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Seizure threshold manipulation in electroconvulsive therapy via repetitive transcranial magnetic stimulation. A novel way of augmentation?

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abstract

Introduction: A high seizure threshold (ST) is an impeding factor in certain patients, potentially preventing a successful electroconvulsive therapy (ECT) treatment. Several pharmacological and non-pharmacological methods have been put forward to augment ECT in such patients, however, to this date, only a handful of case reports existed about the potential role of repetitive transcranial magnetic stimulation (rTMS), as an augmentation method.

Objectives: and Methods: In this randomized, double-blinded, sham controlled study, we set out to test the hypothesis of whether the application of high frequency transcranial magnetic stimulation (HF rTMS) lowers the seizure threshold for electroconvulsive therapy and whether it has an effect on other aspects of ECT treatment, such as seizure duration (SD), efficacy and safety.

Results: 46 patients treated for a major depressive episode, indicated for ECT, were recruited to this study. A significantly lower seizure threshold was observed in the experimental group during ECT titration, on average a decrease by 34.55%, from 34.23 mC to 22.4 mC, $p < 0.001$ (Wilcox test). We had not observed a significant effect of TMS stimulation before ECT on seizure duration or clinical outcome. Another potentially important observation of this study is that 4 patients in the experimental group developed transient symptoms of hypomania/mania, all of which were stabilized after the combined stimulation protocol was halted spontaneously within a week, without the need to administer mood stabilizers.

Conclusion: It is likely that HF rTMS stimulation prior to ECT is a novel and simple way of reducing the ST, which is useful in certain groups of patients undergoing this important treatment modality.

Introduction

Electroconvulsive therapy (ECT) is a safe and effective biological treatment modality used in psychiatry for a variety of neuropsychiatric conditions [12,26,30]. However, there are patients who respond poorly to standard ECT protocols **e** one of the major reasons is the presence of certain impeding factors, such as a high seizure threshold (ST) (Loo et al.) [9].

Different modalities with the potential to augment ECT have been examined in the past [9], as early as the 1950's [6]. Hyperventilation for instance, was shown by Bui-Alvarez et al. [3] to lower the ST by as much as 45%, however, other authors have failed to reproduce this result, with some observing no significant changes to the seizure threshold [5]. A more consistent and known effect of hyperventilation is a prolonged seizure duration, in some studies as much as 50s [23]. The reported variances in seizure duration, however, are quite high. Newer studies by Nishikawa et al. and Porter et al. [14,17] suggested that the combination of hyperventilation and the application of remifentanil prior to ECT might significantly prolong SD. The effect of hyperventilation on clinical outcome has been described as moderate at best by some authors [5].

Another examined modality is pretreatment with caffeine, theophylline and xanthines [9]. Caffeine was shown to increase the seizure duration in several studies, the prolongation varies from 49%

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to 127%. So far, there is not enough evidence to demonstrate that caffeine significantly affects the seizure threshold. The effect of caffeine administration on clinical outcome is not conclusive, some authors suggesting a moderate effect. Caffeine was described in several case reports to have caused concerning adverse effects **e** prolonged seizures requiring a pharmacological intervention, severe anxiety and agitation after the procedure and cardiac arrythmias. Similarly to caffeine, the use of theophylline prior to ECT was shown to increase the seizure duration. No study to date was published that assesses the role of theophylline in clinical outcome. Furthermore, a concerning drawback in the usage of theophylline is a risk of status epilepticus **e** 3 case reports have been published of this AE appearing in patients undergoing ECT while administered theophylline. Xanthines have also been used to prolong seizure duration, as described in a study by Stern et al. [25] So far, however, no conclusive data besides a handful of case reports exist regarding its effect on clinical outcome or seizure threshold.

In the study published by Gilabert et al. [4], sleep deprivation was proposed as a safe modality to augment ECT. It was demonstrated that it significantly reduces the seizure threshold and increases seizure duration, with little to no risk associated in its usage. The experimental group showed a lowering of the ST from 190.4 mC to 151 mC between the first and last ECTapplication. No major effect on clinical outcome was observed.

A case series was published by Yi et al. [31], where authors described 3 elderly patients in whom the application of flumazenil improved seizure quality, however, it was not clear whether it affected the seizure threshold as well.

Ketamine was also considered to augment ECT treatment. In a study conducted in 2017 by Trevithick et al. [29], however, no evidence was found for low dose ketamine usage in ECT as the results excluded greater than small to moderate benefit with 95% confidence.

Finally, in 2018 a case series report was published by Rotharmel et al. [21], putting forward the idea of augmenting ECT treatment via rTMS. They reported an effect on reducing the ST, prolonging seizure duration and increasing the efficacy of ECT. In 2019, our team published a case report of a patient with an extremely high seizure threshold (Albrecht et al.) [1], in which the application of high frequency repetitive transcranial magnetic stimulation (HF rTMS) prior to each ECT session resulted in a reduction of ST by half.

Study aims

In this randomized, double-blinded study, our primary goal was to test the hypothesis, whether the application of HF rTMS before ECT lowers the seizure threshold. Our secondary goal was to assess whether this rTMS "pre-stimulation" influences other aspects of ECT treatment, such as seizure duration (SD), efficacy and safety.

