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Comparable seizure characteristics in magnetic seizure therapy and electroconvulsive therapy for major depression

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Abstract
Electroconvulsive therapy (ECT) is highly effective for treatment-resistant depression (TRD); however, its use for less severe forms of depression is somewhat limited by a lack of control over current spreading to medial temporal lobe memory structures, resulting in various cognitive side effects. In contrast, magnetic seizure therapy (MST), which uses high frequency repetitive transcranial magnetic stimulation (rTMS) for local seizure induction, has been associated with reduced cognitive side effects. To assess whether different characteristics of seizures induced by both methods are responsible for the differences in neuropsychological side-effect profile, we studied seven TRD-patients undergoing both MST and ECT in an open-label, within subject, controlled crossover pilot study. Comparison parameters included seizure-related ictal characteristics, including motor activity, electromyogram (EMG), electroencephalogram (EEG), and postictal recovery and reorientation times.Our results showed no differences in motor activity or EMG and EEG characteristics, thus implicating similar electrophysiological processes in seizure induction with MST and ECT. In line with previous studies, we observed shorter postictal recovery and reorientation times following MST.The ictal characteristics of induced seizures were found similar with ECT and MST suggesting that the more focal seizure induction associated with MST may account for the more beneficial neuropsychological side effect profile of MST.

1. Introduction

Major depressive disorder (MDD) is a very prevalent disorder with a lifetime risk of 7–12% in men and 20–25% in women (Kessler et al., 2005) and its often a highly disabling condition (Holtzheimer and Nemeroff, 2008). Various forms

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of psychotherapy and pharmacotherapy are currently the most commonly used antidepressant treatments. Though these therapies lead to symptomatic improvement, up to 70% of the treated patients suffering from depression have residual symptoms (Trivedi et al., 2006). Furthermore, the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D) demonstrated that one third of patients do not respond despite completing an algorithm that included four evidence-based treatment steps for depression (Rush et al., 2006). Recurrent episodes of depression are the rule and not the exception (Kessler et al., 1997). Results from the US National Institute of Mental Health's (NIMH) program indicate that the chance of remission decreases significantly if two treatment attempts with adequate dose and duration have already failed. Patients who are unable to respond despite completing two different antidepressant medications of adequate dose and duration are considering having treatment-resistant depression (TRD) (Schlaepfer et al., 2012). Unfortunately TRD frequently results in disability and elevated risk for suicide (Nemeroff, 2007). Electroconvulsive therapy (ECT) is a long-established therapeutic intervention and the most effective treatment for TRD (Sackeim et al., 2008). But its clinical utility is limited to some extent by its burden of neuropsychological adverse effects, including postictal disorientation, as well as transient and long-term cognitive disturbances (UK ECT Review Group, 2003). Up to 79% of the cognitive side effects in ECT (Rose et al., 2003) result from widespread electric current distribution throughout the brain, including temporal lobe structures such as the hippocampus (Lisanby, 2002). Modern developments of ECT techniques have impressively advanced the risk/benefit ratio, although the degree of retrograde amnesia remains a significant risk (Morales et al., 2004). Recent studies have demonstrated that the effectiveness and side effects of ECT are influenced by the site of seizure initiation and dispersion of seizure activity (McCall et al., 2000), which cannot be entirely controlled with current ECT techniques (Sackeim et al., 1994).

New non-convulsive and convulsive brain stimulation techniques with the purpose of less cognitive side effects have therefore been developed with the intention of equaling or topping ECT's efficacy. Better cognitive side effect profiles aimed at improving the quality of life for patients needing non-convulsive or convulsive therapies should increase the endeavor for effective treatments (Morales et al., 2004). A non-convulsive treatment is the repetitive transcranial magnetic stimulation (rTMS), which uses strong, rapidly alternating magnetic fields to non-invasively stimulate the prefrontal cortex (Schlaepfer et al., 2010). More than 35 placebo-controlled rTMS studies have shown moderate antidepressant effects and the cognitive functions were not affected (Janicak et al., 2008). Therefore, rTMS is considered to be a safe treatment method, but without strong antidepressant efficacy in severe depression. Further development of rTMS at higher frequencies (>50 Hz) has demonstrated the ability of using rTMS to induce seizures (Belmaker et al., 2003). The application of rTMS to induce a seizure is referred to as magnetic seizure therapy (MST). The use of MST has been found to produce a more localized seizure that stimulates the superficial cortex while significantly avoiding the medial temporal lobe structures such as the hippocampi responsible for cognition (Lisanby et al., 2003a). During ECT, electricity is applied directly to the scalp, while during MST, electricity is indirectly induced in the brain by magnetic stimuli (George, 2002). MST results in a more focused point of origin of seizures, whereas the secondary generalization of the convulsions involves the entire brain (Morales et al., 2004). Measurements in non-human primates with intracerebral electrodes have supported the hypothesis that MST-induced seizures are more focally than those elicited with ECT (Lisanby et al., 2003c). Furthermore, the electric field induced by magnetic stimulation is less penetrating and insensitive to tissue conductivity (Lisanby et al., 2003b). MST induces neural depolarization at a depth of 2 cm beneath of the scalp; therefore, direct effects are limited to the superficial cortex (Davey et al., 2003). In contrast, the electrical fields during ECT are impeded by scalp and skull and show limited precision in spatial targeting (Geddes and Baker, 1967). This leads to a non-focal, widespread intracerebral current distribution by ECT (Sackeim et al., 1994). Moreover, ECT and MST use different pulse shapes and widths, resulting in different levels of neural stimulations for the same electric field (Deng et al., 2009a, 2009b). The main advantage of MST over ECT involves an improved side effect profile, which includes reduced postictal disorientation and faster recovery and reorientation (Kayser et al., 2011; Kirov et al., 2008).

