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Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression

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ABSTRACT

Major depression is a common mental health problem and associated with significant morbidity and mortality, including impaired social and physical functioning and increased risk for suicide. Electroconvulsive therapy (ECT) is highly efficacious in treatment-resistant depressive disorders, but cognitive side effects are frequently associated with the treatment. Magnetic seizure therapy (MST) is a form of convulsive therapy, using magnetic fields in order to induce therapeutic seizures. First studies suggested that cognitive side effects of MST, including postictal recovery time, are more benign than those resulting from ECT treatment. In this open-label study we tested the hypothesis that MST is associated with clinically significant antidepressant effects in treatment-resistant depression (TRD) as an add-on therapy to a controlled pharmacotherapy.

Twenty patients suffering from TRD were randomly assigned to receive either MST or ECT starting from July 2006 until November 2008. Primary outcome measure was antidepressant response assessed by Montgomery Åsberg Depression Scale. Secondary outcome measures included Hamilton Depression Rating Scale, Hamilton Anxiety Scale, Beck Depression Inventory and 90-Item Symptom Checklist.

Antidepressant response (improvement of 50% in MADRS ratings) was statistically significant and of similar size in both treatment groups. Cognitive side effects were observed in neither group. Characteristics in MST- and ECT-induced seizures were comparable, especially regarding ictal activity and postictal suppression. Thus, MST may be a potential alternative to ECT if efficacy and safety are validated in larger clinical trials.

1. Introduction

Major depression is widely recognized as the world's most burdensome mental health problem in adults (Lopez and Murray, 1998). The disorder is associated with significant morbidity and mortality, including impaired social and physical functioning and increased risk for suicide (Agency for Health Care Policy and Research, 1993; Hirschfeld and Russell, 1997; Wells et al., 1989). Treatment of depressive disorders — especially of treatment-resistant forms - is therefore an important focus of current psychiatric research. Presently available evidence-based treatments lead to symptomatic improvement in most patients. However, up to 40% of patients partially responding to antidepressant therapy suffer from clinically relevant residual symptoms (Fava and Davidson, 1996) and 30% of patient do not respond to four evidence-based treatment steps (Rush et al., 2006). The more treatments fail, and the longer a current depressive episode lasts, the higher is the risk of developing a so-called treatment-resistant depression (TRD) (Rau et al., 2007).

In an effort to find safer and more effective alternatives to antidepressant drugs for treating severe depression, investigators have recently examined a variety of non-pharmacologic modalities, e.g. electroconvulsive therapy (ECT) (Lisanby, 2007), repetitive transcranial magnetic stimulation (rTMS) (O'Reardon et al., 2007), vagus nerve stimulation (VNS) (Schlaepfer et al., 2008), deep brain stimulation (DBS) (Bewernick et al., 2010) and magnetic seizure therapy (MST) (George, 2002).

Electroconvulsive therapy was developed in 1938 and has been demonstrated to be highly efficacious in severely

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treatment-resistant depressive disorders, with more than half of patients achieving remission (Khalid et al., 2008). ECT is the most effective treatment for major depressive disorder (APA., 1994; Ebmeier et al., 2006), but cognitive side effects such as amnesia are commonly reported (Datka et al., 2007; Donahue, 2000; Schulze-Rauschenbach et al., 2005).

Some randomised trials with transcranial magnetic stimulation (rTMS) have suggested similar efficacy as ECT in the treatment of non-psychotic depression (Grunhaus et al., 2000, 2003; Janicak et al., 2002; Schulze-Rauschenbach et al., 2005), although no large comparison trials have been undertaken so far. The feasibility and safety of deliberately induced seizures with the help of repetitive magnetic fields was first demonstrated in non-human primates (Dwork et al., 2004; Kosel et al., 2003b; Lisanby et al., 2001b). One further alternative to ECT is magnetic seizure therapy (MST), a form of convulsive therapy, in which magnetic fields are used to induce therapeutic seizures. In the course of the first human proof-of-concept study, one patient received a course of four MST treatments (Lisanby et al., 2001b). The same group treated another patient successfully with a full course of 12 MST (Kosel et al., 2003a). In contrast to ECT, MST is a more focal form of convulsive therapy (Lisanby et al., 2001b) that targets seizure induction in prefrontal cortex and spares medial temporal structures (i.e. hippocampus), which are involved in the development of cognitive side effects of ECT (Kosel et al., 2003a; Lisanby et al., 2003a; Lisanby, 2002; Moscrip et al., 2006). It has been demonstrated in primate models of MST that magnetically induced seizures are different from seizures induced by electrical convulsive stimulation (ECS) in regard to neurophysiological effects on the hippocampus (Lisanby et al., 2003a).

Only few results have been published since the first application of MST in the year 2000 (Lisanby et al., 2001b). Preliminary studies suggest that MST possesses antidepressant efficacy (Kayser et al., 2009; White et al., 2006), good feasibility and better tolerability in comparison to ECT (Lisanby et al., 2003a). First studies have suggested a more benign cognitive side effects profile of MST as compared to ECT (Kayser et al., 2009; Kosel et al., 2003a; Lisanby et al., 2003b), including faster postictal recovery time (Kirov et al., 2008), reductions in attention deficits and anterograde and retrograde amnesia (Dwork et al., 2004; Khalid et al., 2008; Lisanby et al., 2003a; Moscrip et al., 2006).

