontotemporal at first titration session	25 (30.1)
Initial seizure threshold, in milliCoulombs	62.2±44.8
Anatomical MRI# characteristics, in milliliters (n=69)	
Intracranial volume, including cerebrospinal fluid	1458±142
Total volume of cerebrospinal fluid	376±45
Total volume of gray matter	538±61
Total volume white matter	544±62
Total volume of white matter hyperintensities	3.0; 1.1-9.8

*standard deviation; **interquartile range; ^Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; ***Montgomery-Åsberg Depression Rating Scale; ****Mini-Mental State Examination; #Magnetic Resonance Imaging.

Table 2 Outcome measurements of patients (n=83) treated with right unilateral (RUL) and bifrontotemporal (BL) electroconvulsive therapy (ECT)

Group	n	Total number of ECT sessions	*P*-value	MADRS* score			MMSE** score		
				Pre-ECT	Post-ECT	*P*-value	Pre-ECT	Post-ECT	*P*-value
All patients	83	17.4±7.4		36.1±8.6	13.3±9.8	<0.001†	28; 26-29	29; 27-30	0.11††
Start with RUL	27	13.7±7.3	0.16‡	35.8±9.0	9.1±7.1$	<0.001†	28; 26-29	29; 27-30	0.02††
Start with BL	25	15.6±5.8		38.0±8.6	10.4±9.0	<0.001†	27; 25-29.5	28; 25-29	0.13††
Change in BL during course	31	22.0±6.4	<0.001‡‡	34.8±8.1	19.3±9.7$	<0.001†	29; 27-30	28; 27-29	0.51††
Unipolar depression	70	17.5±7.6	nsº	35.9±8.4	13.5±9.8	nsº	28; 25.8-29	28; 26.8-29	0.03º
Bipolar depression	13	16.9±6.5		36.9±9.7	12.3±10.5		28; 26-29.5	30; 28.5-30	
Nonpsychotic depression	60	17.6±7.1	nsºº	35.1±8.3	14.4±10.3	nsºº	29; 27-29.8	29; 28-30	0.01ºº
Psychotic depression	23	16.8±8.2		38.7±8.8	10.5±7.9		26; 25-27	27; 24-29	

*Montgomery-Åsberg Depression Rating Scale; **Mini-Mental State Examination; †Paired-samples tests used for comparing pre- and post-ECT scores; ††Wilcoxon signed ranks tests used for comparing pre- and post-ECT scores; ‡Comparing the patients who started with RUL and BL using t-test; $Comparing post-ECT MADRS scores of patients who did not (n=27; 9.1±7.1) and who did (n=31; 19.3±9.7) change electrode placement during the ECT course using t-test showed *P*<0.001; ‡‡Comparing patients who did not (n=52; 14.7±6.6) and who did (n=31; 22.0±6.4) change electrode placement during the ECT course using t-test; ºns= not significant, comparing unipolar and bipolar depressed patients; ººComparing nonpsychotic and psychotic patients.

ECT sessions (*P*=0.81). In addition, bipolar patients used concomitant antiepileptics more often (*P*=0.01) and antidepressants less often (*P*=0.02) compared to unipolar depressed patients.

Seventy percent (n=57) of the patients responded to ECT, and 48% (n=40) reached complete remission. In the total group, median post-ECT MMSE score was 29 (IQR, 27-30) and did not differ from the pre-ECT median MMSE score (*P*=0.11). In RUL-treated patients, the post-ECT median MMSE score was significantly higher than before ECT (*P*=0.02).

Predictors of post-ECT MADRS score

Using the multivariate regression analysis, with adjustment for age, sex and baseline MADRS score (Table 3), thereby entering only variables with *P*<0.1 at the first univariate analyses, lower post-ECT MADRS score (meaning better effectiveness) was independently predicted by a diagnosis of depressive disorder with psychotic features (β=-0.25; *P*=0.04; Figure 2A) and having had previous ECT course(s) (β=-0.35; *P*=0.003; Figure 2A). Baseline MMSE score was not associated with post-ECT MADRS score (*P*=0.55). None of the anatomical MRI characteristics were individually predictive of the post-ECT MADRS score and therefore not entered into the final multivariate analysis.

Predictors of post-ECT MMSE score

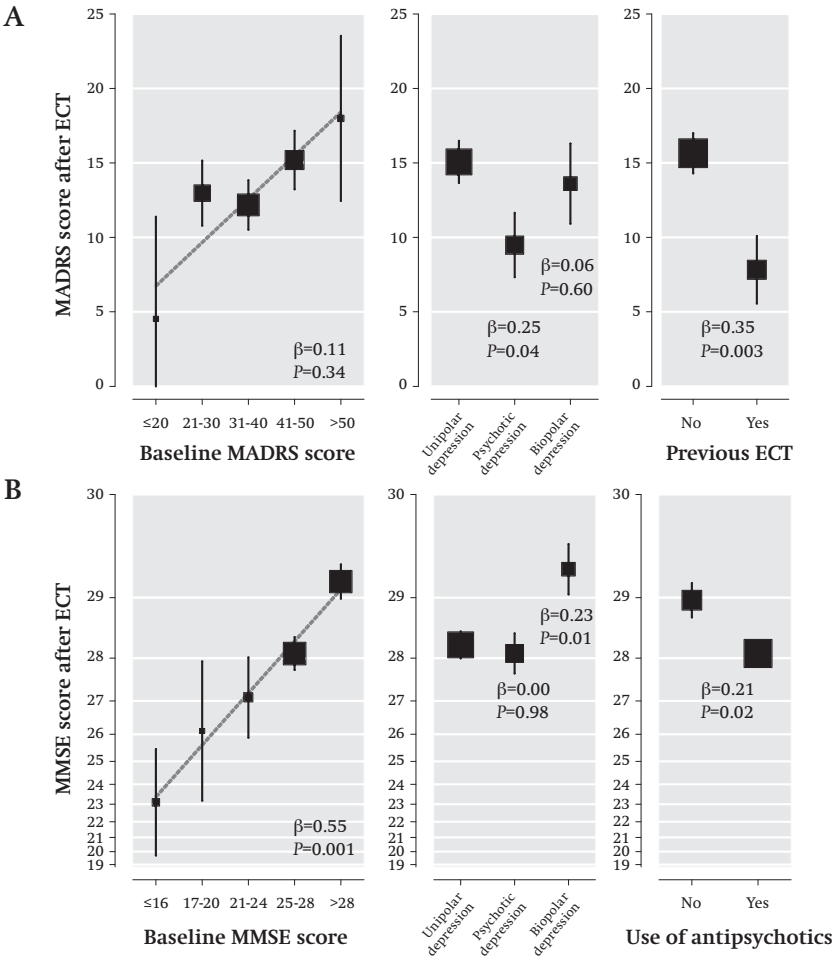
As expected, post-ECT MADRS was inversely associated with the post-ECT MMSE score (β=-0.20; *P*=0.02). Adjusted for age and sex, a higher baseline MMSE score was associated with a higher post-ECT MMSE score (β=0.55; *P*<0.001; Figure 2B). Using multivariable regression analysis (Table 4), with adjustment for age, sex, electrode placement and baseline MMSE, thereby entering only variables with *P*<0.1 at the first univariate analyses, higher post-ECT MMSE score (meaning better cognitive functioning) was independently predicted by having a bipolar depression at baseline (β=0.23; *P*=0.01; Figure 2B). Concomitant antipsychotics use during the ECT course was an independent predictor of a lower post-ECT MMSE score (β=-0.21; *P*=0.02; Figure 2B), meaning more cognitive dysfunction. In a sensitivity analysis, we additionally adjusted for the pre- and post-ECT MADRS scores, yielding similar results. The post-ECT MADRS score seemed to be a confounder for the post-ECT MMSE score (β=-0.20; *P*=0.02).

Table 3 Multivariate regression analyses to detect baseline patient, treatment and anatomical predictors of the Montgomery-Åsberg Depression Rating Scale (MADRS) score after electroconvulsive therapy (ECT) in 83 patients

	Univariate correlates of MADRS score at endpoint, adjusted for MADRS score at baseline		Multivariate correlates of MADRS at endpoint, only variable with *P*<0.1 in univariate analyses and adjusted for MADRS score at baseline, age and sex	
Patient variables	β-coefficient	*P*-value	β-coefficient	*P*-value
Male gender	0.07	0.57	0.01	0.93
Age	-0.12	0.30	0.04	0.71
Cumulative Illness Rating Scale score	0.08	0.50		
Diagnostic category, according to axis 1 of DSM-IV-TR[$] :				
Depressive disorder with psychotic features	-0.23	0.06	-0.25	**0.04**
Bipolar disorder, depressive episode	-0.11	0.35	-0.06	0.60
MMSE[*] score at baseline	0.07	0.55		
Treatment characteristics				
Had ECT before	-0.33	**0.002**	-0.35	**0.003**
Use of seizure threshold influencing concomitant pharmacotherapy:				
Benzodiazepines	-0.07	0.56		
Anti-epileptics	-0.05	0.65		
Antidepressants	-0.06	0.57		
Antipsychotics	0.04	0.72		
Initial seizure threshold	-0.15^	0.33		
Z-scores of anatomical MRI characteristics (n=69)				
Intracranial volume, including cerebrospinal fluid	0.05	0.69		
Volume of total cerebrospinal fluid	0.02	0.90		
Volume of gray matter	0.12	0.35		
Volume of white matter	-0.10	0.92		
Volume of white matter hyperintensities	-0.02	0.85		

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; [*]Mini-Mental State Examination (lnMMSE at baseline was used in analyses); ^also adjusted for electrode placement

Figure 2 Relationship between 83 patients who underwent electroconvulsive therapy (ECT), and (A) scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) and (B) Mini-Mental State Examination (MMSE), with their baseline scores, diagnostic category, previous treatment with ECT and concomitant use of antipsychotics, respectively *



*Data are presented as adjusted means by ANCOVA, adjusted for (A) sex, age, baseline MADRS score, diagnostic category, and previous ECT, and (B) age, baseline MMSE score, diagnostic categories, IST level, and the use of antipsychotics when appropriate. The size of each square is proportional to the number of patients. Vertical lines indicate standard errors. Beta-coefficients and *P*-values are calculated by linear regression analysis.

Table 4 Multivariate regression analyses to detect baseline patient, treatment and anatomical predictors of the score of the Mini-Mental State Examination (MMSE)*

	Univariate correlates of MMSE score at endpoint, adjusted for MMSE score at baseline		Multivariate correlates of MMSE score at endpoint, showing *P*<0.1 in univariate analyses and adjusted for MMSE at baseline, age, sex and electrode placement	
Patient variables	β-coefficient	P-value	β-coefficient	*P*-value
Male gender	0.07	0.43	0.07	0.40
Age	-0.13	0.20	-0.18	0.09
Cumulative Illness Rating Scale score	-0.04	0.67		
Diagnostic category, according to axis 1 of DSM-IV-TR^ :				
Depressive disorder with psychotic features	-0.07[$]	0.50	0.003	0.98
Bipolar disorder, depressive episode	0.22[$]	**0.02**	0.23	**0.01**
MADRS** score at baseline	0.15	0.10		
Treatment characteristics				
Had ECT before	-0.03	0.75		
Use of seizure threshold influencing concomitant pharmacotherapy:				
Benzodiazepines	0.14	0.12		
Anti-epileptics	0.002	0.98		
Antidepressants	0.06	0.51		
Antipsychotics	-0.12	**0.048**	-0.21	**0.02**
Initial seizure threshold	0.27[$$]	**0.03**	0.20	0.09
Z-scores of anatomical MRI characteristics (n=69)				
Intracranial volume, including cerebrospinal fluid	0.16	0.14		
Volume of total cerebrospinal fluid	0.16	0.12		
Volume of gray matter	0.11	0.31		
Volume of white matter	0.13	0.23		
Volume of white matter hyperintensities	-0.15	0.15		

*MMSE scores were transformed in lnMMSE scores owing to nonnormally distribution;**Montgomery-Åsberg Depression Rating Scale; ^Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; [$]also adjusted for MADRS score at endpoint; [$$]also adjusted for known confounders (age and electrode placement)

Discussion

As has been shown before, our prospective study demonstrated that having had ECT before and presence of psychotic depression at baseline were independent predictors of increased effectiveness of ECT. Furthermore, we found that concomitant use of antipsychotics predicted poorer cognitive outcome, whereas a baseline bipolar depression predicted better cognitive outcome after ECT. These findings remained when we additionally adjusted for the severity of residual depressive symptoms.