Subjects and methods

Subjects

A group of 46 patients between the ages of 18**e**74 treated for a major depressive episode and referred for ECT at the Department of Psychiatry of the First Faculty of Medicine and General University Hospital in Prague were recruited to the study throughout the year 2019 (Fig. 1) [13]. This study was approved by the Ethical Committee of the General University Hospital in Prague (n. 1933/18 S-IV) [19]. All patients met the following criteria: no other axis 1 disorder, age equal to 18 or higher, score equal or higher than 20 on the Montgomery-Asberg Depression Scale (MADRS), no ECT in the last 3 months, no known significant neurological disease. All subjects were hospitalized throughout the study and signed a written informed consent. Diagnostically, the subjects were categorized according to the International Classification system of Diseases (ICD-10), their precise distribution is summarized in Table 1. The total number of ECT treatments and concomitant medication was determined by the patient's treating psychiatrist based on the clinical manifestation of the subject. Two subjects were eventually not included in the study **e** one refused to continue with further administration of rTMS and ECT, one patient was discovered to have a major neurological comorbidity during the course of ECT. In the end, the study totaled 44 patients (21 in the experimental group and 23 in the control group). There were 16 females (F) and 7 males (M) in the control group compared to 11 females and 10 males in the experimental group. No significant difference between the age in the experimental and control groups were found. We also compared the dosage of benzodiazepines administered to both group of patients (calculated to equivalent doses of lorazepam in milligrams **e** eq/l using the Ashton Manual) [15] and did not find any significant differences between their use in the experimental and placebo groups respectively. No significant differences were found in the dosage of propofol/succinylcholine during the titration of ECT and in the usage of concomitant medication (Table 2).

Study design

The study was undertaken as a double-blinded, randomized, sham stimulation, controlled study. Subjects were divided into the experimental and control group via blocked randomization, using the randomization software Sealed Envelope (block size 2 and 4) [24]. One co-author of this study (LTH) was selected to perform this randomization, another co-author administered real or sham stimulation, but was blinded to the block size (AJ). The electroconvulsive team (ECT psychiatrist, ECT nurse, anesthesiologist and anesthesiologist nurse), the subjects, the attending psychiatrists and the rater were blinded to the allocation of the subjects in the experimental/control group.

Prior to the first ECT session, we measured the cortical motor threshold (CMT) in all patients using Medelec Synergy® EMG. After a brief explanation of the TMS procedure, the patients were seated on a chair. Two pre-gelled single-use electrodes were placed on the region of the right abductor pollicis brevis. The neutral electrode was placed on the volar side of the right antebrachium. The center of the coil (Magstim D70 remote coil) was at first placed 5 cm lateral of the vertex on the interauricular line, with the handle in the parasagittal plane. It's localisation was then optimised according to the application of pulses and the resulting MEP as shown through the Medelec Synergy software. The measurement was initiated in each patient at 20% energy level, in the absence of motor evoked potential (MEP), this energy was gradually increased by 5%. The CMT was defined as the lowest stimulus intensity at which TMS (Magstim® Rapid2 with D70 remote coil) produced a motor evoked potential in at least 5 out of 10 trials, as described by Rossini et al. [20]. The left dorsolateral prefrontal cortex (LDLFPC) was then identified in each patient using neuronavigation (Visor™2ST) on the basis of individual native MRI scans.

Subjects allocated in the control group were stimulated in a time interval of 30**e**80 min before each application of ECT with the Magstim AirFilm Sham Coil on the LDLFPC region using the following parameters (a total of 900 pulses, frequency 15 Hz, 900 pulses divided into 6 trains, intertrain 60s, duration of 1 train 10s).

Subjects allocated in the experimental group were stimulated in a time interval of 30**e**80 min before each application of ECT with the Magstim Airfilm Coil Rapid on the LDLFPC region using the following parameters (100% of the individually measured CMT, a total of 900 pulses, frequency 15 Hz, divided into 6 trains, duration of 1 train 10s, the intertrain was calculated automatically by the

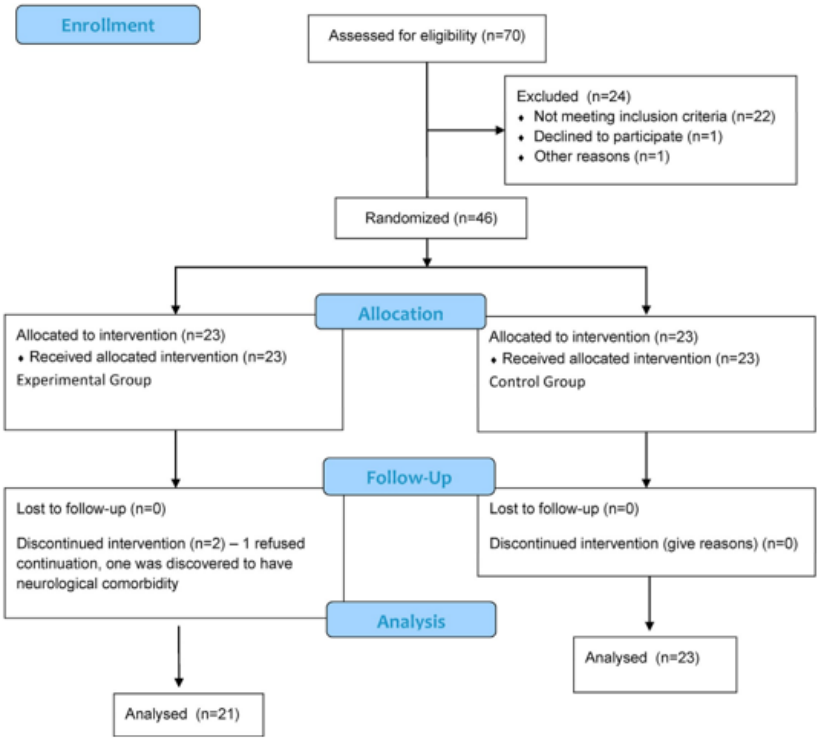


Fig. 1. Consort diagram flow of patient enrollment, allocation, follow-up and analysis (CONSORT 2010 flow diagram. CONSORT flow diagram template courtesy of http://www.consort-statement.org/consort-statement/flow-diagram, available via CC-BY license).