In this study twenty patients were assigned to receive either complete courses of treatment with either MST or ECT. We hypothesized that MST would lead to clinically significant antidepressant effects in treatment-resistant depression (TRD), as an add-on treatment to a controlled drug therapy.

2. Methods

2.1. Patients

The study was approved by the Institutional Review Boards (IRBs) of the University Bonn. The protocol has been registered at ClinicalTrials.gov with the identifier NCT00770783. Ten patients received MST (experimental) and ten other patients ECT (active comparator) at the University Hospital Bonn, Department of Psychiatry and Psychotherapy, from July 2006 to November 2008 (see Table 1 for demographic data). All patients met the diagnostic criteria for a major depressive disorder and were in a current episode as diagnosed with Structured Clinical Interview for DSM IV (Diagnostic and Statistical Manual of Mental Disorders IV) (APA, 1994). No patient suffered from a psychotic depression. Treatment resistance was defined as failure to respond to at least two treatments from different treatment categories during the current major depressive episode (MDE). For study inclusion, patients had to receive a score $\geq$20 on the 28-item Hamilton Rating Scale of Depression. Furthermore, convulsive therapy had to be clinically indicated. The exclusion criteria were a secondary diagnosis of, or signs of delirium, dementia, amnesia or other cognitive disorders and/or diagnosis of non-affective psychotic disorders. Further exclusion criteria were alcohol or substance dependence within the previous twelve months or abuse within the previous six months and a history or diagnosis of clinically relevant cardiac disease. Diagnosis of clinically relevant injury, disease of the central nervous system, magnetic material in the head or implanted medical devices (i.e. cardiac pacemaker, vagus nerve stimulator, medical pumps) also lead to exclusion.

Table 1
Patients' Demographic and Clinical Characteristics.

	MST	ECT
	Mean (SD)($n = 10$)	
DSM IV diagnosis	8 MDD, 1 BPI, 1 BPII	8 MDD, 2 BPII
Gender	60% f	70% f
Current Age (years)	48.80 (8.35)	52.8 (11.43)
Age MDD/BP onset (years)	32.80 (8.61)	37.1 (7.64)
Length of current Episodes (years)	6.01 (10.42)	3.5 (4.12)
Number of Lifetime Episodes	6.10 (7.56)	6.7 (7.8)
Number of Medications	18.40 (7.53)	17.9 (8.17)
Psychotherapy	90%	90%
Number of Hospital stays	3.70 (1.89)	4.1 (2.18)
Attempted Suicides	3/10 [0.80 (1.62)]	2/10 [0.3 (0.67)]
Pension/Unemployment	60%	70%
Family History	60%	50%

Diagnostic and Statistical Manual of Mental Disorders, DSM IV; Mean, Standard Deviation (SD); Major Depression Disease, MDD; Bipolar Disorder, BP.

Generally, patients with depression are judged as being able to give informed consent. Nonetheless, we required – without stipulation by the IRBs – in addition to the patient's own consent the agreement of the closest caregiver and requested a waiting period before signing the informed consent form of two weeks after the information meeting. The randomization to the treatment groups was carried out according to CONSORT (Consolidated Standards of Reporting Trials) (Moher et al., 2001a, 2001b) (see Fig. 1). Patients were recruited from their treating psychiatrist, responded to contributions in media, or were referred from the University Hospital outpatient clinic.

2.2. Magnetic seizure therapy (MST)

MST was performed using a MagPro MST device (MagVenture A/S, Denmark). Biphasic waveform stimulation, pulse width 370 μs, was delivered using a twin coil, containing two individual coils, each of a diameter of 13 cm. The pulse had a dampened cosine waveform. During the stimulation, the center of the coil was placed at the vertex. The peak magnetic field induced about 2 Tesla at the coil surface. At the beginning of each trial we treated with 100, 200, 300, etc. pulses in train (reflecting approximately 3x seizure threshold in ECT), afterwards we chose stimulation depending of the seizure threshold up to 600 pulses in a train. MST seizure threshold was defined as the minimum number of pulses required to induce a tonic-clonic seizure. Stimulation amplitude (i.e. an expression for power output level) was 100%. Stimulation frequency was 100 Hz and train duration up to 6 s. Repetition Rate was from 0.1 to 250 pps. To obtain comparability between all MST patients, the stimulation parameters were kept constant throughout the whole study.