In line with earlier results,[7] having had ECT course(s) before was a predictor of increased effectiveness. This finding is most probably due to confounding by indication, as a previously positive ECT outcome will increase the chance of being treated with ECT again. In addition, our results confirm earlier findings regarding enhanced effectiveness of ECT in psychotic depressed patients[6] but did not support the previously reported positive association with higher age and concomitant use of antidepressants.[8,9,13] Data about the length of the current depressive episode were not available in a standardized manner and could therefore not be related to effectiveness of treatment. Electroconvulsive therapy was equally effective with regard to depression in bipolar and unipolar patients, as was shown before.[30] Compared to other studies, the average number of total ECT sessions in our study was high.[2] A possible reason for this is that the use of ultra-brief pulse width in the larger group of initially RUL-treated patients caused the longer treatment duration compared to brief pulse BL-treated patients.[23,31]

None of the anatomical head MRI scan variables were predictive of effectiveness of ECT, which contrasts with earlier studies showing poorer outcome of treatment (with antidepressants) in patients with more subcortical gray matter hyperintensities and increased CSF volume.[15,32-34] Because we did not determine separate volumes of the hippocampus and medial temporal lobes, no further comparison with the literature can be made.[16,24]

In clinical practice, cognitive impairment is no contraindication for ECT.[4] Indeed, in our study, the baseline MMSE score was not associated with effectiveness of ECT, meaning that poorer cognitive functioning before ECT did not predict worse effectiveness. Otherwise, a higher MMSE score at baseline strongly predicted better post-ECT cognitive functioning, as has been reported before.[17,20] In the patients exclusively treated with RUL (using stimuli with ultrabrief pulse width) ECT, the median post-ECT MMSE score was one point higher than before ECT, which matches with earlier findings showing less cognitive adverse effects with ultrabrief RUL ECT.[23] That a higher post-ECT MADRS score was associated with a

lower post-ECT MMSE score was probably due to the presence of (residual) depressive symptoms that are associated with (persistent) memory impairment.[35,36] Moreover, due to less clinical response, more total ECT sessions were administered (a median of 21 sessions [IQR, 15.5-24.5] in the group of patients who showed less than 50% decrease of post-ECT MADRS score, compared to a median of 15 sessions [IQR, 10-21] in those who decreased by 50% or greater; P=0.02), as well as more often occurrence of electrode placement switch to BL (68% [n=17] in patients showing less than 50% decrease of post-ECT MADRS score, compared to 23% [n=13] in the better outcome group; P<0.001), which factors both may have led to a lower post-ECT MMSE score.[21]

A diagnosis of bipolar depression unexpectedly predicted better post-ECT cognitive function which, as far as we know, has not been reported before. Besides, the more often use of concomitant antiepileptics and less often use of antidepressants, no differences between the bipolar and unipolar depressed patients were found; especially not regarding the expected predictors of the post-MMSE score age, use of BL electrode placement, and duration of the ECT course.[21,23] Presence of bipolar disorder and the use of lithium and antiepileptics were associated with more cognitive impairment.[37] This remarkable finding is new and should be replicated before drawing further conclusions.

Although psychotic depression predicted better effectiveness of ECT, the consequent use of antipsychotics during the ECT course predicted more cognitive dysfunction. An explanation for this result may be that patients who use antipsychotics during the ECT course might be a distinct group with more severe depression and a probably higher risk for cognitive adverse effects. In addition, the presence of persisting psychotic features or (postictal) delirium may have been the reason for the continuing use of antipsychotics during the ECT course. In general, anticholinergic activity of psychotropic medications negatively affects cognitive functioning, especially in older adults,[38] which may have been another cause of poorer post-ECT cognitive functioning in our study. In addition, antipsychotic medication may have slightly decreased the patients' ST compared to nonusers (without being noticed because of the rather crude titration protocol), resulting in administration of electrical stimuli a little too well above the ST.[39] Because not the absolute electrical stimulus dose but the dose relatively exceeding the ST was suggested to predict cognitive adverse effects of ECT,[40] this may explain more cognitive dysfunction in ECT patients using concomitant antipsychotics. On the other hand, in a few randomized controlled trials no differences were shown in memory effects of ECT between patients with and without concomitant antipsychotics use, but these studies included mainly patients with schizophrenia.[41,42]

Several limitations should be addressed. First, of the 114 patients only, 83 patients (and for the MRI analyses, 69 patients) could be included, limiting the generalizability of our results to all ECT patients because the more cognitively impaired, the more severely somatically ill and the catatonic patients were excluded. Second, mood disorders were classified according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* by at least 2 clinically experienced psychiatrists but not confirmed using a standardized diagnostic instrument, which might have led to less accurate ascertainment of the diagnosis. Third, two thirds of the patients used concomitant psychotropic medication during the ECT course, as was decided on clinical grounds (e.g., to avoid withdrawal symptoms, to reduce psychosis or postictal delirium, or for sedation). Because this concomitant use was only registered for the overall type of medication without controlling for the clinical indication, analysis of the effects of specific types of (antipsychotic) medications and dosage was not possible. Fourth, the MMSE was used to evaluate global cognitive functioning before and after ECT and that we did not examined retrograde amnesia, which is a cognitive dysfunction of more concern in ECT.[17] Finally, the automatic FSL process to estimate the volumes of CSF, gray and white matter, and WMH also had several limitations, which are described elsewhere in more detail;[25] in short, imperfections in the registration and segmentation process may have led to some measurement and systematic error in establishing the separate volumes.

In conclusion, this prospective, observational study confirmed that psychotic depressed patients and those who were previously treated with ECT responded better to ECT. Unexpectedly, having a bipolar depression predicted better cognitive function after ECT, whereas the use of antipsychotics during ECT and the presence of more persistent depressive symptoms following ECT were associated with a poorer cognitive outcome.

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8

Electroconvulsive therapy for catatonia: *treatment characteristics and outcome in 27 patients*

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Abstract

Background: Electroconvulsive therapy (ECT) has been described as an effective treatment option for catatonia in retrospective case series. We aimed to investigate treatment characteristics and outcome of patients with catatonia who were treated with ECT.

Methods: The medical records of 27 patients with catatonia treated with ECT (between 1991 and 2009) were scrutinized for clinical and treatment characteristics. Outcomes were measured using the Clinical Global Impression - Improvement (CGI-I) scale. Patients who improved (defined as CGI-I scores 'very much' or 'much improved') were compared with those who did not improve (defined as a CGI-I score 'no change' or 'very much worse').

Results: Mean age of all patients was 49 ± 19 years, of whom fifteen (56%) were female. Of all patients, 13 (48%) had a diagnosis of a mood disorder and 12 (44%) of a psychotic disorder. ECT was mostly started after ineffective pharmacotherapy (n=23; 85%) within 2 to 3 months after catatonia had been diagnosed. In total, 16 (59%) patients improved. Improvement was significantly associated with younger age (P=0.05), presence of autonomic dysregulation at baseline (P=0.02), especially higher body temperature (P=0.02), daily ECT during the first treatment week (n=15 [56%]; P=0.03), longer duration of electroencephalogram seizure activity at last ECT-session (P=0.04), and less morbidity in the year after ECT (P=0.03). Three of the 11 non-improved patients died in the year after ECT compared with none of the improved patients.

Conclusions: Most of our patients with catatonia benefited from ECT, especially younger patients with autonomic dysregulation. Daily administration of ECT may be more effective, whereas longer duration of seizure activity at the final ECT-session was related to better response to ECT.

Introduction

Catatonia is characterized by motor abnormalities including rigidity, catalepsy, waxy flexibility, mutism, stupor, negativism, posturing, stereotypy, echophenomena, and mannerisms. Catatonia is closely associated with the presence of mood disorders, psychotic disorders and toxic states.[1] The estimated prevalence of catatonia among psychiatric inpatients is reported to range from 8 to 38%; this wide range is possibly due to difficult differential diagnosis from other disorders.[2] Catatonic patients are at risk of severe complications, such as pneumonia, decubitus, malnutrition, dehydration, contractures and thrombosis. Moreover, patients who experienced malignant variant of catatonia (lethal catatonia or neuroleptic malignant syndrome) show autonomic instability with hyperthermia, tachycardia or bradycardia, hypertension or hypotension, tachypnea, diaphoresis, and cardiac arrhythmia, whereas a high percentage of them ultimately die.[1] In case reports and case series, benzodiazepines and electroconvulsive therapy (ECT) are described as effective treatment options for catatonia. However, data from randomized clinical trials on the effectiveness of these treatments are not available,[3] and large clinical studies are sparse. Therefore, this retrospective study describes patients with catatonia who were treated with ECT.

Method

The medical records of all patients treated with ECT (n=285) at the Rijnstate Hospital (a large teaching hospital in Arnhem, the Netherlands) in the period 1991 to 2009 were retrospectively examined. Of the 27 patients who had a diagnosis of (severe) catatonia, the medical records were scrutinized regarding 3 sets of variables:

1. Patient characteristics, including sex, age, psychiatric diagnosis (according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition),[4] medical comorbidity, and severity of catatonia with the Clinical Global Impression for Severity (CGI-S) scale.[5] Earlier treated patients (1991-2001; n=4) were rated using the CGI-S retrospectively from the medical charts by 2 independent psychiatrists; all other 23 patients were rated by the treating psychiatrists before and after treatment. Furthermore, the presence of autonomic dysfunctions was determined according to the presence of hyperthermia (body temperature ≥ 38° Celsius), tachycardia or bradycardia (≥ 100 or ≤ 60 beats per minute, respectively), hypotension or hypertension (systolic blood pressure, ≤ 90 or ≥ 140 mm Hg), tachypnea (≥ 20 breaths per minute), diaphoresis, and/or cardiac arrhythmia. Severe catatonia was defined as, next to catatonia, autonomic dysfunctions and/or alterations of consciousness being presence;

2. Treatment characteristics, including first treatment of catatonia, time interval before any treatment and before ECT, and characteristics of ECT; and
3. Outcome characteristics, including outcome as assessed with the Clinical Global Impression for Improvement (CGI-I)[5] scale and morbidity and mortality in the year after ECT.

Statistical analysis

Categorical data are presented as numbers and percentages and continuous variables as mean ± SD values or medians with interquartile ranges (IQR) when appropriate. Improved patients (defined according to the CGI-I as those rated as 'very much' or 'much improved') were compared with nonimproved patients (defined according to the CGI-I as those rated as 'no change', 'minimally', 'much', or 'very much worse') using the χ^2 and Fisher exact tests for frequencies and independent t-tests for normally distributed continuous variables. The SPSS for Windows version 13.0 (SPSS Inc, Chicago, Illinois) was used for all analyses, and the level of significance was set at $P \leq 0.05$.

