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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-naïve 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.e., 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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