2.3. Electroconvulsive therapy (ECT)

ECT was delivered with a Thymatron IV, ECT device (Somatics LLC, USA & Canada). Stimulus parameters are the following:

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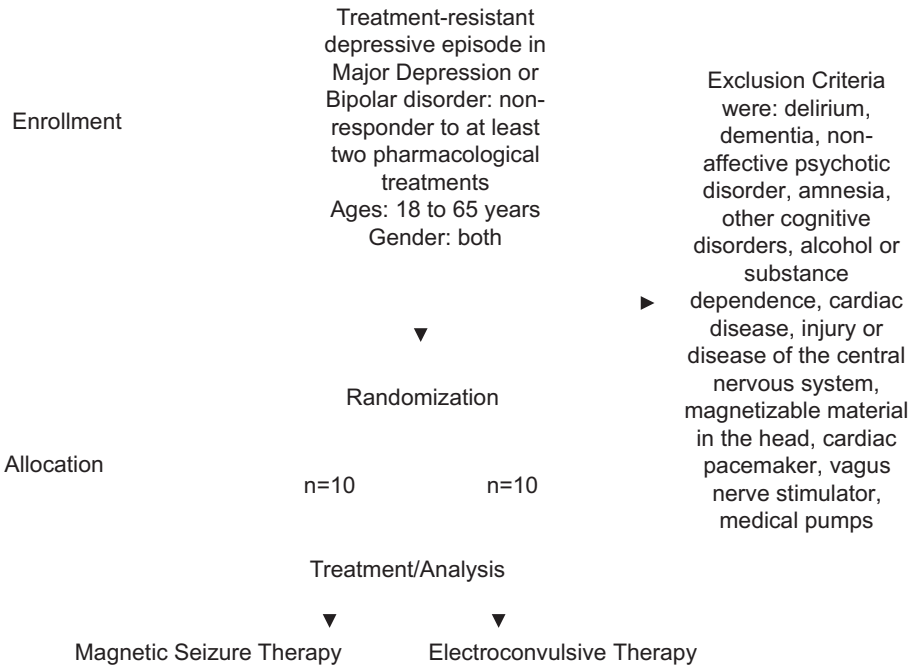

Fig. 1. Flow of participants through each stage of a randomized trial MST/ECT.

waveform was bipolar, a brief pulse current, square wave, frequency and duration of stimulation (5–8 s) depending on the energy set, pulse width 0.5 ms, duration of stimulation 4–8 s. We used right, unilateral (RUL) stimulation by using the titration method in our clinical treatment protocol (three times seizure threshold); achieving similar response rates as in the published literature (Bailine et al., 2009; Khalid et al., 2008; Sackeim et al., 1993, 2000).

2.4. Common course of MST and ECT

Seizures were elicited under general anesthesia with intravenous propofol (1.5–2.5 mg/kg, mean dose: 100 mg). During the full course of anesthesia, patients were oxygenated with 100% O_2. They received earplugs to protect against the high-frequency clicking noise of the MST machine, and a robber bite block was inserted to prevent dental damage. The right leg was cuffed prior to the administration of the muscle relaxant intravenous succinylcholine (1–1.5 mg/kg, mean dose: 80 mg). Duration of motor seizure activity was monitored by the cuffed ankle method. Two channels of prefrontal electroencephalogram (EEG) were recorded from frontal and mastoid electrodes. Seizure duration was measured from the beginning of the stimulation (with the MST/ECT device) to the end of the motor activities and EEG activities, respectively. Usually, MST and ECT treatment was administered twice a week and all patients received twelve treatments of MST or ECT. Antidepressant medication was kept stable for one month (±5 days) prior to treatment and was not stopped or changed during the treatment.

Table 2
Psychopathological measures at baseline and post MST/ECT treatments.

		Baseline mean (SD)	Post mean (SD)	mean difference (SD)	F value	*p* value	η2
MADRS	group	28.75 (5.5)	16 (9.3)	−12.75(8.9)	$F_{(1;19)} = 41.1$[a]	$p < 0.001$	0.684
	MST	31.2 (6)	15.9 (9.67)	−15.3(8.8)	$F_{(1;19)} = 1.7$[b]	n.s.	
	ECT	26.3 (3.83)	16.1 (9.45)	−10.2(8.7)			
$HDRS_{28}$	group	28.25 (4.6)	16.10 (8.79)	−12.15(9.62)	$F_{(1;19)} = 31.9$[a]	$p < 0.001$	0.627
	MST	30.7 (5.03)	18.3 (9.63)	−12.4(11.9)	$F_{(1;19)} = 0.01$[b]	n.s.	
	ECT	25.8 (2.62)	13.9 (7.72)	−11.9(7.33)			
BDI	group	34.15 (11.93)	25.15 (15.95)	−9(10.02)	$F_{(1;19)} = 16.15$[a]	$p \leq 0.001$	0.459
	MST	36.5 (10.96)	25.8 (17.13)	−10.7(12.94)	$F_{(1;19)} = 0.56$[b]	n.s.	
	ECT	31.8 (12.97)	24.5 (15.57)	−7.3(6.17)			
HAMA	group	20.05 (5.07)	11.85 (6)	−8.2(7.19)	$F_{(1;19)} = 25.99$[a]	$p < 0.001$	0.578
	MST	22.4 (4.38)	12.9 (7.42)	−9.5(8.58)	$F_{(1;19)} = 0.64$[b]	n.s.	
	ECT	17.7 (4.79)	10.8 (4.32)	−6.9(5.65)			
SCL-90	group	117.11 (59.34)	79.74 (63.81)	−37.37(55.56)	$F_{(1;18)} = 8.6$[a]	$p < 0.01$	0.323
	MST	133.78 (59.47)	87.56 (64.84)	−46.22(54.18)	$F_{(1;18)} = 0.42$[b]	n.s.	
	ECT	102.1 (58.06)	72.7 (65.5)	−29.4(58.44)			