Magstim Rapid 2 device depending on the measured CMT and lasted between 44s and 102s).

ECT itself was conducted in general anesthesia (applied by an anesthesiologist) induced by propofol (1,5 mg/kg) and myorelaxation by succinylcholine (20e30 mg). All patients were adequately ventilated with 100% O2 throughout the procedure. The subjects were not hyperventilated prior to ECT application.

Table 1
Basic characterization of subjects (N-number of subjects, biological sex, age, ICD-10 diagnoses, equivalent dose of benzodiazepines calculated to lorazepam e eq/l, propofol dose during ECT titration, baseline and end MADRS score).

	Experimental	Control
N	21	23
sex	11 F/10 M	16 F/7 M
age	mean ¼ 48.19, SD ¼ 14.68	mean ¼ 48.48, SD ¼ 15.09
F063	0 yes/21 no	2 yes/21 no
F314	1 yes/20 no	1 yes/22 no
F321	4 yes/17 no	4 yes/19 no
F322	2 yes/19 no	2 yes/21 no
F323	0 yes/21 no	5 yes/18 no
F331	5 yes/16 no	4 yes/19 no
F332	8 yes/13 no	4 yes/19 no
F412	1 yes/20 no	1 yes/22 no
eq/l	Mean ¼ 0.71, SD ¼ 0.18	mean ¼ 0.8, SD ¼ 0.47
propofol	Mean ¼ 123.33, SD ¼ 22.89	mean ¼ 125.65, SD ¼ 26.42
T0 MADRS	Mean ¼ 34.85	SD ¼ 6.95 mean ¼ 30.74, SD ¼8.81
T2 MADRS	Mean ¼ 13.14	SD ¼ 8.34 mean ¼ 11.1, SD ¼ 8.4

The seizure threshold (ST), defined as the stimulus dose at which there was definite evidence on the EEG of a generalized bilateral seizure activity e the presence of epileptiform transients such as spikes and sharp waves, clearly distinguishable from the background.

Table 2
Pharmacological treatment used in both groups and respective comparative Fisher tests.

Experimental	control	p-value	adjusted p-value	
BZD	17 yes/4 no	20 yes/3 no	0.6927	1.0000
antic	7 yes/14 no	8 yes/15 no	1.0000	1.0000
hypn	1 yes/20 no	1 yes/22 no	1.0000	1.0000
Li	1 yes/20 no	3 yes/20 no	0.6086	1.0000
AP1	21 no	23 no		
AP2	14 yes/7 no	13 yes/10 no	0.5477	1.0000
AP3	21 no	23 no		
NaSSA	6 yes/15 no	7 yes/16 no	1.0000	1.0000
SARI	0 yes/21 no	3 yes/20 no	0.2341	1.0000
SSRI	7 yes/14 no	7 yes/16 no	1.0000	1.0000
SNRI	7 yes/14 no	13 yes/10 no	0.1434	1.0000
TCA	2 yes/19 no	2 yes/21 no	1.0000	1.0000
Vort	2 yes/19 no	1 yes/22 no	0.5988	1.0000
Ago	2 yes/19 no	1 yes/22 no	0.5988	1.0000

(BZD-benzodiazepines, antic-antiepileptics, hypn-hypnotics, Li-lithium, AP1 e 1st generation antipsychotics, AP2 e 2nd generation antipsychotics, AP3 e 3rd generation antipsychotics, NaSSA - Noradrenergic and specific serotonergic antidepressants, SARI - Serotonin antagonist and reuptake inhibitors, SSRI - Selective serotonin reuptake inhibitors, SNRI - Serotonin and norepinephrine reuptake inhibitors, TCA e tricyclic antidepressants, vort-vortioxetine, Ago e agomelatin).

EEG was monitored via a two-channel bifrontal placement of EEG electrodes. ECT was titrated with a right-unilateral (RUL) placementof electrodes on the MECTA spECTrum™ 5000Q. All subjects had their seizure threshold determined using the stimulus dose titration technique as described by Sackeim et al. [22]. ECT was administered using a first titration stimulus dose at 9.6 mC (frequency 20 Hz, pulse width 0.3 ms, amplitude 800 mA, stimulus duration 1s) for all participants. If no seizure occurred, this dose was raised to 19.2 mC (frequency 20 Hz, pulse width 0.3 ms, amplitude 800 mA, stimulus duration 2s), 38.4 mC (frequency 20 Hz, pulse width 0.3 ms, amplitude 800 mA, stimulus duration 4s) and 76.8 mC (frequency 20 Hz, pulse width 0.3 ms, amplitude 800 mA, stimulus duration 8s) respectively. During the second ECT session, subjects were subsequently treated with 6x ST RUL ECT (using the MECTA spECTrum™ 5000Q titration table). The respective 6x ST parameters are as follows - 76.8 mC (frequency 20 Hz, pulse width 0.3 ms, amplitude 800 mA, stimulus duration 8s), 115.2 mC (frequency 30 Hz, pulse width 0.3 ms, amplitude 800 mA, stimulus duration 8s), 230.4 mC (frequency 60 Hz, pulse width 0.3 ms, amplitude 800 mA, stimulus duration) or 460.8 mC (frequency 120 Hz, pulse width 0.3 ms, amplitude 800 mA, stimulus duration 8s) Seizure length was used as an outcome predictor in this study **e** if the seizure length on the EEG was lower than 15s, the ECT dose was raised by the ECT team during the next session. In general, the ECT team raised the respective parameters in this order **e** time of application, frequency, pulse width and amplitude until a maximum would be reached in each respective parameter. If the seizure length was longer than 70s, the ECT team would reduce the dose during the next session. HF rTMS (or sham rTMS in the placebo group) and ECT was administered three times a week on alternating work days (Monday, Wednesday, Friday). MADRS was used to stratify the severity of symptoms by a rater, who was blinded to the patient's allocation within the experimental/control groups. It was administered 3 times in total **e** one day before the commencement of the treatment, after five combined rTMS/ECT sessions (if the patient had less than five sessions it was administered one dayafter the last rTMS/ECT session) and at the end of hospitalization. The patients were clinically monitored by their treating psychiatrists twice a day for the presence of any adverse effects.