Results

Patient characteristics

Table 1 presents the demographic and clinical characteristics of all patients with catatonia who were treated with ECT. In 15 patients (56%), autonomic dysregulation was present. At baseline, one third (n=9) of the patients were scored on the CGI-S as 'extremely ill', almost half (n=13) as 'severely ill', and the remainder (n=5 [19%]) as 'markedly ill'

Treatment characteristics

The treatment characteristics of the patients with catatonia are summarized in Table 2. Treatment started on average within 18 ± 40 days after onset of the first symptoms of catatonia. Nineteen (70%) patients were initially treated with benzodiazepines. Mean time interval before ECT was 62 ± 97 days after onset of catatonia. Bifrontotemporally electrode placement (93%) was almost exclusively used, and a mean of 15 ± 10 ECT sessions was given. During the first week of treatment, daily ECT was given to 15 (56%) of the 27 patients. After 2 weeks, 15 (56%) patients still received ECT (of which 4 daily), and in 12 (44%) patients, ECT had been discontinued. All patients were treated with a constant current (0.9 Ampère) and brief pulse (0.5-1 millisecond) ECT device (Thymatron DgX and later Thymatron IV, Somatics Inc., Lake Bluff, Illinois, USA). Mean administered electrical stimulus at the first ECT session was 214 ± 113 milliCoulombs (mC), mean motor seizure duration (as

Table 1 Baseline characteristics of the study population (n=27)*

Demographic characteristics	
Female	15 (56)
Age in years (mean ± SD†, range)	49.1 ± 19.2, 19-84
Clinical characteristics	
Psychiatric diagnosis#	
Psychotic disorder	12 (44)
Schizophrenia	10 (37)
Psychotic disorder not otherwise specified	2 (7)
Mood disorder	13 (48)
Depressive disorder, without psychotic features	3 (11)
Depressive disorder, with psychotic features	3 (11)
Bipolar disorder	7 (26)
Alcohol and substance abuse	3 (11)
Mental retardation/autistic disorder	2 (8)
Somatic comorbidity#	13 (48)
Cardiovascular	2 (7)
Neurological, including related to catatonia (n=4)	10 (37)
Any abnormality cerebral CT/MRI†	8 (33)
Infectious disease	3 (11)
Catatonia characteristics	
Presence of autonomic dysfunction#	15 (56)
Hyperthermia (≥ 38° Celsius)	9 (33)
Highest temperature (°Celcius); mean ± SD, range††	37.8°C ± 1.1°C, 36-40°C
Cardiac arrhythmia§	9 (33)
Hypotension and/or hypertension§§	5 (19)
Excessive transpiration and/or saliva production	13 (48)
Clinical Global Impression-Severity-score	
Not, borderline, mildly, or moderately ill	0 (0)
Markedly ill	5 (19)
Severely ill	13 (48)
Extremely ill	9 (33)

*Data are presented in numbers and percentages unless otherwise mentioned; †Standard deviation; #More than one answer possible; †For 3 patients cerebral computerized tomography (CT) or magnetic resonance imaging (MRI) was missing and 'any abnormality' was defined as presence of white matter lesions (n=3), cerebral infarction (n=1), hematoma (n=1) or other (n=3); ††In Fahrenheit (F); mean ± SD, range = 100°F ± 34°F; 96.8-104°F; §Tachycardia was defined as more than 100 and bradycardia as less than 60 beats per minute; §§Hypotension was defined as a systolic blood pressure ≤ 90 mmHg and hypertension as a systolic blood pressure ≥ 140 mmHg.

Table 2 Treatment characteristics of the study population (n=27)*

Pre-treatment			
Benzodiazepines	19 (70)		
Lorazepam in mg‡ at first treatment per 24 hours†	6.3 (± 5, 1-20)		
Bromocriptine, amantadine, or other drug	4 (15)		
Time interval before catatonia treatment in days†			
Before any treatment other than ECT (n=22)	17.9 (± 40.3, 1-175)		
Before ECT (n=24)	62.1 (± 96.6, 3-386)		
Characteristics of ECT§			
Electrode placement			
Bifrontotemporal	25 (93)		
Unilateral according to d'Elia	1 (3)		
Not described	1 (3)		
Dosage method at first ECT session			
Half-age method	11 (41)		
Fixed-high dose method	10 (37)		
Empirical titration method	2 (7)		
Age-based method in unilateral ECT	1 (4)		
Not described	3 (11)		
Re-stimulation necessary at first session (n=23)	9 (39)		
Total ECT sessions (n=25)†	14.6 (± 10.3, 1-34)		
Frequency of ECT sessions	**1st week**	**2nd week**	**3rd week**
Daily	15 (56)	7 (39)	4 (27)
Interval 1 day	2 (7)	4 (22)	1 (7)
Interval 2 days	4 (15)	1 (6)	2 (13)
Otherwise	6 (22)	6 (33)	8 (53)
	first ECT session (n=22)		**last ECT session (n=21)**
Electrical dose in milliCoulombs†	214 (±113, 50-504)		471 (± 241, 101-1008)
Seizure activity in seconds†			
Motor seizure activity (cuff method)	49 (± 35, 24-64)		33 (± 24, 15-49)
EEG seizure activity	68 (± 47, 37-97)		47 (± 31, 22-72)
Post-ictal suppression index in %†	81 (± 29, 0-98)#		72 (± 32, 0-97)##

*Data are presented in numbers and percentages and n=27 unless otherwise mentioned; ‡ mg = milligram; †Mean (± standard deviation -SD-, range); §constant current (0.9 Ampère) and brief pulse (pulse width 0.5-1 ms) device; # n=14;## n=15.

measured with the cuff method at the nonparalyzed limb) was 49 ± 35 seconds, and mean EEG seizure activity was 68 ± 47 seconds. Because of lack of seizure adequacy, at the first ECT session, restimulation was required to 9 (39%) patients.

At the final ECT session, mean administered electrical stimulus was 471 ± 241 mC, mean motor seizure duration was 33 ± 24 seconds, and mean EEG seizure duration was 47 ± 31 seconds.

Differences between improved and nonimproved patients

As assessed with the CGI-I, 16 (59%) of the 27 patients improved, of whom 11 (41%) showed 'very much' and 5 (19%) 'much' improvement. Ten patients (37%) showed 'no change' and one patient (4%) scored 'very much worse' on the CGI-I. In the year after ECT, 14 (58%) patients experienced morbidities (cognitive dysfunction [n=7], cardiovascular [n=3], neurological [n=3], infectious [n=2], other [n=5]), and 3 (12%) patients died of pneumonia, of whom 2 after ineffective ECT.

Table 3 Differences between improved and nonimproved patients according to the CGI-I°

	Improved n=16	**Nonimproved** n=11	*P*-**value**
Age, mean ± standard deviation (SD), in years	43 ± 18	58 ± 18	0.05*
Autonomic dysfunction present	12 (75)	3 (27)	0.02**
Highest body temperature during catatonia^	38.2 ± 1.1	37.2 ± 0.8	0.02***
Any abnormality cerebral CT/MRI^^	5 (31)	3 (27)	ns****
Mean time interval before ECT (in days)	31 ± 33.3	105.7 ± 136.4	ns
ECT frequency in first week			
Daily	10 (63)	5 (45)	0.03*****
Interval 1 day	2 (13)	0 (0)	
Interval 2 days	3 (19)	1 (9)	
Other	0 (0)	5 (45)	
Mean duration seizure activity ± SD at last ECT-session, in seconds	43 ± 22	20 ± 22	0.03#
Motor seizure activity	61 ± 28	33 ± 28	0.04##
EEG seizure activity			
Morbidity in year after ECT present	5 (36)	9 (64)†	0.03###
Patients who died in year after ECT	0 (0)	3 (27)	0.06####

°CGI-I=Clinical Global Impression-Improvement consisting of 7 items ranging from 'very much improved' to 'very much worse'; data are presented in numbers and percentages unless otherwise mentioned; ^In ˚Celcius ± SD; ^^For 3 patients cerebral computerized tomography (CT) or magnetic resonance imaging (MRI) was missing; *t=-2.078;*df*=21.283; **Fisher's exact test=6.014;*df*=1; ***t=2.620;*df*=22.840; ****not significant; *****X^2=9.271;*df*=3; #t=2.370;*df*=17.127; ##t=2.252;*df*=18.000; ### X^2=7.059; *df*=2; ####Fisher's exact test=2.536; *df*=1.

Table 3 shows the significant differences between the patients who improved (n=16) and those who did not (n=11). Improvement was significantly related with younger age (*P*=0.05), presence of autonomic dysregulation at baseline (*P*=0.02), especially higher body temperature (*P*=0.02), daily ECT during the first treatment week (n=15 [56%]; *P*=0.03), longer duration of motor and EEG seizure activity at the final ECT session (*P*=0.03 and *P*=0.04, respectively), and less morbidity in the year after ECT (*P*=0.03).

Discussion

Retrospective evaluation of the 27 patients with catatonia who were treated with ECT revealed that more than 50% of the patients recovered completely. Improved patients were younger and more often showed autonomic dysregulation at baseline. Especially increased highest body temperature was correlated with a better outcome. ECT was mostly started after unsuccessful treatment with benzodiazepines, mainly within 2 to 3 months after onset of catatonia. The patients were treated with a mean of 15 ECT sessions (mostly administered bifrontotemporally) and, in the first week of treatment, mostly provided daily. Improved patients had a longer duration of seizure activity at the final ECT session, and showed less morbidity in the year after ECT.

The finding that 59% of our patients with catatonia benefited from treatment with ECT is not in line with 3 other studies showing higher effectiveness of ECT in 47 (85%) of 55 patients,[6] 7 (88%) of 8 patients,[7] and 26 (93%) of 28 patients[8] with catatonia. However, these latter studies differed from ours in that their patients were more often woman[8] and more often with a diagnosis of a primary mood disorder.[7-9] Comparable with our study, others have reported successful ECT after failure of benzodiazepine treatment of catatonia, with all patients nonresponsive to benzodiazepines (4 of 28 patients[10], and 9 of 18 patients[11]) responding to ECT within 1 week. Because our patients were treated with ECT after a mean time interval of 2 months, treatment delay may have negatively influenced treatment response in our group. Another retrospective study also reported that patients with catatonia who had been exposed to antipsychotics before ECT seemed less responsive to ECT.[6] In the present study, 40% (n=12) of the patients experienced a primary psychotic disorder and 32% (n=9) had used antipsychotics just before ECT, which may have resulted in decreased effectiveness compared with other studies. Furthermore, 32% (n=9) of our patients with catatonia experienced neurological comorbidity; these patients may be less responsive to ECT than other forms of catatonia.[12]

In addition, our data indicate a physician-related delay of at least 2 months before starting ECT for catatonia. Although the mean time interval before ECT among the improved patients was much less than that among the nonimproved group, this difference did not reach statistical significance. The results also show that, particularly, patients with autonomic dysregulation may benefit from ECT. These findings emphasize the importance of prompt, accurate diagnosis and treatment of catatonia. Moreover, particularly in the case of autonomic dysregulation, ECT should be considered as first-line treatment. Although our nonimproved patients were older, ECT remains an important treatment option because some of our older patients with severe catatonia recovered completely.

Our finding that the improved patients had more often received daily ECT sessions in the first week may be clinically relevant. In practice guidelines,[13] no explicit advice is given about the frequency of ECT in severely ill patients. Although the risk of cognitive adverse effects is reported in higher ECT frequency,[14] these adverse effects must be balanced against the risks of morbidity and mortality due to catatonia. Therefore, we believe that good clinical practice entails that, initially, daily ECT should be given for severely ill patients until remission of autonomic dysfunctions.

Although not statistically different from the improved patients, the nonimproved patients were treated with a lower total mean number of ECT sessions. It is therefore possible that the nonimproved patients were treated less persistently with ECT. The finding that longer duration of seizure activity at the final ECT session seemed to be related to better outcome was in line with our clinical impression that in several patients, seizure adequacy improved simultaneously with the clinical condition of the patient during the ECT course (e.g., lower electrical dosage needed to elicit longer seizure activity, more adequate seizure expression on EEG, and higher post-ictal suppression index). This leads to several interesting questions, for example, how do seizure characteristics predict the effectiveness of ECT in catatonia, and is there any influence of the natural course of catatonia on brain activity and seizure threshold? Although hard to realize in clinical practice, prospective examination of this clinical impression may help to further elucidate catatonia and its underlying cerebral dysfunctions.

The retrospective design of our study does not allow to draw firm conclusions. In addition, the diagnoses were made without using standard diagnostic instruments or catatonia rating scales; however, they were made by experienced psychiatrists with all relevant information at their disposal. Furthermore, the clinical outcome was standardized using the CGI-I. Because patients with catatonia are infrequently

seen in clinical practice, retrospective studies may be valuable in allowing to share practice-based knowledge on the treatment of catatonia.

In conclusion, in the present study, ECT was mostly an effective treatment option for catatonia, especially in younger patients with autonomic dysregulation. Daily administration of ECT in the first treatment week seemed to be more effective for catatonia. Treatment procedures were comparable to those in patients with more common indications for ECT, and longer duration of seizure activity at the final ECT session was related to better outcome. In the present study, the physician's delay in starting ECT indicates the importance of prompt, accurate diagnosis and treatment.

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9

Retrospective study of continuation electroconvulsive therapy in 50 patients

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Abstract

Background: To examine patient and treatment characteristics in continuation electroconvulsive therapy (c-ECT), defined as prolonged treatment with ECT with a maximum frequency of once a week to prevent relapse.