Montgomery-Åsberg Depression Rating Scale, MADRS; Hamilton-28-Items Depression Rating Scale, $HDRS_{28}$; Beck Depression Inventory, BDI; Standard Deviation (SD). Hamilton Anxiety Scale, HAMA; 90-item Symptom Checklist (sum score), SCL-90.

[a] ANOVA for repeated measures with the factor time (baseline vs. post).

[b] ANOVA with the factor treatment (MST vs. ECT).

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Table 3
Neuropsychological tests at different time-points of MST/ECT treatments (trials 1,4,8 and 12).

		1. treatment mean (SD)	4. treatment mean (SD)	8. treatment mean (SD)	12. treatment mean (SD)	F value	p value	η2
Verbal learning and memory: words								
WORDS immediate recall		6,20 (1,96)	7,28 (1,85)	6,60 (1,67)	6,65 (1,79)	$F_{(3;54)} = 2.04$[a]	$p = 0.12$	
	MST	6,40 (1,51)	6,60 (1,27)	6,30 (1,16)	6,90 (1,37)	$F_{(1;18)} = 0.19$[b]	$p = 0.67$	
	ECT	6,00 (2,40)	7,95 (2,14)	6,90 (2,08)	6,40 (2,17)			
WORDS immediate recognition	group	13,45 (3,32)	13,13 (2,79)	13,55 (2,04)	13,25 (2,10)	$F_{(1,91;34,39)} = 0.39$[a]	$p = 0.67$	
	MST	13,80 (1,14)	13,20 (1,87)	13,30 (1,64)	13,30 (1,83)	$F_{(1;18)} = 0.01$[b]	$p = 0.92$	
	ECT	13,10 (4,65)	13,05 (3,59)	13,80 (2,44)	13,20 (2,44)			
WORDS delayed recall	group	3,10 (1,92)	2,90 (2,05) $p = 0.69$	2,20 (2,19) $p = 0.035$	2,20 (2,04) $p = 0.048$	$F_{(3;54)} = 2.93$[a]	$p<0.05$	0.14
	MST	3,80 (1,93)	3,30 (2,01)	2,20 (2,25)	2,70 (2,11)	($F_{(1;18)} = 1.04$[b]	$p = 0.32$	
	ECT	2,40 (1,71)	2,50 (2,12)	2,20 (2,25)	1,70 (1,95)			
WORDS delayed recognition	group	11,95 (2,93)	11,45 (2,50)	11,75 (1,83)	12,18 (1,84)	$F_{(3;54)} = 0.53$[a]	$p = 0.67$	
	MST	12,40 (2,22)	11,70 (2,11)	11,70 (1,16)	12,05 (1,42)	$F_{(1;18)} = 0.12$[b]	$p = 0.74$	
	ECT	11,50 (3,57)	11,20 (2,94)	11,80 (2,39)	12,30 (2,26)			
Visual spatial learning and memory: shapes								
SHAPES immediate recognition	group	6,50 (1,54)	6,50 (1,43)	6,10 (1,80)	5,53 (2,19)	$F_{(3;54)} = 2.75$[a]	$p = 0.05$	
	MST	6,60 (1,08)	6,40 (1,17)	6,30 (1,49)	6,45 (1,54)	$F_{(1;18)} = 0.85$[b]	$p = 0.37$	
	ECT	6,40 (1,96)	6,60 (1,71)	5,90 (2,13)	4,60 (2,41)			
SHAPES delayed recognition	group	5,60 (1,70)	5,73 (1,97) $p = 0.80$	5,30 (1,95) $p = 0.56$	4,08 (2,10) $p = 0.01$	$F_{(3;54)} = 5.92$[a]	$p = 0.001$	0.248
	MST	5,70 (1,57)	5,50 (2,12)	5,30 (2,05)	4,65 (1,92)	$F_{(1;18)} = 0.11$[b]	$p = 0.75$	
	ECT	5,50 (1,90)	5,95 (1,89)	5,30 (1,95)	3,50 (2,22)			
Verbal memory: Wechsler Memory Scale								
logical memory I: immediate recall	group	11,90 (4,46)	13,60 (3,80)	12,65 (4,51)	14,03 (5,08)	$F_{(3;54)} = 2.46$[a]	$p = 0.07$	
	MST	11,70 (3,86)	14,00 (2,91)	12,50 (3,95)	14,25 (4,11)	$F_{(1;18)} = 0.01$[b]	$p = 0.94$	
	ECT	12,10 (5,20)	13,20 (4,66)	12,80 (5,22)	13,80 (6,13)			
logical memory II: delayed recall	group	9,55 (5,69)	11,80 (4,69)	11,30 (5,36)	11,60 (5,67)	$F_{(3;54)} = 2.49$[a]	$p = 0.07$	