The purpose of electrical stimulation in ECT is to therapeutically induce an initial focal and secondary generalized grand mal seizure using serial administration of electrical current through the brain under general anesthesia (Rasimas et al., 2007). Generalized grand mal seizures can be controlled by monitoring both ictal motor responses (convulsions) and ictal electroencephalogram (EEG) activity (electrophysiological activity of the brain during the seizures). The traditional opinion that the therapeutic benefit depends on an adequate ECT-induced seizure lasting at least 25 s (Weiner et al., 1991), although retained in contemporary guidelines of ECT practice, was not necessary (Swartz, 2009). The clinical view changed, and ictal parameters such as ictal EEG seizure amplitude (Krystal et al., 1995), degree of EEG postictal suppression (Nobler et al., 1993, 2000), ictal heart rate (Swartz, 2000), and ictal EEG coherence (Krystal, 1998) were considered to be significant predictors for adequate therapeutically seizures. This fundamental paradigm shift, which has gained support in the past two decades, has potential clinical relevance in guiding ECT treatments (Mayur, 2006).

Previous studies showed differences in electroencephalogram (EEG) during MST induced seizures compared to ECT induced seizures. Specifically, MST treated groups demonstrated ictal activities with lower amplitudes and a relative absence of postictal suppression (White et al., 2006). However, the development of MST devices has progressed; for example, an increase in stimulation amplitude and frequency has changed the EEG semiology of MST (Kayser et al., 2011). Although ECT invoked generalized grand mal seizures, these were not able to shed light on the mechanism of action (Sackeim, 1994). But generalized seizures triggered by ECT show characteristic phases (Weiner et al., 1992), including spike and polyspike activity. After a variable period, this shifted to a slow wave phase, followed by a brief period of complete bioelectric suppression ("postictal supression") (Azuma et al., 2007).

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In the present study, a full treatment course of MST was given to the patients. As all patients were non-responders to MST, a full treatment course of ECT was subsequently administered. We investigated the ictal characteristics of both brain stimulation methods (MST and ECT) in each patient. The present study was designed to analyze and compare ictal and periictal EEG characteristics between MST and ECT in the same patients and to measure recovery and reorientation times following treatments. In line with our previous results (Kayser et al., 2011) we hypothesized that ictal characteristics in MST and ECT would be similar, but patients would show significantly faster recovery and reorientation after MST.

2. Experimental procedures

2.1. Design overview

Seven patients, who received a clinical course of MST and subsequently a clinical course of ECT between October 2007 and September 2009 at the University Hospital of Bonn, Department of Psychiatry and Psychotherapy, were included in the study. They provided written informed consent to participate in an approved study protocol by the institutional review board (IRB) of the University Hospital Bonn, Germany, which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The study was designed as an open-label, within-subject, controlled crossover trial. The protocol was registered at ClinicalTrials.gov with the identifier NCT00770783.

Patients were diagnosed based on DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders IV); six patients met diagnostic criteria for MDD and one patient for bipolar II disorder (BPII). DSM-IV criteria were determined using clinical interviews and medical records. Patients need to be currently depressed in order to fulfill DSM criteria for MDE. All pateints were right-motor dominant. Inclusion criterion was failure to respond to two different adequate trials ($>$5 weeks at maximum recommended or tolerated dose) of primary antidepressant medication during current depressive episode. Treatment resistant meant persistence of significant depressive symptoms despite two treatment trials with antidepressant medications from different pharmacological classes, each used in an adequate dose for an adequate time period. Patients with two or more antidepressant medication in the current episode were included in this study, too. Adequate dose was defined as an oral dose that is close to the manufacturer's recommended maximal dose. An adequate length of treatment means weeks of treatment during patient has had an adequate dose for at least 5 weeks. Medication intolerance is defined as inability to achieve or maintain an adequate therapeutic dose of an antidepressant drug due to side effects adapted to Thase and Rush 2000 . Exclusion criteria were: delirium, dementia, non-affective psychotic disorder, amnesia, other cognitive disorders, current or unstably remitted substance abuse (aside from nicotine), cardiac diseases, injury or disease of the central nervous system, ferrous material in the head, cardiac pacemaker, vagus nerve stimulator, or medical pumps. Clinical interviews and medical records were used to assess possibly diagnoses leading to exclusion of the study.