Methods: Medical charts of 50 patients (mean age, 59 years; 74% were female) undergoing c-ECT were examined retrospectively for patient and treatment characteristics. Electrical stimulus dosage, seizure duration, and post-ictal suppression indices between the first and the last 4 ECT sessions were compared, and their associations with the time interval between c-ECT sessions were analyzed.

Results: Almost all patients (n=46; 92%) experienced recurrent medication-resistant mood disorders. During a median c-ECT period of 393 days (interquartile rate, 211-677 days), the frequency of c-ECT ranged from once a week (n=15; 30%) to once every 4 to 6 weeks (n=17; 34%), and ECT was administered almost exclusively bifrontotemporally (n=46, 92%). The mean time interval between consecutive c-ECT sessions was 19 (SD ± 11) days. The number of days between c-ECT sessions correlated positively with median seizure duration (motor activity: r=0.390, P=0.005; electroencephalographic activity: r=0.351, P=0.013).

Conclusions: In 50 patients with long-standing, recurrent, medication-resistant mood disorders who were treated with c-ECT, increased time interval between consecutive c-ECT sessions was correlated with increased seizure duration. Whether bifrontotemporal c-ECT requires a lower frequency to sustain remission compared with unilateral c-ECT needs further investigation.

Introduction

In patients with depression, electroconvulsive therapy (ECT) is effective in the short term, but without further prophylactic treatment, relapse rates are high.[1] In some highly medication-resistant patients, continuation ECT (c-ECT) is the only treatment option for lasting relief of severe depression and for prevention of relapse.[2,3] The cumulative probability of survival without relapse or recurrence of depression at 5 years was 73% for patients treated with c-ECT and 18% for patients treated with antidepressants alone.[4] Others found a modest effectiveness for c-ECT that was comparable to continuation pharmacotherapy in preventing relapse of depression and superior in effectiveness compared to a historical placebo control group.[5]

To provide effective ECT, the charge needed to elicit a seizure must exceed the seizure threshold and, in right unilateral electrode placement, be even substantially more (e.g., 6-12 times) than the seizure threshold.[6] Because the seizure threshold seems to increase during a course of ECT (albeit not in all patients), it is suggested to make adjustments towards higher electrical stimulation during the ECT course.[2,7] Seizure duration, however, was shown to decrease during a course, even after administration of higher electrical stimuli.[8-10] According to the anticonvulsant hypothesis of the mechanisms of action of ECT, increase of seizure threshold and decrease of seizure duration may be markers of anticonvulsant brain processes that are thought to promote and sustain remission of depression.[11] They may, however, also be the outcome of changes in brain neurophysiology that accompany remission.[11] For example, compared to nonresponders, responders to ECT had a larger seizure threshold increase during the course,[10,11] although not consistently.[12,13] Seizure threshold seemed to return to previous baseline values within a few weeks to months after completing ECT.[11,14,15]

When the time interval between ECT sessions exceeded 60 days, seizure durations were shown to increase again, which corresponds to the decrease of the seizure threshold or loss of anticonvulsive action of ECT.[8] Furthermore, in case of a rapid decrease of seizure threshold with greater spacing of the c-ECT sessions, electrical dosage might be in excess of what is needed to sustain remission, because the dosages used at the end of the index ECT are often continued in c-ECT.[11] However, others reported no increase in seizure duration with an increase in time interval during c-ECT.[16]

Research on c-ECT is sparse, and the time interval between sessions seems important for management of c-ECT. Therefore, this retrospective cohort study examines possible correlates of the time interval between c-ECT sessions on the

one hand and patients' and treatment characteristics, such as seizure duration and the amount of post-ictal suppression (PIS) on the electroencephalography (EEG), on the other. As also suggested by others,[10] we hypothesized that the longer the time interval between c-ECT sessions (*a*) the longer the seizure duration and (*b*) the smaller the amount of PIS.

Methods

Subjects

During the period 1997 to June 2009, all patients treated with c-ECT at the Rijnstate Hospital (a 600-bed general teaching hospital; n=18) and the University Medical Center Utrecht (n=32; 1,042 beds) were included in the study. We defined c-ECT as treatment with ECT at a maximum frequency of once a week to sustain remission of depression, following an index ECT course of twice a week. The patients' characteristics (sex, age, psychiatric diagnosis, length of illness before index ECT, severity of depression, and severity of somatic comorbidity) were retrieved from their medical records. Psychiatric diagnosis, as assessed by experienced psychiatrists, was classified according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[17] Depression severity was measured using the Hamilton Depression Rating Scale (HDRS).[18] The HDRS at the start of the index ECT and at the end of the c-ECT (or the last available HDRS of the c-ECT period) were used. The severity of somatic comorbidity was assessed using the modified Cumulative Illness Rating Scale (CIRS).[19]

Data on the initial 4 sessions of the index ECT and the last 4 sessions of the c-ECT were collected from the patient medical records. The initial seizure threshold was recorded, if present, in milliCoulombs (mC). From the first and the last 4 ECT sessions, the mean electrical stimulus dosage in mC, the median dosage of the used anesthetic (in milligrams [mg]), the median of seizure duration (measured as motor activity at the cuffed limb, and seizure activity on the EEG, in seconds [s]), and the median of PIS (in percentage [%]) were calculated. Furthermore, the time interval between consecutive c-ECT sessions, the number of previous sessions, and the electrode placement (right unilateral according to d'Elia or bifrontotemporal) were noted.

ECT and measurement of seizure threshold

ECT was administered using the Thymatron IV (Somatics Incorporation, Lake Bluff, Illinois, USA), after induction of anesthesia intravenously with etomidate (1.5 mg/kg body mass) or methohexital sodium (1-1.5 mg/kg) and muscle paralysis

with succinylcholine (0.5-1 mg/kg body mass) intravenously and with appropriate oxygenation (100% oxygen, positive pressure) until the resumption of spontaneous respiration. EEG parameters were recorded and calculated by the Thymatron IV device, which provided the PIS in %.

The initial seizure threshold at the first ECT session was measured by an empirical titration method according to the guidelines of the American Psychiatric Association.[3] If the starting stimulus dose failed to elicit a seizure of at least 20 seconds' duration measured with the cuff method, stimulus charge was increased according to the titration schedule (for patients aged < 50 years: 5%, 10%, 20%, 40%, and 80%; for patients aged ≥ 50 years: 10%, 20%, 40%, and 80%), and the patient was restimulated after 30 seconds. At the second session, the dosage was set at 2.5-times seizure threshold for bifrontotemporal treatment and at 6-times seizure threshold for unilateral treatment. Dosage was adjusted during the course of the ECT to maintain seizure duration of at least 20 seconds as measured with the cuff method. The patients were treated twice weekly. The experienced clinicians decided to reduce the treatment frequency when a maximum response had been reached or a plateau in response occurred. First, ECT was administered once a week, followed by once in 2 weeks, once in 3 weeks, and so on, and each reduction in frequency was based on clinical judgments.[3] When patients showed signs of relapse, after reevaluation of the psychiatric diagnosis and other treatment options, the ECT frequency was increased and tapered when a plateau was reached again.

Statistical analysis

Data were analyzed using SPSS for Windows, version 15 (SPSS Inc., Chicago, Illinois, USA), calculating frequencies and percentages for categorical variables, and mean and standard deviation (SD) values or median values and interquartile rates (IQRs) for continuous variables. Furthermore, from the first 4 index ECT sessions and the last 4 c-ECT-sessions, the mean (± SD) used electrical stimulus dosage, and the median and IQR of the seizure duration and the PIS were calculated. Data of the 4 sessions were used to prevent influence of single outliers or missing data.

For comparison of the first 4 and the last 4 ECT sessions, paired t-tests were used for normally distributed continuous variables (mean of the first and last 4 electrical stimuli) and Wilcoxon signed rank tests were used for nonnormally distributed continuous variables (median of the first and last 4 seizure durations, PIS values, and dosage of anesthetics). Possible correlations between the first index ECT sessions and the last c-ECT-sessions and between the time interval of consecutive c-ECT sessions on the one hand and patients' and treatment characteristics on the other were calculated using Pearsons' correlation coefficients, and Spearman's rho

in case of nonnormally distributed variables. The time interval of right unilateral c-ECT (n=4) was compared with that of the bifrontotemporal c-ECT (n=46) with the Mann-Whitney U-test. Level of significance was $P \leq 0.05$.

Results

Patients' characteristics

The demographic and clinical characteristics of the 50 patients are summarized in Table 1. Most patients were female (n=37; 74%) and the mean age (± SD) was 59 ± 14 years. Almost all patients (n=46; 92%) were experiencing a medication-resistant mood disorder, mostly recurrent (n=43; 86%). The median illness duration was 10 years (IQR, 4-18.5 years). The mean HDRS at the start of the index ECT was 23 ± 8 points (n=30) and 10 ± 7 points at the last c-ECT sessions or end of treatment (n=29; paired t-test=5.542; *df*=26; *P*<0.0001). The mean CIRS score regarding somatic comorbidity remained unchanged.

Treatment characteristics

Table 2 summarizes the treatment characteristics of the 50 patients treated with c-ECT. Most of them were treated with ambulatory c-ECT (n=47; 94%). The ECT was administered mostly bifrontotemporally (n=46; 92%), and in most cases, methohexital (n=29; 58%) or etomidate (n=19; 38%) were used as an anesthetic. Dosages of anesthetics at the first and last 4 sessions showed no significant differences. The median initial seizure threshold, which was measured in 40 patients, was 63 mC (IQR, 49-151 mC).

The mean time intervals between the 2 ECT sessions were 19 ± 11 days; in the bifrontotemporal c-ECT a median of 20 days (IQR, 7-28 days; n=46), and in right unilateral c-ECT a median of 14 days (IQR, 7-26.5 days; n=4; Mann Whitney U-test=81.000; Z=-0.395; *P*=0.72). At the last 4 c-ECT-sessions, 15 patients (30%) were treated once a week and 17 patients (34%) with time intervals exceeding once every three weeks. A median of 28 (IQR, 16-59) ECT sessions was administered during a median c-ECT period of 393 days (IQR, 211-676 days).

Comparison of first index ECT and last c-ECT sessions and their correlations

Table 3 shows that at the start of the index ECT, the mean values of the mean values of electrical stimulus dosage were 167.3 ± 120.6 mC and 360.7 ± 255.9 mC in the first 4 and last 4 c-ECT sessions, respectively. These mean values differed significantly (paired t-test -5.479; *df*=49; *P*<0.001) and also correlated significantly

Table 1 Characteristics of patients (n=50) treated with continuation electroconvulsive therapy (c-ECT)*

Sex	
Male	13 (26)
Female	37 (74)
Current age, mean ± standard deviation (SD); range, in years	59.3 ± 14.2; 20-85
Psychiatric diagnosis	
Depressive disorder, recurrent, severe without psychotic features	33 (67)
Depressive disorder, recurrent, severe with psychotic features	10 (20)
Bipolar I disorder, last episode depressive	3 (6)
Schizoaffective disorder, bipolar type	2 (4)
Bipolar II disorder	1 (2)
Not described	1 (2)
Psychotic features present	13 (26)
Severity of depressive symptoms according to the HDRS[$]	
at start of the index ECT, mean ± SD (n=30)	23.0 ± 8.2[¶]
at study entrance or at end of c-ECT treatment (n=29)	10.1 ± 6.9[¶]
Duration of disease before index ECT, median; IQR[#], in years	10; 4-18.5
Severity of somatic comorbidity at start of the index ECT, measured with CIRS[$$], mean ± SD (n=47)	21.0 ± 2.6
Indication for continuation ECT	
Psychopharmacological drugs resistant	46 (94)
Psychopharmacological drugs contraindicated	2 (4)
Patients' preference	1 (2)
Not described	1 (2)

*Data are presented in numbers with percentages unless otherwise specified; [#]Interquartile range; [$]Hamilton Depression Rating Scale is a validated, observer-rated scale to measure severity and change of depressive symptoms, ranging from 0-54;[¶]Paired t-test=5.542; d*f*=26; *P*<0.0001; [$$]Modified Cumulative Illness Rating Scale is a validated, observer-rated scale to measure severity of illnesses, ranging from 14-70.