Statistical analysis

For the comparison of the monitored variables between the experimental and control group, the *t*-test was used, in the case of variables where it was not possible to expect the normality of division, the Mann-Whitney *U* test (Wilcox test) was used. Differences in the biological sex were tested using the χ^2-test. Tests with a result of less than 5% were considered to be significant. The Spearman correlation test was used to analyse the relationship between the time interval of rTMS/ECT and ST. Analysis was performed in the statistical package R version 3.6.1 (R Core Team, 2019) [18].

Results

Using the Mann-Whitney *U* test, a significantly lower seizure threshold was observed in the experimental group, on average a decrease by 34.55%, from 34.23 mC to 22.4 mC, $p < 0.001$ (Fig. 2).

No significant difference in the duration of the seizure during titration was discovered between the experimental and the control group (Table 3).

No significant difference in the outcome of treatment via MADRS at the beginning (T0) and end (T2) was registered. Mean improvement in the experimental group: 20.4 points compared to 19.7 points in the control group (Table 3).

No significant difference was discovered in the number of total ECT applications. The mean number of applications in the experimental group: 7.9 compared to 7.21 in the control group (Table 3).

A significantly lower charge was recorded during the 2nd ECT application (when 6xST RUL was administered). During the rest of the course, no significant differences in the administered charge were recorded between the experimental and control group. There was not a significant difference in the number of patients in each respective group, where the ECT dose was raised (17 patients from the experimental group and 14 from the control group had their final ECT dose higher than their original 6xST). The ECT dose was lowered in two subjects throughout the course. In one case it was lowered in the control group during the 14th application in a patient due to a prolonged seizure in the previous session. The other case was a subject in the experimental group where the dose was lowered during the 12th ECT application for the same reason, however it was then increased again. (Table 4).

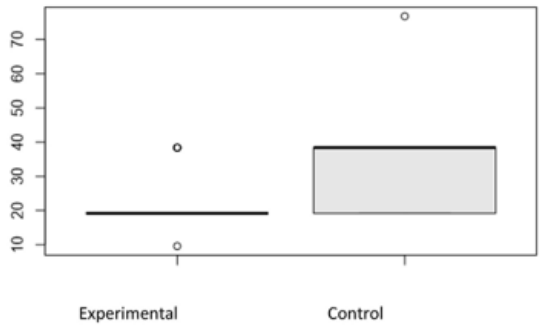
We have not found any correlation between the time interval of rTMS/ECT and seizure threshold (Fig. 3).

Finally, we would like to mention that 4 patients in the experimental transitioned from severe depression to hypomania/mania. This mood change was progressively registered by the attending psychiatrists clinically at first and subsequently rated on the Young Mania Scale, where these patients scored between 25 and 30 points. All subjects who experienced this transition were patients who were indicated for ECT due to reccurent depressive disorder (F33.), in one case with a moderately severe depression phase (F33.1), the other three cases with a severe depression phase (F33.2). In two cases, this switch occurred within five applications of rTMS/ECT, the other two cases occurred within 9 and 10 applications respectively. An euphoric mood, a quick flow of ideas, fast speech, a reduced need to sleep and an increased need for physical activity were present. None of the patients experienced psychotic symptoms, they co-operated throughout the entire treatment and had insight into this condition. After these symptoms occurred, the treatment protocol was halted by the treating psychiatrists. The patients were then observed and their mood stabilized spontaneously, in all cases, within a week after the cessation of rTMS/ECT. No additional pharmacological intervention (mood stabilizers) was administered during this phase.

Discussion

The results of our study seem to confirm the finding from our previous case report. Subjects in the experimental group have a significantly lower seizure threshold, the difference between mean STs in both groups was 34.55%. We hypothesize that this was possible due to HF rTMS administered shortly before ECT, which resulted in increased cortical excitability, thus lowering the energy needed to induce an epileptiform seizure. According to some studies, the after-effects of HF TMS may last up to 90 min after stimulation [8,10], depending on its intensity, pulse number and frequency. Further studies are needed to determine whether decreasing the time between rTMS and ECT, increasing the stimulation intensity or frequency would result in an even more significantly lowered seizure threshold.

In our study, we used the same stimulation protocol as in our previous case report, however, we decided to select LDLFPC as the rTMS stimulation location instead of the supplementary motor area (SMA). This is a common localisation of standard rTMS protocols used to treat depressive disorders (10). Furthermore, we had the experience of SMA stimulation being uncomfortable for the patient, as the localisation near motor areas causes generalized muscle twitches during the procedure. We have not chosen a standard protocol used to treat depression and opted for a lower total number of stimuli in order



	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	SD	N	NA's
Exp.	9.6000	19.2000	19.2000	22.4000	19.2000	38.4000	8.2209	21	0
Contr.	19.2000	19.2000	38.4000	34.2261	38.4000	76.8000	12.8882	23	0

Wilcox test: p = 7e-04

Fig. 2. Seizure threshold differences during ECT titration in compared groups.