All patients first underwent MST. After failure to respond to treatment (12 treatments of MST), patients were offered the possibility to undergo subsequent ECT treatments (12 treatments of ECT).

The primary clinical outcome measure was used the 28-item Hamilton Depression Rating Scale ($HDRS_{28}$) (Hamilton, 1967). Response was defined as 50% reduction of depressive symptoms measured by $HDRS_{28}$ compared baseline to post-treatment values. Secondary outcome measure was the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Beck Depression Inventory (BDI) (Beck, 1987). Clinical outcome measures ($HDRS_{28}$, MADRS and BDI) were assessed at baseline and post-treatment of MST and ECT.

Patients were recruited by referral from either their treating psychiatrist, the university hospital outpatient clinic or via response to advertisements. Psychotropic medication prescribed prior to MST/ECT was continued and remained unchanged throughout the treatment courses. Both treatments were administered on a twice-a-week schedule. All subjects followed the same sequence.

2.2. Magnetic seizure therapy

We used a MagPro MST device (MagVenture A/S, Denmark) to generate pulses of biphasic waveform. A twin coil containing two individual round coils, each an average diameter of 13 cm, was applied. We used standard EEG positions according to the international 10–20 system when positioning the coil. The middle of the coil was placed firmly against the patient's head and positioned over Cz for vertex stimulation. Because the inside of the twin coil heats up approximately to 36 °C, the twin coil was cooled down to 10–12 °C prior to stimulation. Peak magnetic field of 2–4 T was induced at coil surface. The magnetic field is proportional to the current. MST seizure threshold titration was performed by starting with 100 Hz and 1 s stimulation (100 pulses). Stimulations were applied approximately every 30 s, increasing in duration by 1 s with each stimulation until a seizure was induced. Subsequent dosage of MST was set at 100 Hz and 6x seizure thresholds or the maximum output capacity of the device (1000 pulses at 100 Hz). The seizure threshold was identified during the first session. Stimulation amplitude was 100% (maximum stimulation output). Patients wore ear protectors during the treatment to protect against the high-frequency clicking noise of the MST device.

2.3. Electroconvulsive therapy

ECT treatment was administered with a square wave, customized brief pulse stimulus, and constant-current device (Thymatron IV, Somatics LLC, USA & Canada). Pulse width was 0.5 ms, current was fixed at 0.9 A, frequency was adjusted (range 30–120 Hz) to maximum duration (up to 8 s) with a maximum stimulus level of 1008mC. Seizure threshold was defined as the minimum electrical dose necessary to induce an adequate seizure, and was used to guide the dosing of ECT. It was quantified during the first treatment using the empirical titration procedure. We used 6x seizure threshold for unilateral and 3x for bilateral (BL) stimulation. Standard bifrontotemporal and d'Elia electrode placements were used for right unilateral (RUL) and bilateral (BL) ECT, respectively. Five patients were given RUL and two patients BL ECT. ECT devices using Thymatron IV provide an opportunity to monitor induced seizures with EEG, electrocardiogram (ECG), and electromyogram (EMG). Prefrontal EEG channels were set at Fp1 and Fp2, according to the international 10–20 system. ECG was assessed with three electrodes placed on the thorax. EMG was measured with two electrodes affixed to the cuffed leg (for a description see Section 2.4.).

2.4. Seizure monitoring

Total seizure duration was measured from the start of stimulation until the termination of observed ictal activities in the EEG. Duration of visible motor seizure activity was monitored by the "cuffed technique", in which an extremity is isolated from perfusion by a blood pressure cuff that is inflated above systolic pressure prior to injection of muscle-paralyzing agent. This allows the tonic-clonic motor component of the seizure to be timed by direct visualization. Motor seizure activity was observed from the onset of stimulation to the end of visible motor activity.

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The EEG was recorded with left and right frontal (approximating Fp1 and Fp2) leads. Reference electrodes were positioned on ipsilateral mastoid processes to avoid pulse artefacts. Ictal and periictal EEG parameters, including polyspike phase duration (s), polyspike phase maximum amplitude (mV), slow wave phase duration (s), slow wave phase maximum amplitude (mV), regularity (global seizure strength, 7-point scale ranging from 0 to 6), stereotypy (global seizure patterning, 4-point scale ranging from 0 to 3), and postictal suppression (degree of postictal suppression, 4-point scale ranging from 0 to 3), were manually rated using standard methods from the literature (Azuma et al., 2007; Weiner and Krystal, 1993a). The polyspike phase was defined as the activity between the end of stimulation and the point at which visually identifiable slow wave activity fully replaced early chaotic polyspike activity. The slow wave phase was defined as the activity from this time point until seizure termination. Maximum amplitudes during these two phases were defined by the largest peak-to-peak excursions and the mean maximum amplitude was determined for each patient. Seizures were rated as stereotypic when a clear progression from low amplitude chaotic polyspike activity to high amplitude slow wave activity was registered. Seizures were interpreted as showing regularity when slow wave activity of high amplitude regularly dominated during the slow wave phase. Greater numbers of high amplitude, slow wave activity suggest increasing stereotypy and regularity of the ictal EEG. Postictal suppression was rated as follows: 0=no precise seizure ends; 1=seizure termination is clear, but suppression is poor (not flat); 2=good seizure suppression, but crossover to flat be gradual; and 3=good seizure suppression (very flat) and crossover is abrupt adapted to Azuma et al. (2007). Two experienced psychiatrists, one of whom is also a trained neurologist, manually rated ictal and periictal EEG parameters. Both psychiatrists rated together, resulting in no inter-rater reliability.