and positively (Pearson's correlation coefficient, 0.287; *P*=0.043). In the first 4 index ECT sessions, the median values of the median values of motor and EEG seizure activity duration were 36 seconds (IQR, 32-49 seconds) and 59 seconds (IQR, 44-73 seconds), respectively. In the last 4 c-ECT-sessions, the median values of the median values of motor and EEG seizure activity duration were 38 seconds (IQR, 28-47 seconds) and 52 seconds (IQR, 40-66 seconds), respectively. These median values between the first 4 and last 4 sessions did not differ significantly, but the median of EEG duration in the first 4 sessions correlated significantly and positively with

Table 2 Treatment characteristics of patients (n=50) treated with continuation ECT (c-ECT) *

Type of ECT, duration and treatment setting:	
Mean number of days between two c-ECT sessions ± SD#	19.3 ± 11.2
in right unilateral c-ECT (n=4)	15.8 ± 10.5
in bifrontotemporal c-ECT (n=46)	19.6 ± 11.4
Total number of c-ECT sessions, median; IQR#	27.5; 15.8-58.5
Duration of c-ECT period, median; IQR, in days	393; 211-676
ECT provided ambulatory	47 (94)
Characteristics of c-ECT and anesthesia:	
Bifrontotemporal electrode placement	46 (92)
Right unilateral electrode placement according to d' Elia	4 (8)
Initial seizure threshold (n=40), median; IQR, in mC#	63; 48.9-151.1
Use of etomidate, median dose and IQR, in mg#	19 (39); 20; 18-20¶
Use of methohexital, median dose and IQR, in mg	29 (59); 105; 72.5-127.5¶¶
Use of propofol, median dose and IQR, in mg	1 (2); 20; 20-20
Most recent frequency of c-ECT:	
Once a week	15 (30)
Once every two weeks	9 (18)
Once every three weeks	9 (18)
Once every four weeks	10 (20)
Once every five weeks	5 (10)
Once every six weeks	2 (4)

*Data are presented in numbers with percentages unless otherwise specified; #IQR=Interquartile range; SD=standard deviation; mC=milliCoulombs; mg= milligrams; ¶Median dose of etomidate at index-ECT was 20 mg (IQR, 19-20 mg); Wilcoxon Signed Ranks test revealed no difference compared with dose at c-ECT, Z=-1.394, *P*=0.16; ¶¶Median dose of methohexital at index-ECT was 110 mg (IQR, 78.8-150 mg); Wilcoxon Signed Ranks test revealed no difference compared with dose at c-ECT, Z=-0.631, *P*=0.53.

the median EEG duration in the last 4 sessions (Spearman *r*=0.294, *P*=0.043). The median values of the PIS of the first 4 (90%; IQR, 85-95%) and the last 4 (94%; IQR, 89-96%) sessions differed significantly (Wilcoxon signed ranks test; Z=-2.327; *P*=0.02) and were also significantly and positively correlated (Spearman *r*=0.470; *P*=0.001).

Correlation of the time interval between consecutive ECT sessions and patients' and treatment characteristics

A higher number of days between c-ECT sessions correlated moderately but significantly with increased median duration of motor seizure activity (Spearman *r*=0.390; *P*=0.005) and with increased median duration of EEG seizure activity (Spearman *r*=0.351; *P*=0.013) as assessed during the last 4 c-ECT sessions (Figure 1).

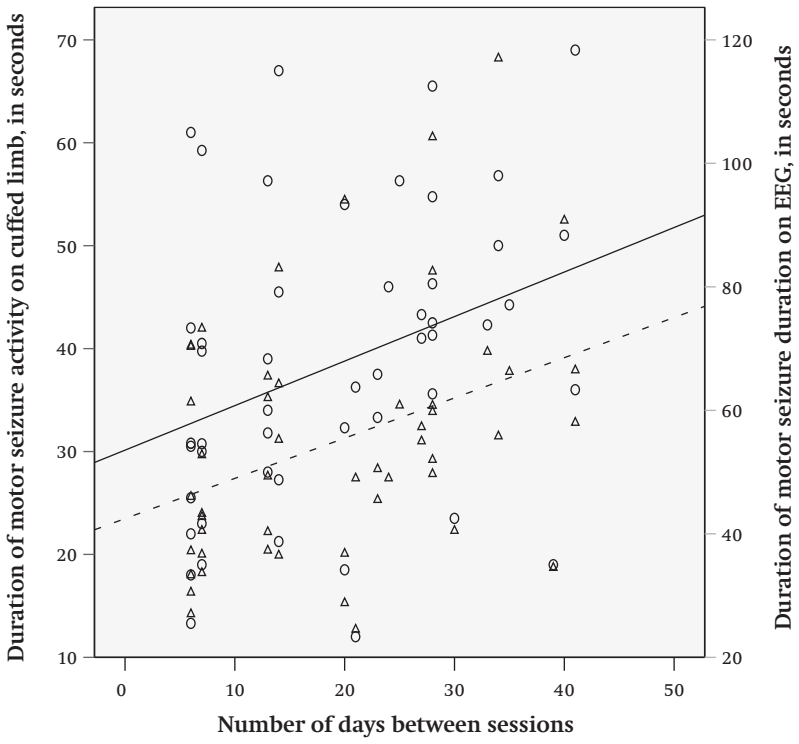
Table 3 Comparison of treatment characteristics in 50 patients treated with electroconvulsive therapy (ECT), calculated from the first 4 index ECT sessions and the last 4 continuation (c-ECT) sessions, and their correlations

	At first 4 index ECT sessions	At last 4 c-ECT sessions
Mean stimulus dose ± SD* of, in mC*	167.3 ± 120.6#	360.7 ± 255.9#
Median duration of motor seizure activity; IQR*, in seconds	35.5; 32-49.3†	38.3; 27.8-47.2†
Median duration of EEG seizure activity; IQR, in seconds	58.9; 44.1-72.6††	52.4; 39.6-65.7††
Median post-ictal suppression index, in %; IQR	90; 85-94.5¶	94.0; 89.4-95.9¶

*IQR=Interquartile range; SD=standard deviation; mC=milliCoulombs; #paired t=-5.479; d*f*=49; *P*<0.0001; higher used electrical dosages at index ECT correlated with higher dosage at c-ECT, Pearson's correlation coefficient 0.287; *P*=0.043; †Wilcoxon Signed Ranks Test showed no significant difference, *P*=0.589; no significant correlations between duration of motor seizure activity between index ECT and c-ECT, Spearman *r*=0.263, *P*=0.074; ††Wilcoxon Signed Ranks Test showed no significant difference, *P*=0.589; longer duration of EEG seizure activity at index ECT correlated with longer EEG seizure activity duration at c-ECT, Spearman *r*=0.294, *P*=0.043; ¶Wilcoxon Signed Ranks Test: Z=-2.327; *P*=0.02; higher PIS at index ECT correlated with higher PIS at c-ECT, Spearman *r*=0.470; *P*=0.001.

The median PIS of the last c-ECT sessions showed no significant correlation with the time interval (Spearman *r*= -2.39; *P*=0.095). Higher patient age correlated moderately with higher initial seizure thresholds (Spearman *r*=0.504; *P*=0.001), with increased mean of the used electrical dosage of the last 4 c-ECT sessions (Pearson *r*=0.301; *P*=0.033) but not significantly with the median values of motor or EEG seizure duration.

Figure 1 Correlation time interval and seizure activity



Discussion

In this retrospective study among 50 patients who were treated with c-ECT, the frequency of c-ECT ranged from once a week to once every 4 to 6 weeks, whereas the mean time interval between consecutive c-ECT sessions was 19 days. A median of 28 ECT sessions was administered during the entire c-ECT period of a median of 393 days. Compared with the baseline, the HDRS scores seemed to be decreased in c-ECT, which indicates the ability of c-ECT to sustain remission of depression. The electrical stimulus dosage increased significantly between the start of the index ECT and the 4 last sessions of c-ECT, and higher electrical dosage at index ECT was associated with higher electrical dosage administered in c-ECT. In addition, an increased time interval between consecutive c-ECT sessions correlated moderately with increased seizure duration but not with PIS, a parameter for seizure adequacy in ECT.

The association we found between increased seizure duration and increased time interval of c-ECT is in accordance with another study that showed increased seizure duration when time intervals exceeded 60 days; the latter authors suggested that the increase of seizure duration was a sign of decreased seizure threshold or loss of anticonvulsive action.[8] In our study, however, seizure duration increased when the time interval was less than 60 days.

In a comparable retrospective study among 41 patients (mean age, 63 years; 76% were female) undergoing c-ECT predominantly because of a mood disorder, patients were treated almost exclusively with right unilateral c-ECT; the time interval of treatments was mostly once every 2 weeks (n=10), and no patient was treated less than once every 3 weeks.[20] In our study, the patients were almost exclusively treated bifrontotemporally, the median time interval was 20 days, and 17 patients (34%) were treated with time intervals longer than once every 3 weeks. These differences might signify that the optimal time interval in bifrontotemporal c-ECT is longer compared to right unilateral c-ECT.

Seizure threshold increase is greater in bilateral index ECT than with unilateral ECT,[21] and it has been suggested that seizure threshold would rapidly decline with greater spacing of c-ECT-sessions.[11] In the present study, it was not possible to verify this decline because we did not measure seizure thresholds during the c-ECT period. Therefore, we cannot exclude that the electrical dosage was in excess of that which was needed to sustain remission. For this reason, some authors suggest repeated measurements of seizure threshold during ECT,[11] particularly after 2 months of treatment.[8]

Because our study was retrospective, the results must be interpreted with caution, as various confounders (such as concomitant medication use or substance abuse) might have influenced seizure thresholds, electrical stimulus dosage used, seizure duration, and PIS. In addition, because patients' electrical stimulus dosage during index-ECT and c-ECT was individualized and did not follow standard protocols, the increased electrical dosage at c-ECT is difficult to interpret.

In conclusion, in the present study, electrical stimulus dosage in c-ECT was higher compared with index ECT. An increased time interval between consecutive c-ECT sessions correlated moderately with increased motor and EEG seizure duration, possibly indicating a decrease of seizure threshold or loss of anticonvulsive action when time intervals between c-ECT sessions increase. Further research is needed to determine whether bifrontotemporal c-ECT requires a lower frequency to sustain remission compared to unilateral c-ECT.

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10

Summary, general discussion and future perspectives

Electroconvulsive therapy (ECT) may greatly improve the lives of patients suffering from severe, disabling and life-threatening psychiatric diseases such as depression and catatonia. For decades it has been known that the efficacy of ECT is derived from an induced generalized seizure.[1] However, under normal conditions the human brain is well-prepared to obstruct the spreading of uncontrolled, synchronous neuronal electrical signals, which characterizes seizure activity. Accordingly, seizure activity only develops when the ECT stimulus is capable of exceeding the brain's seizure threshold (ST). The processes underlying seizure provocation, propagation and termination are exciting subject matters that may teach us more about the functioning of the brain and the pathophysiology of severe diseases including mood disorders and epilepsy.

In the literature, the supposed working mechanisms of ECT and its several relevant technical aspects have been described. With respect to treatment effectiveness and (cognitive) adverse effects, there is still an ongoing debate about the most favorable electrode placement, electrical dosage, time interval between sessions and the optimal electrical stimulus parameters.[2,3] While in ECT the goal is to excite large enough populations of neurons by direct electrical stimulation, it is necessary to overcome the resistance presented by the scalp and skull. Studies on how the electrical current finds its way to and through the brain are sparse. Investigations about the conditional working mechanisms for seizure provocation, propagation and termination in ECT and the barriers in these processes are also limited. This thesis explored various clinical and anatomical characteristics of the head and brain that may influence the ST as well as the outcome of ECT in patients.

1. Summary of the main results

In **Part 1**, we first aimed to establish common levels of the initial ST (IST) in patients undergoing ECT. We were also interested in the determinants of ST levels. In our meta-analysis (*Chapter 2*), we found a weighted overall mean level of IST of 68.2 milliCoulombs (mC) (95% confidence interval [CI]: 63.2-73.3 mC) in right unilateral (RUL) and of 116.6 mC (95% CI: 103.7-119.4 mC) in bifrontotemporal (BL) ECT. With these results, we demonstrated that the average ranges of IST levels differed between RUL and BL electrode placement. Also, by using our established weighted IST means, the calculated ranges of the therapeutic stimulus doses in RUL and BL ECT appeared within the ranges of the 'fixed-dose' method in RUL and the 'half-age' method in BL ECT. Therefore, when using these formula-based methods, an electrical dosage can be administered to elicit an adequate seizure for most of the patients. However, there is considerable variation between patients, implying that

some patients are initially treated with a suboptimal electrical stimulus dosage, which can induce unnecessary adverse effects.