	MST	8,70 (4,32)	12,10 (3,64)	11,80 (5,39)	12,90 (5,51)	$F_{(1;18)} = 0.08$[b]	$p = 0.78$	
	ECT	10,40 (6,93)	11,50 (5,76)	10,80 (5,57)	10,33 (5,81)			
Abstract questions	group	4,35 (0,93)	4,25 (1,12)	3,75 (1,16)	4,15 (1,18)	$F_{(2,09;37,67)} = 2.86$[a]	$p = 0.07$	
	MST	4,50 (0,85)	4,30 (1,06)	3,70 (1,06)	4,50 (0,85)	$F_{(1;18)} = 0.35$[b]	$p = 0.56$	
	ECT	4,20 (1,03)	4,20 (1,23)	3,80 (1,32)	3,80 (1,40)			
Picture test	group	4,15 (0,93)	4,25 (0,97) $p = 0.55$	4,90 (0,45) $p = 0.002$	4,75 (0,64) $p = 0.034$	$F_{(1,74;31,28)} = 6.11$[a]	$p<0.01$	0.253
	MST	4,30 (1,06)	4,40 (0,97)	5,00 (0)	4,80 (0,63)	$F_{(1;18)} = 0.88$[b]	$p = 0.36$	
	ECT	4,00 (0,82)	4,10 (0,99)	4,80 (0,63)	4,70 (0,67)			
Verbal fluency								
verbal fluency: semantic categorial	group	31,85 (7,16)	19,20 (6,89) $p = 0.00$	23,85 (8,29) $p = 0.00$	24,33 (8,46) $p = 0.00$	$F_{(2,27;40,85)} = 31.89$[a]	$p<0.001$	0.633
	MST	32,60 (5,78)	19,10 (5,74)	26,60 (7,53)	26,45 (8,49)	$F_{(1;18)} = 0.82$[b]	$p = 0.38$	
	ECT	31,10 (8,58)	19,30 (8,19)	21,10 (8,48)	22,20 (8,28)			
verbal fluency: formal lexical	group	17,50 (7,70)	15,73 (7,90) $p = 0.09$	13,90 (7,66) $p = 0.007$	13,15 (6,35) $p = 0.005$	$F_{(1,97;35,38)} = 7.01$[a]	$p<0.01$	0.28
	MST	18,50 (6,17)	17,40 (7,98)	15,60 (8,34)	15,10 (7,40)	$F_{(1;18)} = 1.06$[b]	$p = 0.32$	
	ECT	16,50 (9,22)	14,05 (7,88)	12,20 (6,93)	11,20 (4,69)			
Neglect								
Neglect: geometric forms	group	61,40 (17,56)	61,33 (18,43)	58,70 (18,59)	60,75 (17,93)	$F_{(1,6;28,81)} = 0.47$[a]	$p = 0.59$	
	MST	54,40 (10,29)	53,50 (10,40)	51,20 (10,17)	52,00 (10,50)	$F_{(1;18)} = 5.28$[b]	$p<0.05$	0.23
	ECT	68,40 (20,89)	69,15 (21,75)	66,20 (22,39)	69,50 (19,95)			
Neglect: letters	group	82,45 (44,51)	74,53 (33,79)	66,95 (18,13)	68,05 (18,56)	$F_{(1,16;20,94)} = 2.96$[a]	$p = 0.10$	
	MST	68,50 (17,35)	64,40 (13,43)	62,90 (13,15)	63,60 (13,48)	$F_{(1;18)} = 2.04$[b]	$p = 0.17$	
	ECT	96,40 (58,73)	84,65 (44,74)	71,00 (22,01)	72,50 (22,40)			
Neglect: nongeometric forms	group	123,80 (59,28)	107,35 (51,67) $p = 0.06$	85,25 (28,16) $p = 0.005$	86,40 (23,57) $P0 = 0.007$	$F_{(1,47;26,39)} = 5.48$[a]	$p<0.05$	0.233
	MST	101,00 (20,63)	95,00 (11,73)	84,80 (14,14)	87,90 (15,10)	$F_{(1;18)} = 1.67$[b]	$p = 0.21$	
	ECT	146,60 (76,40)	119,70 (71,83)	85,70 (38,39)	84,90 (30,66)			

Mean, Standard Deviation (SD).
Corrected results according to Greenhouse-Geisser were presented when Mauchly's sphericity test became significant.
[a] ANOVA for repeated measures with the factor time (post in comparison to baseline) for MST and ECT.
[b] ANOVA for repeated measures with the factor treatment (MST vs. ECT) as between subject variable.

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2.5. Clinical assessment and study design

Brief psychiatric assessments were performed daily during inpatient treatment courses.