2.5. Anesthesia procedure

Anesthesia was induced with 80–100 mg (1.0–1.5 mg/kg) intravenous propofol. Loss of eyelid reflex was considered to be a sign of adequate depth of anesthesia. Muscle relaxation was achieved by 80–100 mg (1.0–1.5 mg/kg) intravenous succinylcholine. All patients were ventilated by facemask with 100% oxygen until full recovery of spontaneous respiration to prevent apnea. Physiological monitoring included pulse oximetry, non-invasive blood pressure monitoring, and ECG. A rubber bite block was inserted into the mouth to prevent dental fractures or tongue lacerations. Seizures were induced 2–3 min after the injection of succinylcholine.

2.6. Measurement of recovery time and time to full reorientation

Recovery and reorientation times during the acute postictal period were assessed immediately after each treatment by a psychologist. Recovery was defined as time until patients opened their eyes and breathed independently. After patients opened their eyes upon command, they were asked their name, age, date of birth, place, and day of the week. Reorientation assessment was terminated when the correct response to four out of the five items was given.

2.7. Statistical analysis

The results are expressed as mean ± SD (standard deviation). Level of statistical significance was set at 5%. Paired *t*-tests were used to assess the mean values in each of the nine EEG characteristics (polyspike phase, slow wave phase, maximum amplitudes in each phase, regularity, stereotypy, postictal suppression, recovery time, and reorientation time) for each patient and each brain stimulation method (MST and ECT). The assessments and analyses of the variables were completed after each treatment. To assess the validity of the variables, Cohen's *d* effect size was calculated. Effect sizes were defined as small $d=0.2$, medium $d=0.5$ and large $d=0.8$. Furthermore, the *t*-test was used comparing the clinical outcome measures ($HDRS_{28}$, MADRS and BDI) at baseline and post-treatment of MST and ECT.

3. Results

3.1. Patient's clinical and demographic characteristics

Mean age of patients was 43.43 (SD 5.59) years. Patients' demographic and clinical characteristics are shown on Table 1. All patients fulfilled DSM-IV criteria for unipolar major depression or bipolar disorder—with depression as the most recent episode. The mean length of the current major depressive episode was 6.29 years (SD 6.04). The number of average of antidepressant treatment courses (pharmacotherapy of adequate dose and duration) was 16.12 (SD 10.79). Patients did not differ in anesthetic variables, motor or EEG measurements of seizure, or number of administered treatments. The seven patients received first 12 MST treatments first and subsequently 12 treatments of ECT. Concerning clinical outcome measures no patients fulfilled response or remission criteria and no significant differences compared baseline to post-treatment values by MST or ECT at $HDRS_{28}$, MADRS and BDI were measured (see Table 1).

3.2. Visual ratings and quantitative EEG measures

Seizures were elicited in all MST and ECT treatments. During seizures, tonic-clonic motor activities in the cuffed leg were observed. In addition, EEG activity via bipolar, frontal-mastoid scalp EEG recordings was confirmed. No significant differences in visible motor and EEG activities between ECT- and MST-seizures were observed with respect to their ictal activities, postictal suppressions, or others aspects of ictal characteristics (see Table 2). However, ECT-seizures lasted longer than MST-seizures, especially regarding polyspike phase durations of ictal activities, but it was not significant. In most ECT- and MST-treatments, typical ictal patterns consisting of high-amplitudes and synchronized theta activities were observed (see Figure 1). There were no temporal changes over time in the ictal characteristics. The results of the power analysis were mostly medium, suggesting enough statistical power to detect possible differences (see Table 2).

3.3. Reorientation assessment

Recovery and reorientation times were significantly shorter after MST compared to ECT (see Table 3). There were no temporal changes over time in the variables. The findings of the power analysis measured by Cohen's *d* were large.

4. Discussion

This study demonstrated similar ictal characteristics in magnetic seizure therapy (MST) and electroconvulsive therapy (ECT) in seven patients suffering from treatment-resistant depression, while observing faster recovery and reorientation times following MST.

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Table 1 Patients' demographic and clinical characteristics.

