Psychological Medicine (2015), **45**, 1073–1092. © Cambridge University Press 2014
doi:10.1017/S0033291714002244

ORIGINAL ARTICLE

Magnetic seizure therapy in treatment-resistant depression: clinical, neuropsychological and metabolic effects

S. Kayser[1], B. H. Bewernick[1], A. Matusch[2], R. Hurlemann[1], M. Soehle[3] and T. E. Schlaepfer[1,4]*

[1] *Department of Psychiatry and Psychotherapy, University of Bonn, Germany*
[2] *Institute of Neurosciences and Medicine (INM-2), Forschungszentrum Jülich, Germany*
[3] *Department of Anaesthesiology and Intensive Care Medicine, University of Bonn, Germany*
[4] *Departments of Psychiatry and Mental Health, The Johns Hopkins University, Baltimore, MD, USA*

Background. Magnetic seizure therapy (MST), despite being in an early phase of clinical research, has been demonstrated to be associated with antidepressant efficacy. However, safety, tolerability and efficacy data in connection with functional brain activity from larger samples are lacking. The aim of this study was to determine clinical and cognitive effects of MST and the influence of MST on regional brain glucose metabolism.

Method. Twenty-six patients suffering from treatment-resistant depression (TRD) underwent MST. Ten patients underwent a randomized trial and 16 patients an open-label study design. The primary outcome criterion was the severity of depressive symptoms assessed with the Hamilton Depression Rating Scale (HAMD). Depressive symptoms, tolerability and cognitive safety, along with social functioning and quality of life parameters, were assessed using various rating scales. A clinical follow-up visit 6 months following the completion of a course of MST and [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scans of 12 patients were analysed.

Results. A significant response to MST was demonstrated by 69% of the patient sample, with 46% meeting remission criteria. Anxiety ratings were significantly reduced in responders and their quality of life was improved. Half of the responders relapsed within 6 months. No cognitive side-effects were observed. FDG-PET scans showed a metabolic increase in the frontal cortex bilaterally and a decrease in the left striatum.

Conclusions. Robust antidepressant and anti-anxiety efficacy of MST was demonstrated, and found to be associated with localized metabolic changes in brain areas that are strongly implicated in depression. Thus, MST presents an effective, well-tolerated and safe treatment option for patients unable to respond to other forms of therapy for depression.

Received 21 January 2014; Revised 9 August 2014; Accepted 14 August 2014; First published online 25 November 2014

Key words: Cognition, efficacy, magnetic seizure therapy, major depression, positron emission tomography.

Introduction

Major depression is usually recurrent, often life-threatening (Bertolote *et al.* 2004), and leads to dysfunctions of mood, motivation and cognition (Austin *et al.* 2001). In approximately 50% of patients, first-line antidepressant treatment is ineffective and about a third of patients do not show a substantial antidepressant response, even after four treatment steps (Rush *et al.* 2006; Lisanby *et al.* 2009). Incomplete recovery or partial remission from depression is classified as treatment-resistant depression (TRD; Schlaepfer *et al.* 2012). In the field of treatment resistance, electroconvulsive therapy (ECT) is currently seen as the main treatment option (Krystal *et al.* 2000), with a remission rate of approximately 70% (Sackeim *et al.* 2000*b*; Petrides *et al.* 2001). However, because of the high relapse rates recorded (~50%) (Sackeim *et al.* 2000*a*; Grunhaus *et al.* 2001; Azuma *et al.* 2007*a*), negative cognitive side-effects (Lisanby *et al.* 2000; Rose *et al.* 2003) and social stigma (Ottosson & Max Fink, 2004), ECT is often used as a last resort (Grunhaus *et al.* 2001). Therefore, there is an urgent need for new therapy strategies in cases of treatment-resistant forms of depression.

A widely recognized shortcoming of ECT is its propensity to be associated with cognitive side-effects (Bernstein *et al.* 1998; Fink, 2001), with about 55% of patients reporting cognitive impairments after ECT (Rose *et al.* 2003). These symptoms have a significant impact on a patient's outcome (Austin *et al.* 2001), impairing functionality, basic autonomy and quality of life (Montgomery & Gale, 2008).

* Address for correspondence: T. E. Schlaepfer, M.D., Department of Psychiatry and Psychotherapy, University Hospital, Sigmund-Freud-Straße 25, 53105 Bonn, Germany.
(Email: schlaepf@jhmi.edu)

Table 1. *Demographic and personality characteristics of patients*

Variable	All patients ($n = 26$)	Responders ($n = 18$)	Non-responders ($n = 8$)	Responders *v.* non-responders	
				p value	χ^2
Sex (% female)	42.3	50	37.5	0.181	1.786
Age at MST treatment (years)	47.2 (10)	47.1 (10)	47.5 (10)	1.000	
Age at onset (years)	31.1 (11)	31.7 (12)	33.4 (8)	0.760	
Time since diagnosis of affective disorder (years)	14.9 (8)	15.2 (8)	14.1 (7)	0.674	
Duration of current episodes (years)	5 (6)	4.3 (5)	6.8 (7)	0.064	
Number of previous depressive episodes during lifetime	4 (5)	2.7 (2)	7.1 (8)	0.228	
Number of previous medical treatment courses during current episode (only adequate trials are listed)[a]	14 (8)	13 (8)	16.8 (5)	0.888	
Psychotherapy (%)	92.3	94.4	87.5	0.609	0.262
Number of hospital stays	3.3 (2)	3.3 (2)	3.3 (2)	0.312	
Number of attempted suicides	0.4 (1)	0.6 (1)	0 (0)	0.082	
Retirement due to depression (% retired)	38.5	43.8	37.5	0.484	0.488
Family history of any mood disorder (%)	46.15	56.3	37.5	0.052	3.768

MST, Magnetic seizure therapy.