Psychopathological scores were assessed at baseline and post treatment (one month plus/minus three days after the last treatments). Primary outcome measure was antidepressant response (50% reduction of depressive symptom severity as assessed by the Montgomery Åsberg Depression Scale (MADRS)) (Montgomery and Asberg, 1979) or remission (MADRS score of less than 10). Secondary outcome measures included the Hamilton Depression Rating Scale ($HDRS_{28}$) (Endicott et al., 1981; Hamilton, 1967) and the Hamilton Anxiety Scale (HAMA) (Hamilton, 1976). Furthermore, self-rating scales were used including the Beck Depression Inventory (BDI) (Beck, 1987) and the 90-Item Symptom Checklist (SCL-90) (Franke, 1995). In order to measure cognitive side effects, neuropsychological assessments (general intellectual ability, language, processing speed, executive function, learning, and memory) were performed at baseline, at several determined time point during treatments and four weeks after end of treatments. Additionally, preliminary information about the safety of the treatment method (i.e. adverse events) was assessed by asking the patient for possible adverse events (e.g. headache, dizziness, muscular pain).

Psychiatric and neuropsychological assessments were performed by an independent psychologist not involved in the treatment.

2.6. Neuropsychological measures and assessment of time to full reorientation

Short-term cognitive effects were assessed immediately subsequently to each treatment. Recovery was defined as the time when patients opened their eyes and brethed indepentently. Time to full orientation after MST and ECT treatment was assessed with parts of the autobiographical memory interview (Kirov et al., 2008) by asking the patient for her/his names, date of birth, age, place and day of the week. We started to interrogate, when patient began to breathe independently, at the end of anesthesia. The point of full reorientation was defined as the time, when the patient was able to recall four of the five named items. Detailed neuropsychological testing (e.g. general intellectual ability, language, processing speed, executive functions, learning and memory) was performed 4 h after MST/ECT treatment by a psychologist not involved in the treatment (see Table 3 for more details).

2.7. Statistical analysis

To evaluate clinical response, all rating scales were analyzed with analyses of variance (ANOVA) for repeated measures and the factor time (baseline vs. post treatments). For group comparisons, the factor group (MST vs. ECT) was added.

Paired-sampled *t*-tests were used in order to compare recovery time and seizure expression of MST- and ECT-treated patients. Analyses for neuropsychological changes were performed without correction for multiple comparisons in order to detect small changes in the small samples as we wanted to observe also minor cognitive impairments. Level of significance was set at 5% for all analyses.

3. Results

3.1. Demographic and clinical characteristics

All patients were diagnosed with a treatment-resistant depressive disorder. As shown in Table 1, both treatment groups were similar regarding their demographic and clinical characteristics.

3.2. Clinical outcomes

3.2.1. Primary and secondary outcome measures

Regarding the primary measure of effectiveness (50% reduction of the MADRS score), six of ten patients treated with MST were responders (three reached remission status, i.e. MADRS score of less than 10). Four of ten patients undergoing ECT responded to the treatment and were classified as remitters. The change of MADRS score at baseline and after respective treatment of both groups is shown in Fig. 2. As can be seen in Table 2, ANOVA for repeated measures revealed a significant improvement between baseline and post treatment in MADRS for both treatment groups. No significant difference between both treatment groups was found. Similar results can be seen for further ratings of depressive symptoms, anxiety and patient-rated psychological and physical distress ($HDRS_{28}$, BDI, HAMA, and SCL-90).

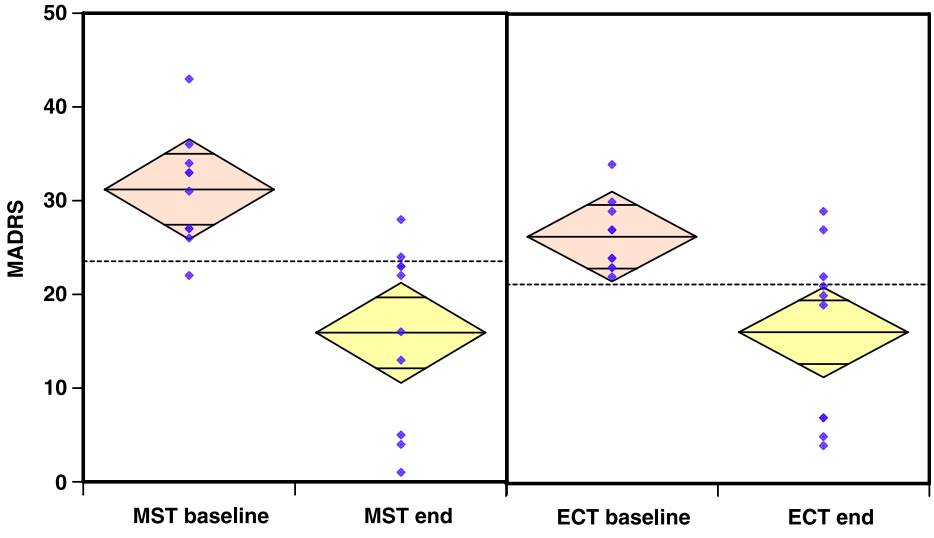

Fig. 2. MADRS score at baseline and at end of treatment. The MADRS score at baseline and after respective treatment of ten MST and ten ECT patients.