Table 3
Comparison between the seizure threshold during titration, average seizure length during titration, change in MADRS score and number of total ECT applications in both groups with respective Wilcox tests.

	p-value adjusted	p-value
charge/mC vs. group	0.0007	0.0028
EEG endpoint vs. group	0.8225	1.0000
To-T2 MADRS vs. group	0.8474	1.0000
Number of ECT applications vs. group	0.3543	1.0000

to make the session shorter before ECT. Alternative stimulation locations or protocols may produce different results.

The "pre-stimulation" via rTMS doesn't seem to affect the duration of seizures, the number of total ECT applications or the efficacy of ECT as measured via MADRS. Based on a previous case report by Rothärmel et al. [21], we expected a cumulative effect of both treatment modalities, however, this was not confirmed statistically. The French team used a different treatment protocol e the report includes 2 patients who were stimulated with an HF rTMS of 20 Hz at 90% of CMT, with 20 trains, the duration of 1 train 2s and the intertrain interval 60s. One patient received 7 rTMS treatments and the other 10. After the course of rTMS was completed, ECT was applied e the authors report that the patients had a reduced ST, longer seizures and also observed an increase in the efficacy of ECT compared to their clinical experience, however a control group was not specified.

Our study did not show a statistically significant difference in the number of patients inwhich the ECT dosewas increased due to a short duration of seizures (defined as EEG epileptiform activity shorter than 15s) e 54.84% of patients in the control group and 45.16% of patients in the experimental group. After the second ECT session, we also did not register significant differences in the delivered charge between both groups. We expected that the average charge in the experimental group would remain lower throughout the entire treatment. However, we need to mention that many patients reached remission within 6 applications of rTMS/ECT and thus only a limited number of subjects continued past the 6th application. We also acknowledge that several recent studies prefer different parameters than seizure length as ECT outcome predictors (seizure quality, speed of postictal

Table 4
Average ECT charge throughout ECT sessions and respective Mann-Whitney tests (application 0 refers to titration and the found seizure threshold, N ¼ number of patients).

ECT application n.	Experimental (mean)	control (mean)	experimental N	control N	p-value	adjusted p-value
(Titration) 0	22.4000	34.2261	**21**	23	0.0007	0.0028
(6x ST) 1	134.4000	205.3565	**21**	23	0.0007	0.0028
2	243.2000	186.7636	**21**	22	0.2340	1.0000
3	259.2000	205.9636	**21**	22	0.4390	1.0000
4	238.0800	214.6909	20	22	0.4885	1.0000
5	245.7600	238.0800	20	20	0.8209	1.0000
6	264.0000	264.0000	**16**	**16**	0.9686	1.0000
7	259.9385	271.7538	**13**	**13**	0.7502	1.0000
8	259.2000	320.0000	**12**	9	0.5775	1.0000
9	277.3333	307.2000	9	6	0.8559	1.0000
10	257.8286	215.0400	**7**	5	0.5518	1.0000
11	384.0000	240.0000	3	4	0.1947	1.0000
12	358.4000	307.2000	3	2	0.7609	1.0000
13	384.0000	384.0000	3	**1**	1.0000	1.0000
14	460.8000	230.4000	**1**	**1**	1.0000	1.0000

suppression) [7], therefore it is possible that using these alternative variables as an outcome predictor might produce different long-term results in future studies. The subjects were also not re-titrated throughout the procedure, therefore it is not possible to make a valid comment about the long-term effectiveness of this "pre-stimulation" based on the results of this study.

We were also interested in whether there is a relationship between the time interval of rTMS/ECT application and seizure threshold. It proved technically challenging to keep this interval the same in all patients **e** however, no correlation was discovered. Some authors state that the after-effects of rTMS stimulation on cortical excitability might last longer than 90 min. We cannot exclude however, that a shorter time interval than 30 min (or longer than 80 min) might produce different results (Fig. 3).

We also think that it is important to mention our experience with 4 patients from the experimental group, who transitioned from severe depression to hypomania/mania. All of these patients scored 25 to 30 points on the Young Mania Rating Scale (2 within five applications and 2 within the 9th and 10th application). None of these patients were diagnosed with bipolar disorder prior to this treatment. None of the patients in the control group in our study were recorded to have manic symptoms, therefore, we cannot rule out the possibility that rTMS stimulation prior to ECT is more likely to induce these symptoms, however larger samples of patients and more studies are needed to confirm this speculation. Literature reports on mania after ECT are varied, with some reports recording an alleged 12.5% incidence in depressed patients undergoing ECT [2]. ECT, however, is more known for its high effectiveness in treating mania [16] and there are even authors who report that ECT is effective in treating manic episodes that were induced by this treatment (Thomas et al.) [27]. This observation is potentially important in case of further studies exploring this combined protocol. It is necessary to closely monitor patients for the presence of manic symptoms. If such symptoms appear, we recommend halting the treatment protocol.

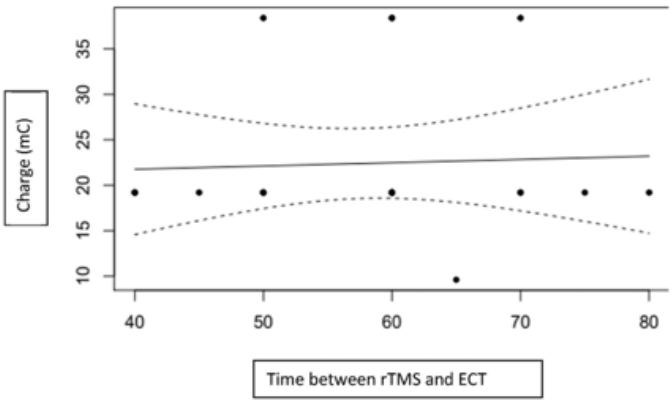
As mentioned above, in all instances, the mood of our subjects spontaneously stabilized within a week after the cessation of rTMS/ECT, without the need for additional pharmacological intervention. We recognize that this might represent a diagnostic challenge, as currently, ECT induced mania is considered as bipolar 1 according to DSM-V. In the Czech republic, we use the ICD classification and our patients were reclassified as F31.8 (Other bipolar affective disorders). These patients are monitored by an outpatient psychiatrist and up to this date, none of them were treated with mood stabilizers and their mood remains stable.