Characteristic	Mean (SD) $n=7$	♯1	♯2	♯3	♯4	♯5	♯6	♯7
Diagnosis using DSM-IV	6 MDD, 1 BPII	MDD	MDD	MDD	MDD	BPII	MDD	MDD
Sex	28.57 (% female)	Male	Female	Male	Male	Female	Male	Male
Age at treatment (Years)	43.43 (5.59)	35	47	45	44	51	45	37
Length of current episode (Years)	6.29 (6.04)	2	2	15	2,5	2,5	15	5
Number of lifetime episodes	4.57 (7.32)	1	2	1	2	21	1	4
Number of past medical treatment courses	16.12 (10.79)	34	8	25	17	18	7	4
Antidepressants	6.71 (3.04)	12	6	7	8	5	2	7
Sedatives	2.25 (1.90)	5	1	1	2	0	0	0
Mood stabilizers	1 (0)	1	0	1	0	1	1	0
Neuroleptics	2.4 (1.95)	5	4	1	1	0	1	0
Thyroid augmentation	1	1	0	0	0	0	0	0
Lithium	1 (0)	0	0	0	1	0	1	0
Number of patients receiving psychotherapy	100%	yes	yes	yes	yes	yes	yes	yes
Number of previous hospitalizations	2.29 (1.50)	5	2	2	2	2	0	3
Suicide attempts (Pretreatment)	0.43 (0.77)	0	2	0	0	0	1	0
Retirement from work	42.85%	yes	no	no	yes	yes	no	no
Positive family history for affective disorders	28.57%	no	yes	no	no	yes	no	no
MST								
$HDRS_{28}$ baseline	29.14 (3.93)	30	25	32	36	26	26	29
$HDRS_{28}$ post-treamtment	25 (4.16)	28	19	28	20	30	25	25
MADRS baseline	31.57 (6.80)	27	28	37	44	24	31	30
MADRS post-treatment	24.57 (1.81)	24	26	28	23	23	24	24
BDI baseline	36 (11.34)	23	39	44	53	24	33	36
BDI post-treatment	34 (12.43)	14	34	49	45	29	34	33
ECT								
$HDRS_{28}$ base	23.14 (3.89)	25	20	31	30	23	21	22
$HDRS_{28}$ post-treatment	23.57 (5.91)	27	22	35	19	18	24	20
MADRS baseline	24.29 (4.11)	23	18	29	30	24	22	24
MADRS post-treatment	23.14 (9.01)	29	13	38	27	13	20	22
BDI baseline	31.86 (11.51)	14	27	48	45	28	30	31
BDI post-treatment	30 (14.62)	16	22	55	44	16	29	30

Standard deviation, SD; number of patient, ♯; Major Depression Disorder, MDD; Bipolar Disorder, BP; Diagnostic and Statistical Manual of Mental Disorders, DSM; Magnetic seizure therapy, MST; Electroconvulsive therapy, ECT; 28-item Hamilton Depression Rating Scale, $HDRS_{28}$; Montgomery–Åsberg Depression Rating Scale, MADRS; Beck depression inventory, BDI.

In our study, we measured ictal characteristics based on the modern definition of adequate ictal patterns according to Azuma et al. (2007). Patients were a part of a larger sample of our ongoing clinical MST study. Because they were non-responder after MST, subsequently they passed ECT treatments, too. To achieve the optimal comparability results we recruited a small sample of our MST non-responders to receive full treatment courses of both MST and ECT, respectively, in a within-subject, crossover study design. However, in this study we demonstrated similar ictal characteristics during MST and ECT. The use of quantitative measures allowed for better comparison of EEGs in different conditions, and because of concurrent use of the muscle relaxant succinylcholine, muscle and movement artefacts were greatly decreased. Ictal characteristics in our study were measured by visual ratings and quantitative EEG patterns, including ictal EEG duration and amplitude, stereotypy, regularity, and postictal suppression or flattening of EEG (Azuma et al., 2007). These variables were used to predict whether or not a seizure was adequate. Inadequate EEG seizures had low amplitude waves, were asymmetric and showed no clear end in the postictal period. With respect to the new definition, we observed for the most part adequate seizures during MST and ECT. Especially, the more pronounced postictal suppression showed no difference in MST and ECT, which is normally known to predict the efficacy (Krystal and Weiner, 1994; Krystal et al., 1995, 2000). But all patients in our study were non-responders to MST and ECT and the power analysis of the ictal characteristics was rarely slight. However, our results were similar to those shown by Azuma et al. (2007). Further research with a larger sample is needed to clarify these discrepancies. As mentioned above, EEG is nevertheless a powerful method to register cortical electrical activity and may be used to monitor the course of events in a seizure. EEG analysis during seizures showed very characteristic patterns which, however, demonstrated large biological variation as well as non-stationary patterns. Complex osci-