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Table 4
Recovery and Reorientation times (minutes) after MST/ECT treatments.

	Group	Mean (SD)	df	T value	*P* value
Recovery	MST	1:42 (0:53)	18	−4.24	0.01
	ECT	4:03 (1:31)			
Reorientation	MST	2:16 (0:57)	18	−5.31	0.01
	ECT	8:21 (3:29)			

Mean, Standard Deviation (SD). Recovery was defined as time when patients opened their eyes and brethed independently. Reorientation was measured similar to Kirov et al., 2008.

Table 5
Seizure expression.

Seizure expression	Group	Mean (SD)	df	T value	*P* value
Motor activity	MST	20.18 s (5.5 s)	18	−1701	1.06
	ECT	24.69 s (6.3 s)			
EEG activity	MST	23.53 s (6.6 s)	18	−2181	0.43
	ECT	31.08 s (8.7 s)			
EEG latency	MST	2.40 s (2.9 s)	18	1037	0.314
	ECT	1.29 s (1.7 s)			

Mean, Standard Deviation (SD).

3.2.2. Neuropsychological assessment

ANOVA revealed significant differences between patients receiving MST or ECT treatment only in the geometrical forms subtest of the neglect test with MST patients achieving better results. Statistically significant fluctuations in performance (e.g. first treatment vs. 4th treatment) were observed in the following tests: words delayed recall, shapes delayed recognition, Verbal fluency, Picture test, Neglect: nongeometric forms (see Table 3).

3.2.3. Adverse effects

No side effects were observed in the MST group. On the contrary, some patients undergoing ECT suffered from headache, nausea or muscle pain after treatment.

3.2.4. Orientation assessment

There was a significant difference in recovery and reorientation times between the treatment groups (see Table 4): Recovery time after MST treatment was 2 min 21 s quicker than after ECT treatment and reorientation time was 6 min 5 s quicker after MST treatment than ECT treatment.

3.2.5. Seizure characteristics

In all patients seizures were elicited during each MST and ECT treatment. Although, generally similar patterns of EEG activity between the treatment groups were observed, some descriptive differences could be measured. In most ECT and MST sessions, typical ictal patterns consisting of high-amplitude synchronized theta activity and equal postictal suppression were assessed (see Fig. 3). Some patients treated with MST showed delayed ictal EEG activity. Seizure duration of motor activity and of ictal activity in EEG was briefer in most MST patients compared to ECT patients. Furthermore, duration of motor and ictal activity in MST-treated patients had about the same length. This was not the case for ECT-treated patients, where the motor activity duration was normally shorter than the EEG ictal activity (see Table 5).

3.3. Discussion

As hypothesized, MST was associated with significant antidepressant effects. The extent of the reduction of depression severity was comparable between both treatment groups and comparable to ones published in other ECT studies (Bailine et al., 2009; Khalid et al., 2008; Medda et al., 2009). In addition, anxiety as well as general psychopathological burden was significantly decreased in both treatments. There was better compliance and tolerability in clinical practice for MST as compared to ECT.

Regarding the variety of non-pharmacologic modalities, ECT is still the treatment of choice in pharmacotherapy-resistant depression (Holtzheimer and Nemeroff, 2006). This highly effective and rapidly acting treatment is usually used only in later steps of treatment algorithms and is often used as a treatment of last resort only. Our patients underwent many other treatments before trying ECT/MST. This is due both to its stigma and its well-recognized cognitive side effects (Fava et al., 2008; Grunze et al., 2002; Prudic, 2008; Steffens et al., 2002). Shortly after ECT treatment, most patients have gaps in their memory for events that occurred close in time to the course of ECT, but the amnesia may even extend back several months or years (Squire, 1974, 1975; Squire and Slater, 1983; Squire et al., 1975, 1981; Weiner et al., 1986). Traditional views note that a temporal gradient characterizes the memory deficits after ECT (Squire, 1986). Retrograde amnesia usually improves during the first few months after ECT. Nonetheless, for many patients, recovery is incomplete, with permanent amnesia for events that occurred close in time to the treatment (Squire, 1986). Furthermore, ECT is associated with greater and more persistent deficits for public (impersonal) than autobiographical (personal) events (Lisanby et al., 2000).

In this study, we did not find substantial cognitive side effects in the ECT group. This might be due to lower stimulation dose as compared to other studies (Lisanby etal., 2003a). Nonetheless, antidepressant response shows that ECT treatment was effective. It has been demonstrated, that electrical dose is not related to clinical improvement (Delva et al., 2000; Sackeim et al., 1993, 2000), but might be related to cognitive side effects (Delva et al., 2000) Therefore, we used RUL at a medium stimulation dose in order to prevent a higher rate of cognitive side effects in the ECT group, negatively impacting on patient compliance (see e.g. Schulze-Rauschenbach et al., 2005 for a similar approach comparing ECT with rTMS). Primate studies (Moscrip et al., 2006) as well as preliminary human studies (Kosel et al., 2003a; Lisanby et al., 2003b; Spellman et al., 2008) revealed no cognitive side effects