Demographic data refer to all 26 patients at baseline. Variables were measured at baseline and post-treatment.

[a] Adequate trials mean dose and duration of medication during 5 weeks at the maximum recommended or tolerated dose.

Data are given as mean (standard deviation) or percentage.

A decade after magnetic seizure therapy (MST) was first posited as a new convulsive brain stimulation method for resistant forms of depression (Lisanby *et al.* 2001), there continues to be little information about its efficacy, safety and tolerability. MST is still in an early phase of clinical research and because of the small number of patients registered in earlier studies, generalizations on the specific efficacy of MST cannot yet be made. Several small clinical studies have shown antidepressant effects and the absence of cognitive side-effects (Lisanby *et al.* 2003; Kayser *et al.* 2009, 2011; Fitzgerald *et al.* 2013). To date, MST studies have not included neuroimaging assessments, with the exception of one case report where metabolic effects were reported (Kosel *et al.* 2003) and a recently published study of 10 patients that indicates increased metabolism in several brain regions following MST (Hoy *et al.* 2013). A key question, therefore, is whether the antidepressant effect of MST is associated with enduring metabolic changes in brain regions related to the mood processing circuitry.

In line with our previous results (Kayser *et al.* 2009, 2011), we hypothesized that MST would have similar antidepressant efficacy as ECT, but without cognitive worsening. The results for 10 patients were partial reported previously (Kayser *et al.* 2011). In the current study an extended sample was assessed and clinical follow-up data were included. In addition, we used an extensive neuropsychological battery, and the effect of MST on brain glucose metabolism was assessed using [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET).

Method

Study design and patients

This study was approved by the Institutional Review Board of the University of Bonn and is registered at ClinicalTrials.gov with the identifier NCT00770783. We studied 26 patients (14 males and 12 females) in an open-label study design. The patients consented to participate in a clinical treatment course of MST in the Department of Psychiatry and Psychotherapy at the University Hospital of Bonn from October 2008 to February 2013 (see Table 1 for demographic characteristics). All patients provided written consent. None of the patients had received ECT, MST or transcranial magnetic stimulation (TMS) prior to the study. The flow of participants through each stage of the study is described in Fig. 1 according to Des Jarlais *et al.* (2004).

We decided to use a sample comprising 10 patients from our previously published study (Kayser *et al.* 2011) plus 16 new patients. Thus, in our current study we report additional data from the first sample

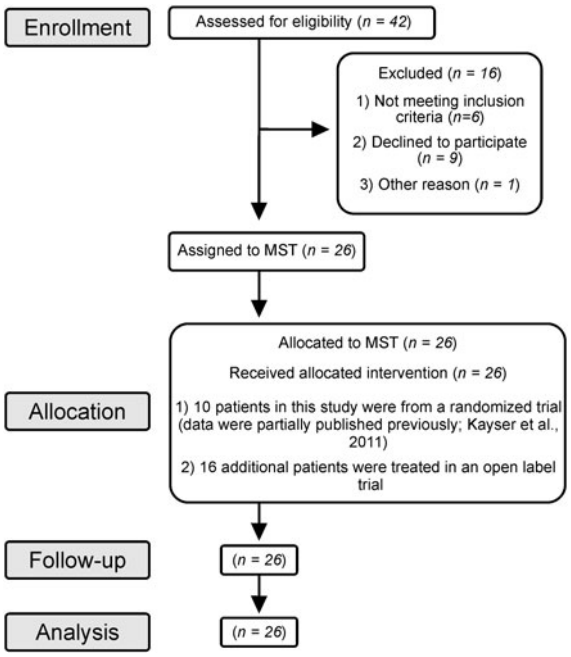

Fig. 1. Flow of participants through the study. Ten patients in this study were from a randomized trial (data were partially published previously; Kayser *et al.* 2011) and 16 additional patients were treated in an open-label trial. MST, Magnetic seizure therapy.

(10 MST-treated patients), namely extended neuropsychological measurements, more clinical data and FDG-PET images. The two samples differed only in the point of randomization to the condition (only the first 10 patients were randomized to receive either MST or ECT). Apart from this difference, the samples underwent the same study protocol (e.g. inclusion criteria, severity of depression, number of treatments, regular assessments). We stopped the second treatment arm (10 ECT-treated patients) because after 10 patients had been treated with either MST or ECT, we observed similar antidepressant efficacy (Kayser *et al.* 2011). On account of the significantly better side-effect profile for MST, we decided to continue the study as an open-label, single-arm study.