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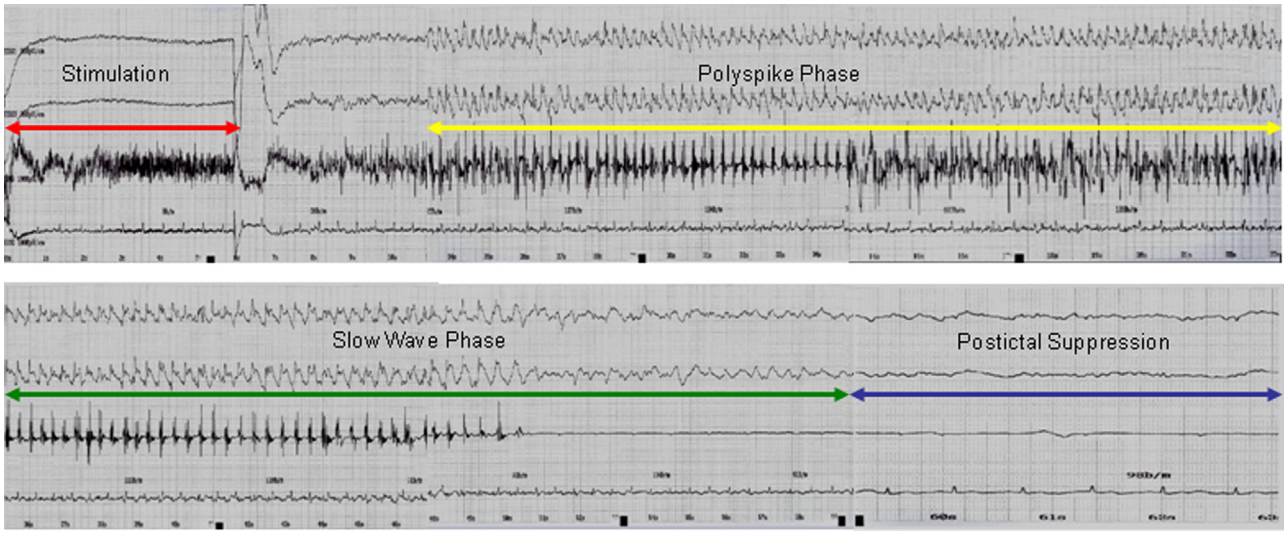

Figure 1 EEG during MST treatment (patient 4, session 6). Prototypical EEG of a MST treatment in EEG (bifrontomastoidal): from top to bottom: Channel 1 (left frontal-mastoidal)+Channel 2 right frontal-mastoidal)=EEG (electroencephalogram); Channel 3 (right foot)=EMG (electromyogram); and Channel 4=ECG (electrocardiogram). Stimulation phase=red; polyspike phase=yellow; slow wave phase=green; postictal suppression=blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

Table 2 Ictal characteristics.

Variable	MST ($n=7$)	ECT ($n=7$)				
	Mean (SD)	Mean (SD)	df	*t*-value	*p*-value	Cohen's *d*
Polyspike phase duration (s)	14.9 (8.46)	22.63 (13.64)	6	2.266	0.064	0.68
Polyspike phase amplitude (μV)	3463.57 (792.67)	3882.42 (820.42)	6	1.024	0.345	0.51
Slow wave phase duration (s)	8.84 (5.15)	10.83 (4.97)	6	0.980	0.365	0.39
Slow wave phase amplitude (μV)	2274.39 (932.85)	2345.43 (757.16)	6	0.125	0.905	0.08
Regularity (0-6)	3.79 (1.04)	4.43 (0.96)	6	1.776	0.126	0.63
Stereotypy (0-3)	1.77 (0.74)	2.17 (0.46)	6	1.724	0.135	0.64
Postictal suppression (0-3)	1.97 (0.51)	1.9 (0.39)	6	0.308	0.769	0.15

Standard deviation, SD; polyspike phase: starting with offset of stimulation and terminating at the point at which visually discernible slow wave activity fully replaced early chaotic polyspike activity; slow wave phase: period from this time point until seizure termination; maximal amplitudes: largest peak to peak deflections in the relevant phase and mean maximal amplitude were determined for each patient. Regularity=global seizure strength, 7-point scale ranging from 0 to 6; stereotypye=global seizure patterning, 4-point scale ranging from 0 to 3; postictal suppression=degree of postictal suppression, 4-point scale ranging from 0 to 3; magnetic seizure therapy, MST; electroconvulsive therapy, ECT; df=degrees of freedom; $p<0.05$; *t*-test (two-tailed); Cohen's *d*: small, $d=0.2$; medium, $d=0.5$ and large, $d=0.8$.

Table 3 Orientation assessment.

	MST ($n=7$)	ECT ($n=7$)				
	Mean (SD)	Mean (SD)	df	*t*-value	*p*-value	Cohen's *d*
Time until Recovery (s)	84 (61.49)	187.8 (73.08)	6	3.208	0.018	1.537
Time until Reorientation (s)	124.83 (71.83)	463.2 (291.28)	6	3.9078	0.008	1.595

Standard deviation, SD; recovery time: end of anesthesia, when patient began to breathe independently and sufficiently. Reorientation time: time until patient could correctly recall four of five of the following items: name, date of birth, age, place, and day of the week; magnetic seizure therapy, MST; electroconvulsive therapy, ECT; df=degrees of freedom; $p<0.05$; *t*-test (two-tailed); Cohen's *d*: small, $d=0.2$, medium, $d=0.5$ and large, $d=0.8$.