Beside this, we have not recorded any AEs using the combined TMS/ECT protocol clinically, however, future studies should include the usage of symptomatic scales throughout the treatment.

It has been debated for a long time, whether the key determinant in neurocognitive side effects and efficacy of ECT is the absolute electrical dose or the dose relative to ST. Since it seems that rTMS has the potential to significantly lower the seizure threshold, this would provide an interesting opportunity to shine more light on this issue, by using rTMS totransiently manipulate the seizure threshold before administering ECT. It might prove advantageous to use this method rather than pharmacological agents, that can confound the outcome of ECT treatments via their psychotropic effects. This "pre-stimulation" might also be useful in countries where ECT devices are more limited in terms of their maximum charge, as is the current situation in the United States. Other modalities, such s transcranial direct current stimulation, might also be an interesting option to explore in terms of possible ST influencing [11].

Study limitations

As mentioned earlier, concomitant medication of patients was decided by the treating psychiatrist, therefore the subjects were on medication that could have affected the seizure threshold, especially the usage of anticonvulsants/benzodiazepines. This is not necessarily



	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	SD	N	NA's
Time	40.0000	50.0000	60.0000	57.8571	65.0000	80.0000	11.5728	21	0
ST / mC	9.6000	19.2000	19.2000	22.4000	19.2000	38.4000	8.2209	21	0

Spearman correlation coeficient, $\rho = 0.0045$, p = 0.9846

Fig. 3. Relationship between the time interval of rTMS/ECT and seizure threshold during titration.

a major drawback as pointed out by other studies exploring seizure threshold in ECT [28], for these patients are representative of those undergoing ECT in the general local community.

The study is limited in the psychometric scales that were utilized, using MADRS to determine the severity of depression symptoms. Future studies may include subjective mood scales and also thorough cognitive and symptomatic scales to determine any difference in cognitive outcome or the presence of other adverse effects in the tested groups.

Another possible study limitation is a rather varied time interval of 30e80 min between the application of TMS and ECT e it proved to be technically and personally challenging to keep this interval shorter, we cannot fully exclude that its reduction (or prolongation) might produce different results.

The seizure threshold was recorded during the titration during the first ECT treatment. The study therefore does not monitor whether the effect of TMS stimulation on ST lasts throughout the rest of the ECT course, as subjects were not re-titrated. Future studies could explore this relationship, for instance, by re-titrating and determining ST after five combined TMS/ECT treatments.

The final weakness of this study is that we have not formally assessed the rater and ECT team for blinding success.

Conclusion

Our studysupports the hypothesis that high frequency transcranial magnetic stimulation applied shortly before an ECTsession can reduce the seizure threshold. This simple and novel method of reducing ST might be useful in certain patients, especially in cases where ECT practitioners struggle to induce a therapeutic seizure even at higher ECT doses or in patients where we expect the ST to be high due to the presence of concomitant medication (high doses of benzodiazepines or antiepileptic drugs that are challenging to withdraw during a course of ECT). We have not observed a statistically significant effect on seizure duration and clinical outcome. A potentially important observation is the presence of manic symptoms in 4 patients from the experimental group e currently, we cannot rule out that the combination of these methods makes it more likely to induce this effect. However, the mood of all patients spontaneously stabilized within a week after the cessation of the treatment. Further studies are needed to confirm this hypothesis and identify the most efficient rTMS protocol and stimulation location to reduce the seizure threshold.

Author contribution

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interests associated with this publication and no significant financial support for this work has been received. No personal relationships with other people or organizations exist that could have inappropriately influenced our work and its outcome.

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Článok B – Lowering the seizure threshold in electroconvulsive therapy using transcranial magnetic stimulation: A case report

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Lowering the seizure threshold in electroconvulsive therapy using transcranial magnetic stimulation: A case report

a b s t r a c t

We demonstrate the feasibility of lowering the seizure threshold using a combined approach of electroconvulsive therapy and transcranial magnetic stimulation. High-frequency transcranial magnetic stimulation of the supplementary motor area shortly before each electroconvulsive treatment session resulted in a reduction of the seizure threshold by half in a male patient with a severe psychotic depressive episode of bipolar affective disorder.

Keywords:
RUL ECT
Ultra-brief pulse
Adverse effect
Lowering seizure threshold
TMS pre-stimulation

Introduction

Electroconvulsive therapy (ECT) is generally viewed as an effective, fast, safe and widely used method of treatment in a variety of severe neuropsychiatric conditions [3,10]. However, it has also been associated with neurocognitive side effects [2].

Transcranial magnetic stimulation (TMS) is likewise a safe, efficacious and well-tolerated method [1], even in resistant cases, but with substantially lower efficacy than ECT [5].

Some patients have a seizure threshold that is near or over the maximum intensity that most devices can deliver, which makes the treatment less effective and increases the risk of adverse effects and cognitive deterioration.

In this article, we outline the case of a patient treated for a pharmacoresistant depressive episode with psychotic symptoms, where we attempted to augment ECT via high-frequency TMS "pre-excitement" (HF-TMS) of the left supplementary motor area (SMA).

Case presentation

A 76-year old right-handed Caucasian male with doctoral education was admitted for a pharmacoresistant depressive episode of bipolar affective disorder with psychotic symptoms. He had already been treated for more than five depressive episodes with various types of medication and once with electroconvulsive therapy resulting in successful remission.