TRD was defined according to Thase & Rush (1997) as patients unresponsive to two different antidepressant treatments of adequate length and dosage during the current episode of depression (TRD at stage 2). For study inclusion, a minimum score of 20 on the 28-item Hamilton Depression Rating Scale (HAMD-28) was required. Exclusion criteria included psychotic features, current clinically significant neurological disorders or medical illness affecting brain function, ferromagnetic material in the head or implanted medical devices. Participants demonstrating current or unstable remitted substance abuse (aside from nicotine), severe personality disorder or a history or diagnosis of clinically relevant cardiac disease were also excluded. A stable drug regimen (including antidepressants, neuroleptics, mood stabilizers and hypnotics) for a minimum of 4 weeks prior to study entry and during the course of the study was required. All patients met diagnostic criteria for major depressive disorder (MDD) or bipolar disorder (BP) according to an unstructured clinical interview based on DSM-IV to develop the diagnoses (APA, 1994). All patients were suffering from a current depressive episode. Patients were recruited by referral from their psychiatrist or from out-patient and in-patient clinics at the Department of Psychiatry and Psychotherapy at the University Hospital of Bonn, or through advertisement.

Clinical outcomes

Psychiatric assessments of depressive symptoms were performed 7 days before starting MST treatment (baseline) and again 7 days after completing the MST course of up to 12 treatments (post-treatment). Patients were classified after treatment as having met the criteria for response, non-response or remission. The primary outcome measure was defined as an antidepressant response ($\geqslant$50% reduction in depression symptom severity) assessed by the HAMD-28 or HAMD-17 using structured interviews relative to baseline scores, or remission (HAMD-28 score $\leqslant$10; HAMD-17 score $\leqslant$8) (Hamilton, 1967). At baseline and post-treatment visits, secondary clinical outcome measures were determined using structured interviews and assessments that included the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979), the Beck Depression Inventory (BDI; Beck, 1987), the Hamilton Anxiety Scale (HAMA; Hamilton, 1976), the Global Assessment of Functioning Scale (GAF; Jones *et al.* 1995) and the 90-item Symptom Checklist (SCL-90; Franke, 1995). Clinically meaningful variations in psychopathology and psychological distress levels and social functioning were determined using the 36-item Short-Form Health Survey (SF-36; Ware & Sherbourne, 1992). The subscales are condensed into one score each for a physical and a mental health dimension. Additional information concerning side-effects of MST was obtained for each patient after each MST treatment using the Columbia ECT Subjective Side-Effects Schedule (CSSES; Devanand *et al.* 1995). Relapse among responders was evaluated using the HAMD-28 at 6 months at the latest (follow-up visit). Responders were advised to contact the study team immediately in case of deterioration prior to this scheduled visit. Relapse criteria were a 10-point increase in HAMD-28 score at follow-up

compared to post-treatment, and a minimum score of 16 on the HAMD-28 was required (Prudic *et al.* 2004).

Neuropsychological measurements

Standardized comprehensive neuropsychological testing in the form of 23 cognitive tests was conducted with 20 patients 7 days before treatment (baseline) and 7 days after MST treatment (post-treatment). We used alternate forms of tests at baseline and post-treatment, if available, as a precautionary measure to reduce learning effects (Benedict & Zgaljardic, 1998). The neuropsychological tests covered general level of performance and cognitive domains such as verbal and visual–spatial learning and memory (along with working memory), language, attention, visual perception and executive function. In addition, the general level of pretreatment verbal intellectual ability was estimated using the German-language Multiple Choice Vocabulary Intelligence Test-B (Mehrfachwahl-Wortschatz-Intelligenztest-B, MWT-B; Lehrl, 2005). The Mini-Mental State Examination (MMSE; Cockrell & Folstein, 1988) was used to screen for global cognitive status. The Verbal Learning and Memory Test (VLMT; Helmstaedter *et al.* 2001) and a German version of the Rey Auditory Verbal Learning Test (RAVLT), which measures declarative verbal memory, were used. The Rey Visual Design Learning Test (RVDLT; Rey, 1964) was included to measure visual–spatial learning and memory, along with the Rey–Osterrieth Complex Figure (ROCF; Bernstein & Waber, 1996) to test visual–spatial learning and memory and perceptual organization. In the VLMT and RVDLT, total learning and delayed free recall, in addition to recognition, were included. Working memory was assessed using two subtests, digit and visual memory span, from the revised Wechsler Memory Scale (WMS-R; Haerting *et al.* 2000). Language ability was assessed by two subtests from the German Wechsler Intelligence Test for Adults (HAWIE; Tewes, 1991): a verbal test (Wortschatztest) and finding similarities (Gemeinsamkeiten finden). Attention was examined with the d2 Attention and Burden Test (d2 Aufmerksamkeits-Belastungstest), for which the total performance score was used (Brickenkamp, 1962). Visual perception using the Hooper Visual Organization Test (VOT; Hooper, 1958) was assessed to test ability to visually integrate objects. According to Baddeley (1990), executive functions were assessed using phonological tasks and visuospatial tasks. Phonological tasks included the Stroop Colour–Word Interference Task (Baeumler, 1985), the Five-Point Test (FPT; Regard *et al.* 1982), the Trail Making Test Part B (TMT-B; Reitan, 1959) and formal-lexical and semantic-categorical verbal fluency. Visuospatial tasks involved the Regensburger Word Fluency Test (RWT; Aschenbrenner *et al.* 2000) to measure divergent thinking as a thought process to generate creative ideas by exploring many possible solutions. The Trail Making Test Part A (TMT-A; Reitan, 1959) enabled evaluation of processing speed.