Based on literature reviews (*Chapter 3 and 4*), we subsequently determined several (established or proposed) clinical, brain anatomical and functional determinants of the IST and the ST during the ECT course. Clinically, a higher ST level was associated with advanced age, male gender, presence of comorbid medical illnesses, use of BL electrode placement, cumulative number of treatment sessions, lower dynamic impedance, and concomitant use of certain psychotropic and non-psychotropic drugs. Anatomical factors such as increased scalp impedance, increased amount of cerebral atrophy, decreased neuronal density, increased neuronal damage marked by white matter hyperintensities (WMH; causing less functional connectivity between brain areas) and increased cerebrospinal fluid (CSF) volume were suggested to be associated with a higher ST. The following three functional brain characteristics can also be proposed to explain a higher ST. Firstly, a decreased metabolism in the brain's prefrontal areas is proposed to explain higher ST. Secondly, an increased sensitivity to GABA through higher expression of GABA-receptors in the brain and thirdly, reduced concentrations of, or sensitivity to, glutamate in the brain can explain a higher ST.

In **Part 2**, we examined which patient, treatment and anatomical MRI characteristics predicted the IST levels and the ST during the ECT course. This prospective clinical study was conducted including 91 patients with serious depression who were undergoing ECT (*Chapter 5*). Our study demonstrated that a higher age and BL electrode placement were independent predictors for a higher IST as well as for higher ST levels at different time points during the ECT course. Furthermore, the absence of a previous ECT course appeared to predict a steeper ST increase during the course, which finding - to our knowledge - has not been reported before. In accordance with the results of this study, we defined age and BL electrode placement as confounders in our subsequent MRI study. This study investigated the relationship between the IST and head and brain morphological characteristics in 74 of the 91 patients.

In this MRI study (*Chapter 6*), after adjusting for age and gender, we found that the volume of CSF independently predicted the IST in RUL as well as in BL ECT, which – as far as we know – has not been reported before. In BL ECT, this relationship was much stronger than in RUL ECT. Moreover, the CSF volume predicted the consecutive ST levels during the ECT course in RUL ECT. These findings seem to support the hypothesis that more brain CSF leads to increased shunting of electrical current. This increased shunting makes the electrical field, which is

required to trigger seizure activity, weaker and more localized. This may result in a consequently higher ST.

In **Part 3**, we conducted an investigation with 83 patients in order to ascertain whether clinical, anatomical and treatment characteristics predicted their post-ECT scores of the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Mini-Mental State Examination (MMSE) (*Chapter 7*). We demonstrated that the presence of psychotic depression and previous ECT exposure predicted a better outcome on the post-ECT MADRS score. Furthermore, the presence of bipolar depression at baseline predicted a better cognitive outcome, whereas the use of concomitant antipsychotics predicted a worse cognitive outcome. Baseline head MRI morphological characteristics were not predictive for post-ECT MADRS and MMSE scores.

In the above-mentioned prospective studies, we examined the ST in a common ECT population consisting of mostly pharmacotherapy resistant and/or psychotic depressed patients. Continuing these studies, we explored the characteristics of the ST in two special patient populations, including patients with catatonia and patients treated with continuation-ECT (c-ECT). In a retrospective study of 27 patients with catatonia (*Chapter 8*), we established that characteristics such as younger age, presence of autonomic dysregulation (especially fever) at baseline, daily ECT during the first treatment week, longer duration of the EEG seizure activity at the last ECT session, and less morbidity in the year after ECT were significantly associated with better clinical improvement. In these catatonic patients, quite often the ST was higher than expected and it was noticed, quite serendipitously, that the EEG improved simultaneously with the patients' clinical condition. This may suggest that (pathophysiological mechanisms of) catatonia also affected the ST.

In our retrospective study of 50 patients treated with c-ECT (*Chapter 9*), we showed that an increased time-interval between consecutive c-ECT sessions correlated moderately with increased seizure duration, but not with increased post-ictal suppression on the EEG. In the literature, shorter seizure duration was related to a higher suprathreshold electrical stimulation,[2,3] and the ST was supposed to decrease within a short period of time to the previous baseline level, at least in some patients.[7] Therefore, when the time-interval between c-ECT sessions increases, a decrease of the ST or loss of anticonvulsant action was suggested.[6]

2. Validity and generalizability of the results of our studies

Our studies may generate various methodological concerns regarding patient selection, study design (retrospective versus prospective), psychiatric diagnosis, technical confounders of the ST titration procedure, and limitations in the computerized analyses of the structural and functional MRI datasets. All these factors may have compromised to some extent the validity of the data and the generalizability of our results.

2.1 Selection bias and study design

In our studies, the included patients formed highly selected samples of the whole group of depressed patients. Therefore, diagnosing and treating patients with ECT in a large general teaching hospital such as Rijnstate in Arnhem (the Netherlands) may have induced bias in our studies. It is likely that the most somatically compromised ECT patients were treated in a general hospital like ours and not in ECT facilities with fewer somatic care capabilities. Several of these patients could be included in our prospective study (29 out of 91 patients [32%] showed a modified Cumulative Illness Rating Scale score ≥ 23). It is likely that in other ECT studies patients with various somatic illnesses were also included. However, in recent large multicenter ECT studies, the somatic conditions of the included patients were not described.[15,16] Therefore, it is unclear whether our included patient population is representative for the entire population of ECT patients. This may have implications for the generalizability of our results and thus for the external validity with respect to future ECT patients. It is important, therefore, that our findings are replicated in different patient samples.

Some potential study patients had to be excluded from our prospective studies, mostly because they could not be exposed to the titration process due to their poor physical condition, extreme agitation that made adequate MRI scanning impossible, and/or inability to provide informed consent. As such, our findings cannot automatically be generalized to these somatically compromised and/or agitated patient groups. Our study group did however consist of severely depressed patients (mean MADRS score at baseline was high, showing 36.2±8.4 points), of whom 35% (n=31) also had psychotic features. This indicates that our prospective study group (*Chapters 5-7*) represents a common population of studied ECT patients.[2,8,15,16] In contrast, our retrospectively studied groups of catatonic (*Chapter 8*) and c-ECT (*Chapter 9*) patients were highly selected samples. This allows for inferences that are internally valid for this specific group of patients. Fortunately, in clinical practice, these patients rarely appear. They often show specific charac-

teristics including persistent treatment-resistance, severe somatic comorbidity, concomitant benzodiazepines use, and treatment with different ECT session frequencies. Therefore, our findings may not necessarily apply to other more mildly somatically ill and depressed patients.

It was further observed that almost all patients used concomitant medication during the ECT course. When treating severely ill patients in daily practice, it is virtually impossible to taper off all medication before ECT, especially regarding essential drugs for physical problems. To taper off all psychopharmacological drugs would also carry the risk of increased suffering to the patient. Although for some drugs, the effect on neuroexcitability in animal studies has been identified, it is not known how these medications might affect the ST in patients undergoing ECT. In our prospective observational studies on ST levels during the ECT course, all medication was continued unchanged during both the treatment period, as well as the titration protocol. However, the generalization of our results to patient populations who are drug-naive or who have been weaned off medication before ECT is likely to be limited.

2.2 Validity of psychiatric diagnoses

A limitation of our study may be that no standard diagnostic instruments (e.g., Structured Clinical Interview for DSM Disorders, or Mini-International Neuropsychiatric Interview) were used for formal psychiatric diagnosis according to DSM-IV-TR criteria. Patients had been referred for ECT from different treatment centers in the Netherlands and several psychiatrists had performed the mental status examinations of the patients and confirmed the psychiatric diagnosis for which ECT was indicated. We were also able to rate the Dutch version of the MADRS,[9,10] in 91% of the study patients, thereby confirming and scoring the severity of the depressive symptoms. Based on this rating, we could ascertain that all our patients indeed suffered from a clinical diagnosis of depression. Regarding our retrospective studies, the diagnoses of catatonia and recurrent therapy-resistant mood disorders had also been confirmed clinically by experienced psychiatrists and classified according to DSM-IV-TR.

2.3 Limitations in the titration process that was used

In ECT, most electrons do not traverse the brain and the exact percentage of electrons that actually reaches the brain is not known. As we hypothesized, excessive shunting of electrons through the scalp and CSF in all likelihood occurs, but it was not possible to measure exactly the amount of shunting. The level of dynamic impedance is the only factor that may indirectly represent the level of shunting. This shunting could be due to factors as environmental temperature,

moisture of the air, electrode placement, electrode-skin interface, resistance of the patient's hair, skin, skull, blood vessels, meninges, brain tissue and amount of CSF. However, we were not able to document these various factors and they, therefore, could not be taken into account. In other aspects, the stable treatment site, the experienced Rijnstate ECT team, and their consensus on how to perform ECT, may have adequately standardized many of the variables involved in the treatment of the study patients.

Another limitation in validity and generalizability of our results is the titration process itself. In ECT, the ST is determined by several physical stimulus parameters, including pulse width, frequency, stimulus duration, and current strength. As other studies may have used different stimulus parameters, a comparison of our ST levels with those of other studies is difficult. Another difficulty in generalization of the estimated ST levels is the definition of adequate seizure duration in our study (≥ 20 seconds of motor and/or ≥ 25 seconds of EEG duration). Although this definition is often used internationally, it may not be comparable with other studies (see *Chapter 2*).[11] Furthermore, with our used titration process, the ST levels were estimated very roughly in large steps of 25-100 mC. Also, our dosage increments during titration were accompanied by higher stimulus frequencies and train durations, not to mention change in pulse width at the final step in RUL ECT. These stimulus parameters supposedly also influenced the level of the ST.[12,13]

An age-based adjustment in our titration protocol was also used in order to reduce the risk of unwanted subconvulsive stimulation in the mostly older patients. However, a truly informative ST would only have been established if an initially subconvulsive stimulus was followed by a stimulus which did elicit a seizure at the consecutive titration step.[3] Our patients aged ≥ 50 years started one step higher (i.c., 50.4 mC) compared to the younger ones (25.2 mC).[14] Consequently, the frequency of a lower IST was underestimated in the older patients. In our titration procedure, a substantial number of patients (n=64; 70%) showed adequate seizure activity at the first step and in these patients an overestimation of the level of the ST ('floor effect') may have occurred. Also, patients with very low STs were not detected with our titration procedure. This means that, for a patient with a very low ST (e.g., 5 mC), in whom the doubling of the threshold during the ECT course had taken place (e.g., 10 mC), we were not able to show this increase during the follow-up, as the first step in our titration protocol was 25 mC. These limitations make it difficult to draw conclusions about our examined ST levels. In clinical practice, however, these titration methods used are the best we have.

2.4 Limitations in the MRI data acquisition and analyses

MRI scanning of the brain serves as a non-invasive research method. The computerized segmentation tools facilitate reproducible estimates of the volumes of CSF, gray matter, white matter and WMH. In our study, some limitations were encountered. Firstly, the acquisition of our patients' MRI data was fully integrated in the daily routine of our department of radiology in the Rijnstate Hospital, creating the opportunity to include very ill patients. However, our method to measure the thickness of scalp and skull on MRI was crude, showing an only moderate ICC ranging from 0.6-0.7 between two independent and experienced raters. Although using the mean of two raters reduced some measurement error, it cannot be excluded that measurement errors may have led to a reduced power in detecting a putative influence of scalp and skull thickness on the IST. Furthermore, the automatic FSL process to determine volumes of intracranial volume, CSF, gray and white matter and WMH, had several limitations. One such limitation may be that the brain extraction tool might have limited outer-brain CSF estimates, causing structural underestimation of the CSF volume. In some individual areas, the segmentation process had failed to make a correct distinction between the different brain tissues and CSF, and the registration processes (to correct for WMH) might have appointed some voxels to wrong structures, leading to slightly erroneous calculations of tissue volumes.