Upon admission, his psychiatric medication consisted of 20 mg of escitalopram and 10 mg of olanzapine. The patient initially refused to undergo ECT and treatment was therefore pharmacological. The daily dose of olanzapine was increased to 20 mg and 30 mg of mirtazapine was added, though without significant effect. The patient had also been diagnosed with several somatic conditions, i.e. hyperlipidemia, hypertension and benign prostatic hyperplasia, but at the time these were fully compensated with pharmacological therapy (5 mg of perindopril, 40 mg of esomeprazole, 20 mg of atorvastatin and 0.4 mg of Tamsulosin). He was classified as ASA 2 with unremarkable laboratory values and a physiological electrocardiogram.

During the first week of hospitalization, the patient's state progressively deteriorated: depression and psychosis worsened, and symptoms of catatonia emerged **e** mutism, stupor, negativism and waxy flexibility. The patient refused to eat and drink.

ECT was initiated without the patient's consent based on the guidelines of the Czech Psychiatric Association and following the Czech legal requirements for involuntary treatment of life-threatening conditions.

General anesthesia was induced by Propofol (1.5 mg/kg) and myorelaxation by 30 mg of succinylcholine; 0.8 mg of atropine was injected subcutaneously 60 minutes prior to each treatment. We planned to administer right-unilateral ultra-brief ECT three times a week (see Table 1). At the first ECT session, the dose was titrated: we started at a higher charge of 76.8 mC (0.8 A; 0.3 ms; 8 s; 20 Hz) due to the patient's high seizure threshold (ST) during a previous ECT session in 2005. However, no ictal activity on a two-channel electroencephalograph (EEG) was recorded. The seizure threshold was eventually established at 153.6 mC (0.8 A; 0.3 ms; 8 s; 40 Hz) and the subsequent seizure lasted 18 s. The therapeutic dose was established at six times the ST (0.8 A; 0.3 ms; 8 s; 120 Hz).

Starting from ECT session two and up to session seven, the protocol was intensified to everyday application due to the patient's severe catatonic state, which is common practice at our department and in accordance with the guidelines of the Czech Psychiatric Association [8]. The charge during the treatment had to be increased to achieve an adequate duration of 20**e**60 seconds of EEG epileptiform activity.

The pulse width was gradually elongated to 0.75 ms [4] and a charge of 1152 mC was reached (the maximum of the European version of the MECTA SpECTrum 5000Q®).

The patient's state improved after the fifth treatment and symptoms of catatonia subsided. The patient was no longer legally

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1935-861X/

Table 1
Course of treatment. Development of the seizure threshold in ECT. Intensified (daily) regiment for catatonia through session two to seven with gradual increase of the charge to obtain a sufficient EEG seizure endpoint (at least 20 seconds). Combined treatment with pre-excitatory stimulation of dominant SMA by 15Hz HF-TMS shortly before each ECT from session ten.

Session No.	TMS pre-stimulation	Duration delivered [s]	Frequency delivered [Hz]	Pulse width delivered [ms]	Charge delivered [mC]	Dynamic impedance [Ohm]	Energy delivered [J]	Seizure EEG endpoint [s]
titration	no	8	20	0,3	76,8	226	14	**0**
1	no	8	40	0,3	153,6	200	24,6	**18**
2	no	8	120	0,3	460,8	220	82,3	**11**
3	no	8	120	0,45	691,2	215	123,2	**8**
4	no	8	120	0,6	921,6	210	163,8	**7**
5	no	8	120	0,7	1075,2	210	185,8	**12**
6	no	8	120	0,75	1152	196	189	**25**
7	no	8	120	0,75	1152	192	186,6	**20**
8	no	8	120	0,75	1152	210	208,8	**20**
9	no	8	120	0,75	1152	207	201,6	**22**
titration	yes	8	20	0,3	76,8	233	14,4	**10**
10	yes	8	60	0,3	230,4	204	38,6	**18**
11	yes	8	60	0,3	230,4	236	48	**20**
12	yes	8	60	0,3	230,4	228	42,1	**20**
13	half dose	8	60	0,3	230,4	257	48,4	**10**

considered to be in a life-threatening condition, was re-informed and agreed to continuation of the ECT.

The patient's mood, however, remained severely depressed. Emotivity was flat and the patient experienced episodes of anxious tension, nihilism, paranoia and micromania. We also suspected a cognitive impairment.

A change of approach **e** a combination of TMS and ECT

We sought a way to lower the seizure threshold of the patient and thus the administered charge during ECT without using standard methods for reducing seizure thresholds (e.g. hyperventilation).

It is widely accepted that high-frequency repetitive transcranial magnetic stimulation (HF-TMS) increases cortical excitability [7] and lowers the ST. Its after-effects may last up to 90 minutes.

The premotor cortex, primary motor cortex (M1) and SMA are all parts of the frontal motoric circuit. SMA has projections to the putamen, subthalamic nucleus and the internal globus pallidus.

Based on these findings, we decided to use HF-TMS of the dominant (in this case left) SMA (rostral region of Brodmann area 6a), as shown in Fig. 1.

The patient agreed to this novel approach and consented to TMS treatment.

The localization of SMA was identified via neuronavigation using the Visor™2ST (with software-based 3D modeling of the native T1 MRI brain scan).

The following parameters of HF-TMS were set: 15 Hz, 900 stimuli in six trains, intertrain 83 seconds. Stimulation intensity was set at 90% of motor-evoked potential (MEP, measured using Medelec Synergy® EMG), or 70% of the device's capacity.