MST procedure, seizure monitoring and anaesthesia

We used a MagPro MST device (MagVenture A/S, Denmark) with a biphasic waveform, a pulse width of 0.2 ms, and voltage 3× ~230 V/16 A (maximum power consumption 11 kVA). A twin coil was set bilaterally at the vertex. Vertex stimulation was chosen because of experience from prior MST studies suggesting reliable seizure induction (Kayser *et al.* 2011; Fitzgerald *et al.* 2013) and the known failure of seizure induction by frontal stimulation (Kirov *et al.* 2008). The stimulation amplitude was fixed at 100%, stimulation frequency at 100 Hz and the duration of stimulation was up to 10 s. The seizure threshold of each patient was measured with an initial dose titration procedure at their first session. Stimulation was provided by successively increasing the pulses per train (starting at 50 pulses and increasing each time by 50 pulses). A delay interval of at least 30 s took place between these stimulation trains of increasing pulses. The first train, which induced a tonic–clonic seizure, was defined as identifiable motor activity of at least 10 s according to Hoy *et al.* (2013) and was regarded as the individual patient's seizure threshold. For further treatment, stimulation was provided by using 6× pulses per train higher than the seizure threshold (i.e. high-dose MST or HD-MST; Spellman *et al.* 2008) or at the maximum output capacity of the device (1000 pulses at 100 Hz). The rationale for choosing these stimulation parameters arose from the results of prior MST studies using similar stimulation regimes that resulted in good tolerability and safety of treatments (Kirov *et al.* 2008; Kayser *et al.* 2011; Fitzgerald *et al.* 2013). Treatments were applied twice a week. Additional MST treatments and/or ECT treatments were offered in the event of a non-response to at least 12 MST treatments. Patients were offered a maximum of 22 treatments (only taken up by one patient) and they did not continue treatment following response. Seven patients underwent additional ECT treatments 14 days after the end of the regular MST treatment course (up to 12 treatments). Treatments were carried out by a psychiatrist.

Electroencephalograms (EEGs) were obtained at each treatment using a Thymatron IV (Somatics LLC, USA) with left and right frontal (Fp1 and Fp2) leads. EEGs were rated with respect to whether an adequate seizure was induced using standard methods (Krystal *et al.* 1992, 1993; Nobler *et al.* 1993; Weiner & Krystal,

1993a, *b*; McCall *et al.* 1996; Azuma *et al.* 2007*b*). Ictal and peri-ictal EEG parameters included polyspike phase duration (from end of stimulation until start of slow wave activity), polyspike phase maximal amplitude (mean maximum amplitude), slow wave phase duration (until seizure termination), slow wave phase maximum amplitude, regularity (including global seizure strength and clonic slow wave phase, 0–6), stereotypy (global seizure patterning, 0–3, with maximum stereotypy between progression from low-amplitude chaotic polyspike activity to high-amplitude slow wave activity, occurring without bold alterability in amplitude), and post-ictal suppression (degree of post-ictal suppression, 0–3). All of these parameters were rated manually for each patient and for each treatment. Anaesthesia was initiated by intravenous propofol (124 ± 30 mg). Muscle relaxation was obtained by succinylcholine (72 ± 14 mg). Patients were ventilated with 100% oxygen by a facemask. Physiological monitoring included pulse oximetry, non-invasive blood pressure measurements and electrocardiograms (ECGs).