In a subgroup of our patients (n=58), we used functional MRI (fMRI), to examine whether the connectivity within the default-mode network (as an indication of the integrity of feedback circuitry within the brain and studied in epilepsy)[4,5] was associated with the IST. Unfortunately, we were not able to establish a reliable default-mode network within our patient group, possibly as a result of disturbances during the fMRI data acquisition. Therefore, we could not examine the association between the IST and an indirect measurement of functional connectivity within the brain.

3. Clinical implications of our study

Our results may have several clinical implications for the daily practice of ECT. The question arises however, as to whether the IST is indeed an important variable to consider in the clinical care of ECT patients. Perhaps thousands of patients are treated each year without any consideration of the individual IST by their treating psychiatrists using effective formula-based dosage methods. Having stated that, our study generates several recommendations for the clinical practice of ECT:

- Clinicians can confidently use the 'fixed-dose' method in RUL and the 'half-age' dosing method in BL ECT, since in most of these patients the electrical doses may induce therapeutic seizures.
- Clinicians are advised to consider raising the stimulus dose during the ECT course, especially in BL treated patients who show limited clinical efficacy, because increasing STs during the ECT course are to be expected in these patients.
- Clinicians should evaluate the necessity of electrical dose adjustments during the ECT course in patients who were previously treated with ECT, as ST stability during the ECT course may be expected. Repeated titration during the ECT course can help to evaluate the extent of the increase in the ST.
- In light of the expected favorable results, clinicians are advised to offer immediate ECT to patients with a psychotic depression and to patients who have had successful ECT before.
- Clinicians are advised to taper off antipsychotics before ECT, but only if the clinical condition of the patient allows doing so. Our study showed some evidence that the use of antipsychotics is associated with an increase in cognitive adverse effects.
- Clinicians may decide to administer daily ECT sessions in the first week to treat a malignant catatonic patient with autonomic dysregulation. This frequency predicted a positive outcome for ECT in our retrospective study.
- In patients treated with c-ECT who experience an increase in cognitive adverse effects, clinicians are advised to estimate the ST again by titration and to adjust the electrical dose accordingly. Our retrospective study suggests a decrease of the ST when the time between the consecutive c-ECT sessions increases.

4. Suggestions for further research

Our results prompt further exciting research questions not only about the use of MRI in ECT practice, but also about the most optimal ECT dosing strategy, the various technical aspects, and the more basic issues of brain functioning and brain diseases.

4.1 Perspectives on MRI research in ECT

Firstly, we should realize that we do not have enough scientific evidence at this time to recommend standard MRI evaluation for patients. This makes it difficult to use their individual brain characteristics in dosing strategies for ECT. More evidence from clinical studies is required to incorporate such an innovative approach in clinical practice. A pre-ECT head MRI scan (or other neuroimaging

technique), however, is always indicated if there is any clinical doubt about the existence of complicating factors in diagnosing or treating the ECT patient. For example, space-occupying processes, severe cerebrovascular diseases, head trauma, and skull damage are all clinical conditions that must be evaluated before initiating ECT.

It is still a matter of debate as to whether adjusting the variable 'volume of CSF' to an ECT dosage algorithm will lead to a better outcome of mood and cognition after treatment. Preferably, other researchers should first replicate our estimated predictive value of CSF volume for the levels of IST and ST during the course. Subsequently, a randomized clinical trial should examine whether a dosing protocol, which adjusts for CSF volume as well as age, would show better outcomes than a protocol in which only higher age determines a higher electrical dosage. More prospective research should also be carried out in order to examine MRI data related to the clinical outcome of ECT. In our study, we did not show predictive values of the total volumes of CSF, gray matter, white matter and WMH for the clinical outcome. Yet further evaluation of these volumes in specific brain structures and areas may yield predictors for both the effectiveness and cognitive adverse effects in ECT. It would be exciting for clinicians in daily practice, if they could use an MRI scan to choose a more proper and individualized ECT dose, as well as to enhance the information they could give to their patients (and significant others) about the benefits and adverse effects of ECT.

4.2 Perspectives on clinical ECT dosing strategies and prediction of adverse effects

As a result of our findings, it is important to explore in a randomized clinical trial whether a repeated dose titration method has a beneficial outcome compared to formula-based dosing methods. Additionally, it is essential to know whether the electrical dosage in those patients who were previously treated with ECT (as opposed to first-time treatment) can be held constant during the course with comparable clinical outcomes. Based on our outcome study, the important clinical question arises as to whether it can be confirmed using observational data, that continuing antipsychotics during the ECT course increases the risk for cognitive adverse effects. It should also be established whether bipolar patients show fewer cognitive adverse effects due to ECT and what might be the determinants for that positive effect. In bipolar patients, for example, it could be hypothesized that the use of lithiumcarbonate or another such mood stabilizer prior to ECT may prevent (or worsen) cognitive adverse effects.

4.3 Perspectives on technical considerations

Several technical topics for further exploration arise from the results of our studies. We have learned that research on the ST lacks an internationally accepted standard dosage titration protocol and we believe that the international ECT researchers should facilitate such standard. ECT devices, which are to be used in studies on ECT, should enable such titration protocols that allow very low dose administration to prevent 'floor effects' in the ST estimation. We have also established that the electrical stimulus parameters should be kept constant during the titration process, thereby using the same pulse width and/or frequency when titrating. These technical considerations should be implemented preferably in replication studies on the predictive value of CSF volume for IST and ST during the ECT course.

4.4 Perspectives on more basic issues in research of seizures and epilepsy

Aside from raising research questions regarding the treatment of psychiatric disorders, ECT can be used as a human model for seizure initiation, propagation and termination. With methods like fMRI and diffusion tensor imaging (DTI), non-invasive examination of the functional connectivity and anatomical connections within the human brain can occur. These variables can be related to the ST, seizure propagation patterns, and possibly the strength of the seizure termination process. This allows for further explorations, including the possibility to examine the feedback systems of the brain on seizure activity with fMRI. The amount of cerebral damage (e.g., due to WMH) in certain parts of the brain might be associated with connectivity patterns and neuroexcitability (e.g., higher or lower ST). An exploratory option to consider is whether cerebral damage may hamper seizure propagation through the human brain and/or the termination process. It is exciting to imagine that some basic research questions about human brain functioning and epilepsy might be examined with the help of ECT patients.

5. Concluding remarks

To conclude, our studies have revealed several exciting subject matters for further exploration regarding seizure thresholds in ECT. Yet, such a complex treatment as ECT encompasses much more than this small technical study. ECT increases the quality of life in these very ill (psychotic and/or suicidal) patients and is sometimes even life saving. Our prospective study replicated - again - high response and remission rates in the patients treated with ECT. Moreover, several practical recommendations for clinicians can be derived from our studies. In particular,

suggestions were outlined regarding predictors of outcome, electrical dosage, session frequency and concomitant medication use. It is intended that this thesis should add to our knowledge about ECT and thereby also helps to improve the care for our patients. That's the most exciting matter of all.

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Samenvatting (in Dutch)
Dankbetuigingen
Curriculum Vitae
List of publications

Spannende zaken bij elektroconvulsietherapie. Studies naar prikkeldrempels.

Elektroconvulsietherapie (ECT) verbetert vaak het leven van patiënten die lijden aan ernstige, invaliderende en/of levensbedreigende psychiatrische aandoeningen zoals depressie en katatonie. Sinds decennia is bekend dat het effect van ECT afhankelijk is van de opgewekte gegeneraliseerde insultactiviteit in de hersenen. Het menselijk brein is echter gemaakt om cerebrale ontregeling met verspreiding van ongecontroleerde, overgesynchroniseerde, neuronale elektrische signalen te voorkomen. Daardoor ontstaat insultactiviteit alleen als de elektrische stimulus in staat is de zogenaamde prikkeldrempel (ST) te overstijgen. De mechanismen die ervoor zorgen dat een insult wordt uitgelokt, zich verspreidt en weer wordt onderdrukt, zijn 'spannende' zaken die ons meer kunnen leren over het functioneren van de hersenen en over de pathofysiologie van ernstige ziekten zoals depressie en epilepsie. In dit proefschrift onderzochten wij diverse klinische en anatomische eigenschappen van hoofd en hersenen bij ECT patiënten die de ST zouden kunnen beïnvloeden.

Vanuit de literatuur zijn er verschillende werkingsmechanismen en relevante technische aspecten van ECT beschreven. Er is tot op heden nog steeds discussie over wat de meest optimale elektrodeplaatsing, de elektrische dosering, het tijdsinterval tussen behandelingen en elektrische stimulus eigenschappen (bijvoorbeeld stroomsterkte, pulswijdte, pulsfrequentie, stimulusduur) zijn in relatie tot het behandeleffect en de (cognitieve) bijwerkingen. Bij ECT is het doel een optimale hoeveelheid neuronen te prikkelen door directe elektrische stimulatie. Het is hierbij noodzakelijk om de weerstand van de hoofdhuid en schedel te trotseren. Studies die onderzoeken hoe de stroom naar en door de hersenen haar weg vindt zijn schaars. Ook de mechanismen die voorwaardelijk zijn voor insultprovocatie, -verspreiding en -beëindiging zijn weinig onderzocht. In dit proefschrift worden diverse klinische en anatomische kenmerken van het hoofd en het brein onderzocht in relatie tot de hoogte van de ST en de effectiviteit van ECT bij patiënten.

Samenvatting van de belangrijkste resultaten

In **deel 1** hebben we de gemiddelde ST bij ECT patiënten vastgesteld door middel van een meta-analyse van de internationale literatuur (*hoofdstuk 2*), waarbij een gewogen gemiddelde initiële prikkeldrempel (IST) werd berekend van 68.2 milliCoulombs (mC; 95%-betrouwbaarheidsinterval [95%-BI]: 63.2-73.3 mC) bij rechts unilateraal

(RUL) behandelde patiënten, en van 116.6 mC (95%BI: 103.7-119.4 mC) bij bilateraal (BL) behandelde patiënten. Hiermee toonden wij aan dat de gemiddelde IST spreiding bij RUL verschilde van die bij BL elektrode plaatsing. Daarbij bleek ook dat de spreiding van de therapeutische elektrische doses, berekend met deze gewogen gemiddelden, in overeenstemming was met de spreiding van de doses die worden toegediend bij gebruik van de zogenaamde "vaste-hoge-dosis" methode bij RUL en bij de "halve-leeftijd" methode bij BL ECT.

Vervolgens onderzochten wij in de wetenschappelijke literatuur (*hoofdstukken 3 en 4*) welke klinische, anatomische en/of functionele kenmerken van ECT patiënten waren vastgesteld of verondersteld als mogelijke voorspellers voor de IST en ST waarden tijdens de ECT kuur. Een hogere leeftijd, mannelijk geslacht, aanwezigheid van somatische comorbiditeit, het gebruik van BL elektrodeplaatsing, een toenemend aantal ECT-sessies, een lagere dynamische weerstand en het gebruik van bepaalde (psycho-)farmaca werden geassocieerd met een hogere IST. Vanuit anatomisch oogpunt werden de volgende kenmerken beschreven als mogelijke factoren die de ST zouden kunnen verhogen: een toegenomen weerstand van de hoofdhuid, toegenomen hoeveelheid hersenatrofie, afname van de neuronale densiteit en toename van het volume aan hersenvocht. Vanuit het oogpunt van functionele herseneigenschappen werd een afgenomen metabolisme in de prefrontale gebieden gesuggereerd als samenhangend met een hogere IST, alsmede toegenomen neuronale schade door wittestofafwijkingen (waardoor een vermindering zou kunnen optreden van de mate van verbintenissen binnen de hersenen), een toename van de gevoeligheid voor gamma-aminoboterzuur (GABA) door een hogere expressie van de cerebrale GABA-receptoren, en een afname van de glutamaatconcentratie in de hersenen.