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llatory, anatomical, and physiological mechanisms behind such dynamic patterns of EEG for ECT were poorly understood before now, and even less well clarified for MST.

Previous MST studies have reported EEG findings of lower amplitudes and less synchronized activity and postictal suppression were reported for MST compared to ECT (Cycowicz et al., 2008; Lisanby et al., 2003a). In contrast, MST seizures in our study resembled those triggered by ECT. Specifically, all ictal activity periods, including high amplitudes and postictal suppression, were similar. More stimulation power in ECT leads to superior ictal characteristics for adequate seizures (Nobler et al., 2000); this concept has guided the development of MST devices and resulted in more powerfully stimulation parameters in the last decade. Therefore, we used high dose MST with 100% stimulation output and 100 Hz, which could be the reason for the potent ictal characteristics. Moreover, MST treatments in our study clearly elicited generalized seizures comparable to those during ECT, except that ECT elicited seizures lasted longer (as seen in polyspike phase duration of EEG ictal activity). Several authors have previously hypothesized that ECT affects deeper brain regions than MST and, therefore, propagation of ECT seizures is ubiquitous and more prolonged (Kosel et al., 2003; Lisanby, 2002). Another reason could be that during MST the stimulation induction was at the vertex and thus closer to the motor strip. MST seizures were shorter than ECT's, in which the stimulation induction was more temporal and occipital. In addition, after an ECT induced seizures the motor component ceased before termination of brain seizure activities. However, the correlation of motor endpoint with EEG endpoint is not entirely clear (Fink and Johnson, 1982), because the duration of the motor component only represents approximately 70% of brain seizure activity (Liston et al., 1988). In general, motor and EEG activity during MST seizures in this study fell within the range previously described by Kayser et al. (2011). Again, MST seizures were shorter than ECT seizures. The electrode placement played a key role for these variations in seizure duration and motor activity during MST and ECT seizures. As mentioned above, the twin coil during MST was placed bilaterally at the vertex, while the electrodes were placed in the temporal region during unilateral or bilateral ECT. The vertex is closer to the motor strip, thus the motor component during MST seizures was shorter than during ECT. Also, MST provides a more focal and powerful stimulation, resulting in strong focal induced seizures. Seizure durations during high stimulated ECT are shorter than at seizure threshold (Fink and Abrams, 1998). Thus, our study confirmed that a number of treatment-related factors, e.g. electrode placement, affect seizure characteristics (Weiner and Krystal, 1993b). We also confirmed that neither brain stimulation method showed changes in seizure duration over time, as has previously been described in ECT literature (Sackeim et al., 1987). This could be due to the use of propofol anesthesia, which corresponds to shorter seizure duration than other anesthetics (Bauer et al., 2009). Furthermore, we could not exclude carry-over effects between the first treatment with MST and the second treatment with ECT. However, if there had been carry-over effects, the seizure threshold would be lower over the course of the both treatments (Sackeim et al., 1987) and seizure duration would be shorter. We did not assess theses features in our study because no temporal changes over time occurred.

A complex pattern of frequencies has been observed in EEG and previous research has established that there are several frequency bands associated with particular points of origin (or processes) in the brain (Gu et al., 2005). Delta waves, for example, may be generated in thalamo-cortical circuit, while Theta waves are believed to reflect activity arising from the limbic system (hippocampus, cingulate gyrus, dentate gyrus, and amygdala), which is important for emotion and memory. In the present study, ECT elicited seizures demonstrated a longer polyspike wave phase than MST induced seizures. This could be one reason that network dysfunctions are longer during ECT, and could perhaps explain why fewer cognitive side effects occur in MST treated patients (Kayser et al., 2009, 2011). Furthermore, we observed higher phase amplitudes in ECT than in MST during ictal EEG phases, but there was no significant relation. This could support the hypothesis that MST is more focal, whereas ECT affects deeper brain regions (Ebner and Hoppe, 1995). For example, seizure expression in the hippocampus is as robust as in the prefrontal cortex with ECT, but manifestly less robust in the hippocampus than in the prefrontal cortex with MST (Morales et al., 2004). Research has suggested that lower frequency bands are generated by global circuits, while higher frequency bands are derived from local connections (Gu et al., 2005). Beta waves (high frequency) are observed in postictal periods and were occurred in the neocortex, hippocampus, and olfactory cortex, and are associated with attention, perception, and cognition. Because MST seizures were shorter, beta waves appeared earlier after the seizures were finished, in contrast to the ECT group, resulting in faster recovery and less confusion of the ECT patients (Kayser et al., 2011); these findings were confirmed in our present study. Furthermore, the shorter duration of the polyspike phase could also be an indication of the faster reorientation observed after MST compared to ECT. This profile might be one of the most important advantages of MST over ECT, as amnesia often occurs after ECT (Sackeim et al., 2007), and memory disturbances consist of both retrograde amnesia (Lisanby et al., 2000) and anterograde amnesia (Sackeim et al., 2008). Probably, duration of postictal disorientation correlates with the magnitude and hardiness of retrograde amnesia following ECT. In the majority of cases, confusion after each ECT treatment and anterograde amnesia are time-limited side effects; however, retrograde amnesia can persist up to six months and in some circumstances more months (Sackeim et al., 2007). In addition, retrograde amnesia following ECT has been described as selective in temporal distribution. Most studies have focused on memory (i.e. primarily temporal lobe tasks) rather than executive functions (i.e. primarily frontal lobe tasks), which might be even more greatly affected (Crowley et al., 2008). The physiological mechanisms underlying ECT related amnesia are not clear, although recent imaging studies have suggested that both mesial-temporal and frontal structures might be affected (Nobler and Sackeim, 2008). Generally, during ECT treatment large portions of the brain (up to 100% with bilateral ECT) are stimulated at high intensities relative to neuronal threshold. MST is more confined to superficial cortex and provides a more focal stimulation than ECT (Deng et al., 2009a, 2009b), consistent with previous clinical studies (Deng et al., 2009a, 2009b; Stecker,