FDG-PET: acquisition and analysis

FDG-PET scans were performed at baseline (7 to 14 days before MST) and post-treatment. In addition, two post-treatment time points were differentiated: <7 days = short-term ($n = 3$ patients; 4.7 ± 2 days) and $\geqslant 7$ days = long-term ($n = 9$ patients; 30.3 ± 14 days). Therefore, both short- and long-term metabolic changes as a result of MST were analysed. Furthermore, results of the responders ($n = 9$ patients) and non-responders ($n = 3$ patients) were compared. Imaging was performed on a PET/computed tomography (CT) scanner in three-dimensional (3D) mode (Biograph; Siemens Medical Solutions, Inc., USA) with a 15.8-cm axial field of view and an in-plane spatial resolution of 4.6 mm according to the European Association of Nuclear Medicine's guidelines for brain imaging using FDG-PET (Bartenstein *et al.* 2002). Blood glucose measured before tracer injection was 87 ± 11 mg/dl. The patients were positioned comfortably in a quiet, dimly lit room with eyes closed several minutes before FDG administration and during the uptake phase of FDG. Emission scans were performed 30 min after intravenous injection of ~200 MBq of FDG. The acquisition time was 20 min. Low-dose CT for attenuation correction was performed within 1 min before PET with the patient in the same position. The acquisition parameters for dual-detector helical CT were 130 kV, 16 mAs, 3 mm slice thickness, and a pitch of 1.2. Twenty-four slices were acquired (field of view = 332.8, 256 × 256 matrix, voxel size = 1.33 × 1.33 × 5.00 mm^3). PET scans were acquired starting 30 min after intravenous injection of 209 ± 40 MBq of FDG. Statistical Parametric Mapping Version 5 (SPM5, Wellcome Trust Centre for Neuroimaging, University College London, UK) was used for statistical analysis. PET images were smoothed using a 3-mm full-width at half-maximum (FWHM) Gaussian kernel with time as the covariate of interest, and scaled to correct for whole-brain mean differences. Differences in voxel-wise regional cerebral metabolic rate of glucose consumption (rCMRGlc) were assessed using a general linear model (GLM) in SPM5. Corrections were made for non-sphericity due to inherent spatial autocorrelation. The resulting t map was thresholded at $p < 0.05$ (two-tailed) after family-wise error (FWE) correction and overlaid on SPM5 single subject's T1-weighted magnetic resonance imaging (MRI) brain template. A volume of interest (VOI) analysis was conducted in individual space using PMOD version 3.1 (PMOD Group, Switzerland). A set of macro-anatomically defined regions was drawn onto each individual brain, covering it entirely. The readout of regional FDG uptake was referenced to the entire brain uptake and then submitted for statistical analysis.

Statistical analysis

SPSS version 17.0 for Windows (SPSS Inc., USA) was used for statistical analyses. For statistical evaluation of demographic and clinical variables, we used a χ^2 test for non-parametric analysis and paired t tests for parametric analysis to compare values as changes from baseline to post-treatment. The z scores were calculated based on comparisons with published age-corrected normative data to score patients' neuropsychological performance relative to the healthy population. Findings resulting in z scores below one standard deviation (S.D.) were classified as below average, z scores of above 1 S.D. as above average. Significance in change between baseline and post-treatment was analysed using paired t tests for each neuropsychological test. A Bonferroni–Holm correction (Holm, 1979) was applied to reduce the type I error rate due to multiple testing in clinical, neuropsychological and imaging results. Stepwise regression was calculated to examine the influence of possible contributing variables on cognitive development. The influence of several predictor variables [responder and non-responder (50% reduction criterion) measured by the HAMD-28, age and gender] on the dependent variable change score (score at baseline minus score at post-treatment) was analysed for each test. Repeated-measures ANOVAs were calculated comparing z scores at baseline and post-treatment for different domains of cognitive function. For all analyses the level of significance was set at 0.05. The effect size was calculated by clinical outcome measurements

using Cohen's *d* (Cohen, 1988) and defined as small (*d* = 0.2), medium (*d* = 0.5) and large (*d* ⩾ 0.8). To calculate the risk of side-effects of MST compared to ECT, the number needed to treat (NNT) was analysed (Laupacis *et al.* 1988). MST was defined as the new therapy and ECT served as the control therapy. We used VLMT values of the present study and the results of the Buschke Selective Reminding Test (SRT; Buschke, 1973) analysed in an ECT study (Sackeim *et al.* 2000*b*); VLMT and SRT count among the cognitive domains verbal learning and memory.

Ethical considerations

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Demographic and clinical results

Patients were diagnosed as having treatment-resistant MDD (17 patients) or BP (eight patients had BP-II and one BP-I) with a mean current depressive episode duration of 5 ± 6 years. There were no significant differences in demographic characteristics or severity of depression between responders and non-responders in baseline values. Patients' demographic characteristics are given in Table 1.

Overall, the sample showed significant improvement ($p < 0.001$) in scores on the HAMD-28 (see Fig. 2), HAMD-17, MADRS, BDI, HAMA, GAF and SCL-90 ($p < 0.028$), even when Bonferroni adjusted, but not on the SF-36 (see Table 2). Eighteen patients (69%) responded to MST as assessed by primary outcome measures (⩾50% reduction in depressive symptom severity on the HAMD-28/17). The mean HAMD-28 score declined from 28.2 ± 5 at baseline to 13.7 ± 9 post-treatment ($p < 0.001$), which was associated with a medium effect size measured using Cohen's *d*. Eight patients were classified as non-responders (see results in Table 2 and Fig. 2). Two-thirds of the responders (46.2% of the sample as a whole) met remission criteria of a HAMD-28 score < 10 or a score < 8 on the HAMD-17. All clinical outcome measures improved in responders but only a few improved in non-responders. The entire sample showed a significant reduction in anxiety symptoms as determined by the HAMA (Hamilton, 1976), with an average HAMA score of 9.9 ± 6, which is far below the cut-off for anxiety disorders in pharmacological studies. The HAMA results showed a greater anti-anxiety effect in responders compared to non-responders. The responders' scores for social functioning, measured by the GAF, changed from 'serious impairment' to 'mild impairment' whereas the non-responders' social functioning remained at 'seriously impaired'. Responders showed lower general psychopathology, and also lower physical and mental health scores on the SF-36. One patient suffered from migraines that were not associated with either MST or anaesthesia. Patients suffered from no additional subjective complaints (CSSES). A 100% adherence to MST and follow-up visits was shown by the patients. Of the 18 responders to MST, half of them had relapsed at or before the 6-month follow-up, mostly between the second and third months after the end of treatment (HAMD-28 score: 32 ± 4 at baseline, 10.5 ± 5 post-treatment and 26.5 ± 3 at follow-up).