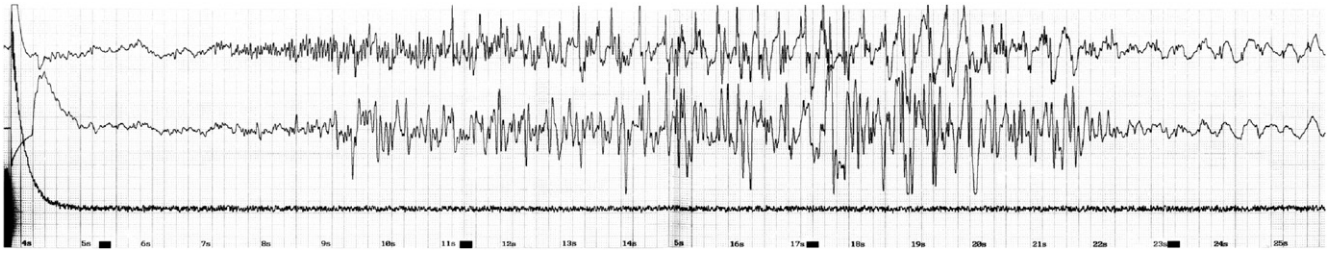

Fig. 3. Magnetic Seizure Therapy: EEG pre-, ictal and postictal as exemplary for MST seizure expression. Typical bipolar, frontal EEG as recorded during MST (Patient 6, treatment 10), magnetic stimulation occurred in the first 4 seconds of the recording. Eight seconds after stimulation there is a typical generalize seizure till 22 s, then the postictal suppression.

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after MST treatment. Similarly, in this study, MST was well tolerated without cognitive side effects.

In this study, we tested a short form of the autobiographical memory interview (Sackeim et al., 1993; Weiner et al., 1986). Time to full reorientation was shorter after MST treatment as compared to ECT treatment. It is debated, if reorientation time is a measure for memory function, as disorientation following ECT can be interpreted as transient retrograde amnesia (Daniel et al., 1987; Sobin et al., 1995). A more detailed assessment of autobiographical memory in further studies could clarify if MST has more benign effects on autobiographical memory functioning.

In contrast to previous studies (Lisanby et al., 2001a; White et al., 2006), it was possible to elicit seizures in each MST treatment session, and although the EEG profile in both groups was similar (e.g. postictal suppression) for the most part, we found some differences between MST and ECT. Delayed onset of ictal activity in some MST sessions was in accordance with the hypothesis of a more focal induction of seizure activity and subsequent secondary generalization. Furthermore, in some sessions synchronized activity in the delta and theta frequency ranges showed reduced amplitudes, also most likely related to the recruitment of more circumscribed neural networks (Buzsaki and Draguhn, 2004). Seizure duration in visible motor activity and especially in EEG recordings was shorter in the MST group than in ECT group. This is in accordance to previous results (Lisanby et al., 2003a), and maybe is yet another indication of focal seizure onset with secondary generalization during MST treatment. Although seizure duration is not a sufficient evidence for the efficacy of ECT (Kales et al., 1997; Nobler et al., 1993; Weiner and Krystal, 1993), EEG recordings of shorter duration than 15 s imply an insufficient electrical stimulus and efficacy (APA, 2001). In this study, we documented equal antidepressant efficacy in MST- and ECT-treated patients despite shorter seizure duration in MST-treated patients. One reason for these positive results could be the similar ictal activity and postictal suppression in both treatment groups (Azuma et al., 2007; Perera et al., 2004).

Although, we have included more patients than previous studies (Lisanby et al., 2001b) (Kayser et al., 2009; Kosel et al., 2003a), but certainly one limitation of our study is the small sample size. Therefore, all results should be interpreted as preliminary until results are replicated in larger patient groups. Especially regarding response rates, larger sample sizes (Husain et al., 2004; Kellner et al., 2010; Sackeim et al., 2009; Sackeim and George, 2008) in multi-center-studies should elucidate response and remission rates.

Another limitation is the fact that recovery and reorientation was unblinded to the treatment method as the assessing psychologist necessarily was present at the treatment and both treatment methods were distinguishable by the use of coil and a clicking noise. However being aware of the treatment method, the assessing psychologist was not informed about the hypothesis for cognitive performance reducing possible rater effects. Furthermore, long-term outcome measures are lacking. In ECT, relapse rates are high (Parvin and Swartz, 2004; Prudic, 2008). It is not known, if the same applies to MST.

In conclusion, preliminary data have demonstrated equal antidepressant effect in MST as compared to ECT and no cognitive side effects. Further studies should clarify if MST could become an alternative treatment for patients suffering from treatment-resistant depression.

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Contributors

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Conflicts of interest

Dr. Schlaepfer declares no conflicts of interest relating to this paper and that in addition to income from the University of Bonn he received compensation as an advisor on the conduct of clinical studies from PNB Neurosciences, Alken, Belgium. All other authors declare that, except for income received from the primary employer, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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