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2005) and in vivo data (Lisanby et al., 2003c). More research could be useful to confirm the hypothesis that ECT affects deeper and more temporal brain regions, whereas MST is more focal and of frontal origin.

The anesthetic propofol is a commonly used agent in ambulatory surgery, because of its favorable side effect profile and its benefit of rapid recovery after anesthesia is stopped. In contrast to other anesthetic agents, such as etomidate, thiopentone, and methohexital, propofol is associated with milder hemodynamic changes (Mayberg et al., 1997, 1999; Videbech, 2000). However, the use of propofol for ECT is limited, because of its reduction of seizure duration compared to barbiturates (Cook et al., 1999). The main reason for this reduction is that propofol increases the seizure threshold and shortens the seizure duration. In our study, we used propofol due to its better side effect profile. As mentioned above, the elicited seizures in both treatment groups showed adequate ictal patterns (Scott et al., 2005).

Currently, there is no consensus regarding the underlying mechanisms of onset and process of seizures elicited by MST. Upcoming questions regarding whether MST is an alternative convulsive therapy to ECT for treatment-resistant depressed patients can only be addressed by further research with larger sample size and randomized studies.

4.1. Limitations and outlook

MST is still in the early stages of clinical testing, but ongoing studies are very promising. One limitation of our study is the small sample size and only to measure non-responders. As the group size enlarges, we will be able to further analyze mechanisms and efficacy of MST and measure ictal characteristics between responders and non-responders. Furthermore, the use of only two EEG electrodes is another limitation when studying ictal EEG characteristics such as topographic and spatial properties. Further studies using the complete 10–20 EEG system or animal studies using intracranial electrodes are needed. The trend towards more focused brain stimulation methods includes MST, which induces seizures without irritating deeper brain regions. Another limitation of our study is that neither patients nor physicians and raters were blinded. To study the contribution of seizure activity in generating antidepressant effects, further studies including a larger samples and blind, randomized study designs are needed. In addition, further MST studies could focus on differences between responders and non-responders in order to determine varieties in ictal characteristics. A large battery of neuropsychological was done, but it will be published in a recent paper with a larger sample of 20 patients and included responder and non-responder. Supplementary, a formal determination of diagnostic criteria as Structured Clinical Interview for DSM-IV is needed assuming to have exact diagnostic criteria.

There are considerable individual differences in seizure morphology, amplitude, and duration (Weiner and Krystal, 1994), as well as medications (Sackeim et al., 2009), anesthetics under treatment, patient age (Zervas et al., 1993), and anatomical variability of the population (Sackeim et al., 2008). All of these variables could be possible sources of variation, and further studies should therefore discuss and observe these variables. Furthermore, we could not eliminate possible carry-over effects due to the crossover study design. Further clinical studies are needed with a larger time period between both treatment methods.

Taken together this study suggested similar mechanism of action concerning ictal characteristics of MST and ECT. Additionally these results were very important for the decision if MST, since the safety and significant antidepressant effects were demonstrated (Kayser et al., 2011; Lisanby et al., 2003a) could be an alternative brain stimulation method for TRD.

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Contributors

Authors SK and BB designed the study and wrote the protocol. Author SK, RH and MS managed the literature searches and analyses. Authors SK and BB undertook the statistical analysis, and author SK and TS wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

Conflict of interest

SK was supported by a Grant of MagVenture A/S Inc. for lectures. BB had no conflict of interests. RH was supported by a German Research Foundation (DFG) grant (HU1302/ 2-2) and by a Starting Independent Researcher Grant jointly provided by the Ministry of Innovation, Science, Research and Technology of the German State of North Rhine-Westphalia (MIWFT) and the University of Bonn. MS had received honoraria for lectures from Covidien Germany (Neustadt/ Donau, Germany). This investigator-initiated study was supported in part (loan of MST device) by a Grant MagVenture A/S Inc. to TS.

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