Neuropsychological measurements

The results of the neuropsychological tests are presented in Fig. 3 and Table 3, and the results for each cognitive domain are presented in Fig. 4 and Table 3. The patients' baseline values were below average, except those for language, visual perception and RVDLT recognition. Significant improvement post-treatment was revealed in several cognitive domains: visual–spatial learning and memory (RVDLT total learning and recall and ROCF recall immediately and delayed), visual perception (VOT) and executive function (Stroop interference and RWT formal-lexical verbal fluency). Analysing the cognitive domains by ANOVA demonstrated significantly improved visual–spatial learning and memory and phonological tasks of executive function. For RVDLT total learning, ROCF recall delayed and TMT-B, a medium effect size as measured by Cohen's *d* was revealed, and for ROCF recall immediately, a large effect size. For the remaining neuropsychological measurements, small effect sizes were measured.

With regard to general level of performance, no signs of impairments were shown. For learning and memory, that is for the subtest RVDLT total learning and recall, and also for ROCF recall immediately and delayed, significant improvement occurred, even by ANOVA. In RVDLT total learning, ROCF recall immediately and delayed showed an improvement from below average to above average when assessed. Within the other subtests (VLMT total learning, recall and recognition, RVDLT and ROCF recognition, WMS digits backwards and WMS block span backwards), the recognition results remained the same. Values for language and attention were also unchanged. For visual perception, the paired *t* test (Bonferroni adjusted) revealed a small but significant

Table 2. *Clinical characteristics of patients*

	All patients ($n = 26$)				Responders ($n = 18$)				Non-responders ($n = 8$)		
Test	Baseline	Post-treatment	p value[a]	Cohen's d	Baseline	Post-treatment	p value[a]	Cohen's d	Baseline	Post-treatment	p value[a]
HAMD-28	28.8 (5)	13.7 (9)	< 0.001	0.7	28.2 (5)	8.3 (5)	< 0.001	0.9	31.8 (4)	24.3 (5)	0.003
HAMD-17	19.8 (6)	10.6 (5)	< 0.001	0.6	19.4 (6)	8.4 (6)	< 0.001	0.7	20.9 (6)	16.3 (5)	0.167
MADRS	29.7 (6)	13.7 (10)	< 0.001	0.7	28.0 (5)	8.1 (5)	< 0.001	0.9	33.4 (4)	24 (6)	0.014
BDI	36.1 (10)	23.0 (16)	< 0.001	0.4	33.5 (11)	17.0 (15)	0.001	0.5	39.9 (10)	35.7 (7)	0.156
HAMA	20.1 (5)	9.9 (6)	< 0.001	0.7	18.9 (4)	8.5 (5)	< 0.001	0.8	22.2 (6)	14.7 (5)	0.062
GAF	4.7 (1)	6.3 (1)	< 0.001	0.6	4.9 (0)	6.5 (1)	0.001	0.7	4.7 (1)	5.0 (0)	0.477
SCL-90	1.4 (1)	1 (1)	0.028	0.2	1.4 (1)	1.0 (1)	0.047	0.2	1.5 (1)	1.2 (1)	0.367
SF-36 mental health	20.3 (6)	17.5 (4)	0.172	0.3	23.3 (3)	14.3 (2)	0.507	0.9	21.9 (4)	21.3 (1)	0.858
SF-36 physical health	42.1 (12)	44.9 (10)	0.388	0.1	41.0 (13)	38.0 (1)	0.012	0.2	43.8 (11)	51.3 (8)	0.253

HAMD-28/17, 28/17-Item Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; BDI, Beck Depression Inventory; HAMA, Hamilton Anxiety Scale; GAF, Global Assessment of Functioning Scale; SCL-90, 90-item Symptom Checklist; SF-36, Short-Form Health Survey.

[a] p values compare the baseline values to post-treatment values using the Bonferroni–Holm correction.

Cohen's d was defined as small ($d = 0.2$), medium ($d = 0.5$) or large ($d \geqslant 0.8$). The level of significance was set at $p < 0.05$.

Data are given as mean (standard deviation).