Pre-stimulation took place 70 minutes prior to each ECT (starting at session ten) using the Magstim® Rapid2 with AirFilm® Coil (Rapid version). After the first pre-stimulation of the patient with HF-TMS, the ECT dose was re-titrated. The seizure threshold (ST) was established at 76.8 mC (0.8 A; 0.3 ms; 8 s; 20 Hz), a reduction of the initial seizure threshold by half (see Table 2).

The therapeutic dose was then established based on EEG seizure duration criteria at 230.4 mC (0.8 A; 0.3 ms; 8 s; 60 Hz).

The patient's mood improved. However, paranoid delusions were still present. Halfway through the fourth HF-TMS session, the patient refused to undergo further TMS co-stimulation after the completion of three out of six trains (delusions concerning concrementation of mandible during TMS). The seizure during the last (thirteenth) session of this ECT course lasted comparatively less time (10 s), perhaps because the TMS dose was lowered by half. The clinical state of the patient stabilized and we decided to discontinue the ECT course.

The patient remained cognitively impaired, most likely due to a pre-existing condition correlating with severe frontal and temporal atrophy on an MRI brain scan. There was no alteration of medication throughout the entire course of ECT. No severe adverse effects or complications resulting from this combined protocol were observed throughout the treatment.

Discussion

ECT is a powerful tool in the armamentarium of a psychiatrist. However, it has been associated with adverse neurocognitive effects. Patients with a pre-existing cognitive deficit and those with a high seizure threshold, including the aforementioned patient, might represent a higher risk group.

There are only a handful of case reports in contemporary scientific literature on the topic of combining TMS and ECT [9]. To our knowledge, none of these describe this type of regular pre-stimulation with TMS shortly before each ECT session. Our approach resulted in lowering the seizure threshold by half.

Disadvantages of this approach might include more difficult time and case management and the rare possibility of inducing an epileptiform seizure during the high-frequency pre-excitatory TMS (in localizations close to the primary motor area). Some safety precautions need to be adhered to: an anesthesiology team needs to be on site, a peripheral intravenous line needs to be inserted before the procedure and an EEG needs to be at disposal.

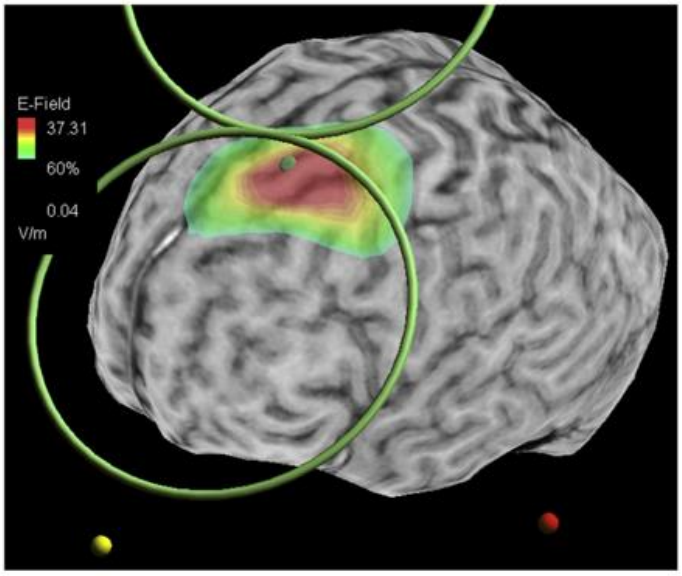
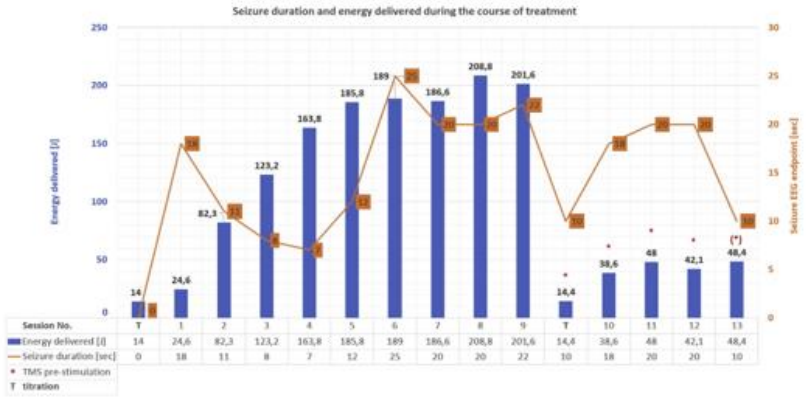


Fig. 1. TMS localization. SMA as identified by neuronavigation using the Visor™ 2ST with software-based 3D modeling of the patient's native T1 MRI brain scan.

Table 2
Seizure duration and energy delivered during the course of treatment. Titration of energy in session one. Throughout session six to nine, maximal energy was used; however, only minimal epileptiform activity was observed. After HF-TMS pre-stimulation (sessions ten to thirteen), the lower seizure threshold was re-titrated. At the last session (session thirteen), after a half-dose of HF-TMS, the seizure duration was only half.



A comparable effect might be expected when ECT is combined with transcranial direct current stimulation. However, we are not aware of any studies on this subject [6].

Conclusion

We demonstrated that it is possible to lower the ST by half using subthreshold HF-TMS in the left SMA prior to each ultra-brief RUL ECT session. We acknowledge that TMS stimulation of other brain areas might lead to different (perhaps even better) results.

Further research on the efficacy of such a treatment is needed. This case demonstrates the feasibility of this combined protocol.

Conflicts of interest

We wish to confirm that there are no known conflicts of interests associated with this publication and no significant financial support for this work has been received. No personal relationships with other people or organizations exist that could have inappropriately influenced our work and its outcome.

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