In **deel 2** onderzochten wij, aansluitend op deze studies, in een prospectieve, observationele studie welke patiënt-, behandelings-, en anatomische MRI-kenmerken voorspellend waren voor de hoogte van de IST en de ST tijdens de ECT kuur. In onze studie bij 91 ECT patiënten met ernstige depressieve symptomen (*hoofdstuk 5*) toonden wij aan dat een hogere leeftijd en BL elektrodeplaatsing onafhankelijke voorspellers waren van een hogere IST, maar ook van hogere ST waarden tijdens de ECT-kuur. Daarnaast lieten wij zien dat, als een patiënt voor het eerst in zijn/haar leven ECT kreeg, de ST vaker en hoger steeg dan bij patiënten die eerder een ECT-kuur hadden ondergaan. We definieerden vervolgens leeftijd en elektrode-plaatsing als mogelijke confounders voor de relatie tussen anatomische kenmerken en IST.

In onze MRI studie (*hoofdstuk 6*) toonden wij aan dat, gecorrigeerd voor leeftijd en geslacht, het totale volume aan hersenvocht onafhankelijk de hoogte van de IST voorspelde, zowel bij RUL als BL behandelde ECT patiënten. Dit was, voor zover wij weten, niet eerder in de literatuur beschreven. In BL toegediende ECT was dit verband sterker dan in RUL ECT. Bovendien voorspelde de hoeveelheid hersenvocht de hoogte van de ST tijdens de ECT-kuur in de RUL behandelde patiënten. Onze bevinding is in overeenstemming met de hypothese dat meer hersenvocht leidt tot meer weglekken van elektrische stroom, gepaard gaande met een zwakker en meer lokaal elektrisch veld dat een insult kan uitlokken. De consequentie daarvan is dan een hogere ST.

In een subgroep van deze patiënten (n=58) probeerden we met functionele MRI in rust (*'resting state fMRI'*) te onderzoeken of er een relatie was tussen de hoogte van de IST en de mate van connectiviteit binnen het zogenaamde default-mode netwerk (als aanwijzing voor de kracht van het negatieve terugkoppelingssysteem van de hersenen, zoals bestudeerd in epilepsie). Helaas is dit niet gelukt, omdat we in onze groep geen default-mode netwerk konden vaststellen, mogelijk door verstoringen bij het verzamelen van de fMRI gegevens.

Tenslotte, onderzochten we in **deel 3** bij 83 patiënten prospectief welke klinische-, anatomische- en behandelingskenmerken voorspellend waren voor de uitkomsten op de Montgomery-Åsberg Depressie Beoordelingsschaal (MADRS) en de Mini-Mental State Examination (MMSE) (*hoofdstuk 7*). Wij lieten zien dat de aanwezigheid van een psychotische depressie en het hebben gehad van een eerdere ECT-kuur voorspellend waren voor een betere eind-MADRS score. Daarnaast bleek de aanwezigheid van een bipolaire depressie een beter cognitief functioneren na de ECT-kuur te voorspellen. Het gelijktijdig gebruik van antipsychotica tijdens de ECT-kuur bleek daarentegen een lager cognitief functioneren na ECT te voorspellen. De MRI kenmerken waren geen van alle voorspellend voor de MADRS en MMSE scores na ECT.

In het hierboven beschreven onderzoek bestudeerden we de gebruikelijke ECT patiëntengroep. Dit zijn patiënten met meestal farmacotherapieresistente en/of psychotische depressies. In het laatste deel van dit proefschrift werden twee bijzondere ECT groepen in relatie tot de ST bekeken, namelijk de katatone patiënten en de patiënten die behandeld werden met onderhouds-ECT (c-ECT). In een retrospectieve studie onder 27 katatone patiënten (*hoofdstuk 8*) beschreven wij dat jongere leeftijd, autonome dysregulatie (met name koorts) aan het begin van de ziekteperiode, dagelijks toegediende ECT-sessies, langere insultactiviteit op het elektro-encefalogram (EEG) bij de laatste ECT-sessie, en minder comorbiditeit in

het jaar na staken van de ECT geassocieerd waren met een betere behandeluitkomst. Bij deze katatone patiënten was de ST vaak onverwacht hoog. Ook viel op dat het EEG tegelijkertijd met de conditie van de patiënt verbeterde, wat suggereert dat (de pathofysiologie van) katatonie de prikkeldrempel beïnvloedt.

In onze retrospectieve studie van 50 patiënten die werden behandeld met c-ECT (*hoofdstuk 9*) lieten we zien dat een toename in het tijdsinterval tussen twee ECT-sessies redelijk correleerde met een toegenomen insultduur, maar niet met een hogere post-ictale onderdrukking van het EEG. Een kortere insultduur werd in de literatuur beschreven bij een hogere (boven de ST uitstijgende) elektrische stimulus. Dit was waarschijnlijk eerder het geval als er meer tijd tussen de sessies in zat, omdat de ST in de tussentijd meer kon dalen. Daarom werd bij een toename van het tijdsinterval tussen de ECT-sessies een afname van de ST of een verlies aan anticonvulsieve werking van ECT gesuggereerd.

In het afsluitende hoofdstuk (*hoofdstuk 10*) wordt een opsomming gegeven van de belangrijkste bevindingen en daaruit voortvloeiende klinische implicaties van ons onderzoek:

- Clinici kunnen met vertrouwen de "vaste-dosis methode" bij RUL behandelde patiënten en de "halve-leeftijd" methode bij BL behandelde patiënten gebruiken, omdat daarmee de elektrische dosis bij de meeste patiënten een therapeutisch insult opwekt.
- Clinici worden geadviseerd te overwegen om tijdens de ECT kuur de stimulusdosis te verhogen, in ieder geval bij BL behandelde patiënten die slechts een beperkte verbetering vertonen, omdat bij deze patiënten steeds hogere STs tijdens de kuur kunnen worden verwacht.
- Clinici zouden bij patiënten die eerder ECT hebben gehad de noodzaak tot aanpassing van de elektrische dosis moeten evalueren tijdens de kuur, omdat bij deze patiënten een constante ST kan worden verwacht. Herhaalde titratiesessies tijdens de ECT-kuur kunnen helpen om vast te stellen in welke mate de ST stijgt tijdens de kuur.
- Clinici worden geadviseerd direct ECT aan te bieden aan psychotisch depressieve patiënten en aan patiënten die eerder gunstig op ECT hebben gereageerd, omdat deze patiënten vaak goed opknappen op ECT.
- Clinici worden geadviseerd om voor ECT de antipsychotica af te bouwen en te staken (indien de klinische toestand van de patiënt dit toelaat), omdat er enige aanwijzingen zijn dat het gebruik van antipsychotica tijdens de ECT-kuur was geassocieerd met meer cognitieve bijwerkingen.
- Clinici kunnen besluiten over te gaan tot dagelijkse ECT sessies bij maligne katatone patiënten met autonome dysregulatie, omdat in onze retrospectieve

studie dagelijkse toediening geassocieerd was met een positieve uitkomst van de ECT.
- Clinici worden geadviseerd bij onderhouds-ECT patiënten die steeds meer cognitieve bijwerkingen ervaren, de ST opnieuw te bepalen met titratie en vervolgens de dosis hierop aan te passen, omdat onze retrospectieve studie een afname van de ST suggereert als het tijdsinterval tussen twee c-ECT sessies toeneemt.

Tenslotte worden in dit hoofdstuk de zwakten beschreven van ons onderzoek, de problemen die we tegenkwamen bij de verzameling, analyse en interpretatie van de resultaten, en doen wij voorstellen voor verder onderzoek.

Dankbetuigingen

Aan de totstandkoming van dit proefschrift hebben veel mensen bijgedragen die ik hiervoor hartelijk wil bedanken. Bovenal geldt mijn grote waardering aan alle patiënten die meededen aan mijn onderzoek. Ondanks de extreem zware tijd waarin zij zich op dat moment bevonden, gaven zij hiervoor hun toestemming. Ik heb daar veel respect voor.

In het ziekenhuis behandelen dokters patiënten nooit alleen en de zorgeenheid psychiatrie van Ziekenhuis Rijnstate is daarbij uniek in zijn soort. Alle verpleegkundigen, vaktherapeuten, klinisch psychologen, overige paramedici, secretaresses, en management bedank ik hartelijk voor hun dagelijkse inzet daarbij.

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Een bijzonder woord van dank is voor Lucas van Oudheusden, inmiddels psychiater in opleiding, en mijn paranimf. Jouw onvoorwaardelijke steun en werk met de (f) MRI data was fantastisch. Onze cursusreis naar Montréal was een verrijking en levenslang memorabel. Erg veel dank, en we zien ons snel weer.

Naast werk is er privé. Vele mensen zijn voor mij belangrijk. Slechts een paar noem ik hier bij naam. Allereerst Peter van den Berg, mijn voorbeeld als het gaat om het combineren van een drukke artsenpraktijk en het bedrijven van wetenschap. Leuk dat ik je al jaren ken, inmiddels samen met je gezin. We gaan vooral weer eens eten.

Jeroen Oldenburg, beste vriend voor het leven, mijn paranimf. Na onze gezamenlijke studietijd is onze hechte band altijd blijven bestaan. Mijn leven heeft vele mooie momenten, mede dankzij jouw aanwezigheid daarin, niet te vergeten samen met Birgit, Ruben en Tom. Ik ga er vanuit dat we dit nog tot hoogbejaarde leeftijd volhouden.

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Een mens kan zijn wie hij is dankzij een metgezel in het leven. Frank is mijn liefste en dat blijft hij.

Curriculum Vitae

Jeroen van Waarde werd geboren op 17 september 1968 in Haarlem. Na het behalen van het diploma voorbereidend wetenschappelijk onderwijs op 2 juni 1987 aan het Bisschoppelijk College Hageveld te Heemstede, studeerde hij geneeskunde aan de Universiteit van Amsterdam. Tijdens zijn studie werd hij van 1990-1991 gekozen als lid van de faculteitsraad, en van 1991-1992 werd hij benoemd als lid van het bestuur van de Faculteit der Geneeskunde. Hij behaalde het artsexamen op 25 januari 1995.

Na het behalen van het artsexamen werkte hij eerst een half jaar als arts-assistent-niet-in-opleiding op de afdeling interne geneeskunde bij het Antonie van Leeuwenhoek Ziekenhuis/Nederlands Kankerinstituut te Amsterdam en vervolgens een half jaar op de afdeling ouderenpsychiatrie van de Frederik van Eedenstichting (thans: AMC De Meren) te Amsterdam.

Hij volgde de opleiding tot psychiater bij Mentrum GGZ (thans: Arkin) in Amsterdam (opleider Dr. R.C. van der Mast). In het kader van de opleiding volgde hij een keuzestage ouderenpsychiatrie in de Valeriuskliniek in Amsterdam (thans: GGZ inGeest), waarin hij kennismaakte met het toepassen van elektroconvulsietherapie. Ook volgde hij een keuzestage ziekenhuispsychiatrie in het Onze Lieve Vrouwe Gasthuis te Amsterdam. Hij werd als psychiater ingeschreven in het register voor medisch specialisten op 1 februari 2001.

Na zijn opleiding werkte hij de eerste periode als staflid op de afdeling psychiatrie van het Leids Universitair Medisch Centrum. Vanaf 1 december 2002 vestigde hij zich zelfstandig in Ziekenhuis Rijnstate te Arnhem, en werkt hij sindsdien in maatschapverband met de heren Dr. B. Verwey, M.E.T.M. Müller, Dr. J.H.A.M. Tuerlings, B.J.H.B. de Pont en R.L.E. Derikx. Daarnaast is hij geregistreerd SCEN-arts voor de regio Arnhem en omstreken.

Van 2003 tot 2011 was hij aangesteld als co-assistentenopleider bij het UMC Sint Radboud, en daarnaast werd hij vanaf 2006 door de Medisch Specialisten Registratie Commissie benoemd als waarnemend partieel opleider psychiatrie. Vanaf 2011 is hij waarnemend opleider psychiatrie. Van 2002-2006 was hij bestuurslid van de sectie Consultatieve- en Ziekenhuispsychiatrie, van 2006-2009 was hij gekozen lid van de ledenraad, en vanaf 2009 penningmeester van het bestuur van de Nederlandse Vereniging voor Psychiatrie. Van 2005-2007 was hij bestuurslid van de Nederlandse Federatie voor Ziekenhuispsychiatrie, en sinds 2007 is lid van de Raad van Toezicht van Stichting MEE Gelderse Poort. Naast zijn klinische werkzaamheden, vervult hij sinds 2011 de functie van medisch manager Acuut en Medisch Facilitair Bedrijf in Ziekenhuis Rijnstate.

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