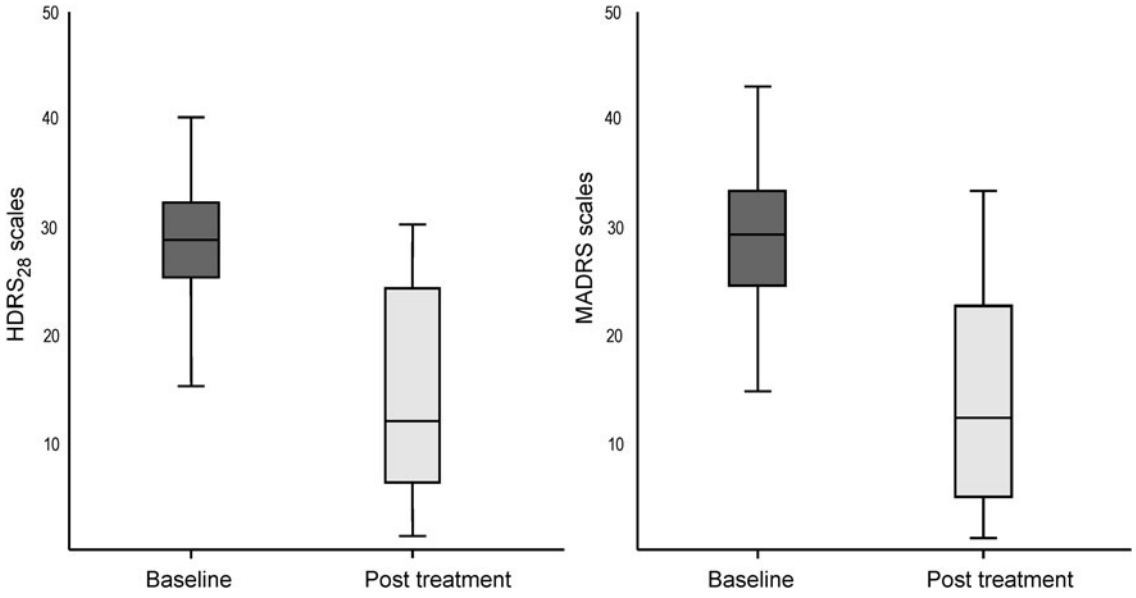

Fig. 2. Clinical outcome showing scores on the 28-item Hamilton Depression Rating Scale (HAMD-28) and the Montgomery–Åsberg Depression Rating Scale (MADRS). 95% confidence intervals (CIs) shown for depression rating scores at baseline and post-treatment.

improvement within the VOT. With regard to executive function, patients showed significant improvement in interference (Stroop). By contrast, decline in performance in verbal fluency was noted. Within the TMT-B the results improved from below average to average. Performances on the FPT, TMT-A and RWT semantic-categorical verbal fluency remained unchanged. Analysis of phonological tasks (Stroop, FPT, TMT-A and TMT-B) by ANOVA showed significant changes whereas visuospatial tasks (RWT formal-lexical verbal fluency and semantic-categorical verbal fluency) were not significantly different by ANOVA. However, a decline in performance of RWT formal-lexical verbal fluency was measured. Stepwise regression analyses revealed no relevant predictor variable [outcome (HAMD-28), age and gender] for change in values in each neuropsychological test. In some domains we observed cognitive improvement. This effect was not correlated with depressive symptoms, age or gender. Detailed results of the NNT analysis are presented in Table 4. In total, in the case of total learning and recall 5 patients and in the case of recognition 6.7 patients must be treated with MST to prevent one adverse event that would have occurred under ECT.

Seizure monitoring

Mean stimulation parameters were set at 650 ± 62 pulses per train, 6.5 ± 1 s stimulation duration, 100 Hz and 100% amplitude. Detailed seizure characteristics are shown in Table 5. The results were non-homogeneous as they were associated with large standard deviations, but ictal characteristics of seizure (e.g. duration of ictal phases, post-ictal suppression) were defined as adequate. No significant differences between responders and non-responders or between non-responders and relapse patients were detected. The duration of seizures was stable throughout the treatment course because of the stimulation parameters chosen. Seizures were successfully elicited in all patients for all treatments.

The treatment course contained an average of 12 treatments (mean 12.0 ± 3, range 10–22). After completing this study, additional MST treatments were given to four patients (16–22 treatments in total) who were non-responders to MST. Subsequent ECT treatments were given to seven non-responders. Five of the non-responders did not want to undergo further MST treatment and one non-responder declined subsequent ECT treatment. ECT treatments were administered using six times the seizure threshold for unilateral and three times for bilateral (BL) stimulation. However, ECT was also ineffective with respect to clinical outcome in the seven non-responders.

Metabolic effects of MST (PET)

Brain metabolic effects in 12 patients (age 46.2 ± 10 years, four females) were analysed by PET. SPM analysis demonstrated widespread changes in metabolic activity in cortical and subcortical areas as an effect of

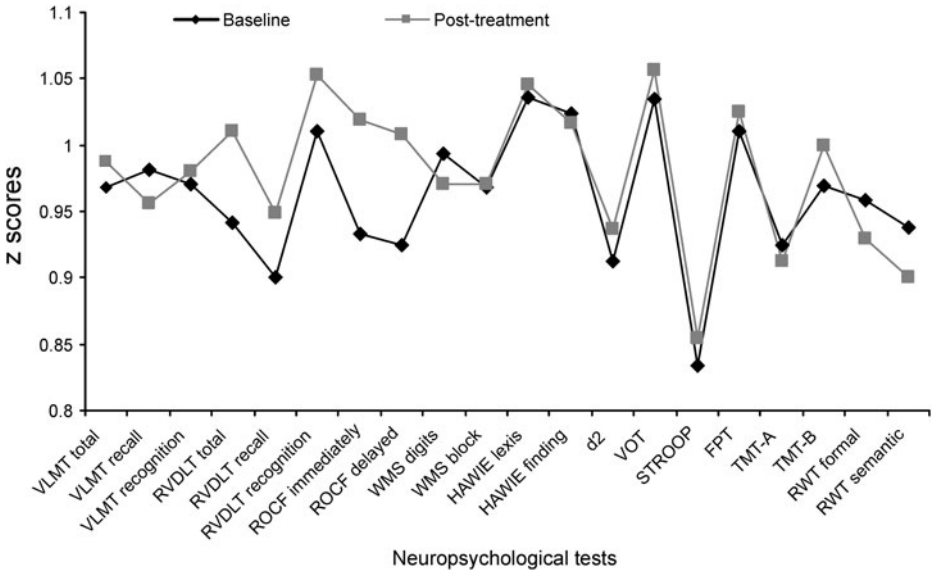

Fig. 3. Changes in neuropsychological tests, showing mean values of *z* scores in each neuropsychological test at baseline and post-treatment values. VLMT, Verbal Learning and Memory Test; VLMT total, total learning; RVDLT, Rey Visual Design Learning Test; RVDLT total, total learning; ROCF, Rey–Osterrieth Complex Figure Test; WMS, Wechsler Memory Scale; WMS digits, WMS digits backwards; WMS block, WMS block span backwards; HAWIE, Hamburg Wechsler Intelligence Test for Adults; HAWIE lexis, HAWIE lexis test; HAWIE finding, HAWIE finding similarities; d2, Attention and Burden Test, total corrected (minus errors); VOT, Hooper Visual Organization Test; FPT, Five-Point Test; TMT, Trail Making Test; RWT, Regensburger Word Fluency Test; RWT formal, RWT formal-lexical-verbal fluency; RWT semantic, RWT semantic-categorical-verbal fluency. Two-tailed paired *t* tests (Bonferroni adjusted) were used. **p* value < 0.05.

MST (see Table 6 and Fig. 5*a,b*). Areas of significant increase involved the frontal cortex bilaterally, whereas the left striatum (caudate nucleus and putamen) displayed a significant decrease. Focal changes detected by SPM in the left frontal cortex were accompanied by constant global rCMRGlc. No significant interhemispheric differences were detected for any region of interest (ROI). An average change in rCMRGlc of cerebral grey matter was −0.3% for the left and right hemispheres. The number of MST sessions did not correlate with any regional change in rCMRGlc. In the long-term subgroup, the right frontal (+0.8% *v.* −1.8%, $p = 0.02$), right putaminal (−0.8% *v.* −5.4%, $p = 0.01$) and right insular (+0.4% *v.* −4.0%, $p = 0.02$) rCMRGlc values were significantly differentiated between the responders and non-responders.

Discussion

This study demonstrates a clear antidepressant effect of MST in patients suffering from severe TRD. MST was also associated with lowered anxiety and an increase in quality of life in responders. No evidence of deterioration in cognition and memory was found. On the contrary, improvements in the cognitive domains of visual–spatial learning and memory, visual perception and executive function were demonstrated. This is of major importance because learning and memory are often impaired following ECT (Sackeim *et al.* 2000*b*). Furthermore, cognitive side-effects are among major causes for non-adherence to ECT (Bernstein *et al.* 1998; Fink, 2001). In addition, using FDG-PET we observed, as an effect of MST, changes in glucose metabolism in brain regions that have frequently been reported as dysfunctional in depression.

Approximately 70% of the patients responded to MST, despite having presented with very severe depression at baseline (APA, 2000). Only a few patients with severe depression have been treated in prior clinical trials solely with MST because MST is still in an early phase of clinical research. For this reason both the results published earlier and our results presented here have limitations in their generalization ability. Three case reports have suggested significant response after treatment (Kosel *et al.* 2003; Kayser *et al.* 2009). Two larger clinical studies have reported a 50% response rate in 20 patients (Kayser *et al.* 2011; Fitzgerald *et al.* 2013). In another study all 10 patients studied showed a significant reduction in depression symptoms (White *et al.* 2006). Thus, the response rates in this study were unexpected. This could possibly be attributed to several variables (e.g. severe depression, anxiety, suicidal risk and recurrent episodes) that were identified in our sample that may be

Table 3. *Neuropsychological assessment of cognitive changes from baseline to post-treatment*

Cognitive domain/neuropsychological test	Baseline	Post-treatment	Paired-samples t tests			ANOVA			Cohen's d
			t value	df	p value[a]	F value	p value	η^2	
General level of performance, mean (S.D.)									
MWT-B (IQ score)	106 (10)			19					
MMSE (Total score)	29.1 (1)	29.1 (1)	0.713	19	0.491				
Learning and memory						$F_{1,16} = 1.92$	0.121	0.520	
Verbal learning and memory						$F_{1,35} = 0.18$	0.839	0.010	
VLMT total learning	0.968 (8)	0.988 (12)	−0.718	19	0.481				0.2
VLMT recall	0.981 (7)	0.956 (14)	0.967	16	0.348				0.3
VLMT recognition	0.970 (8)	0.980 (14)	−0.280	19	0.782				0.1
Visual spatial learning and memory						$F_{1,21} = 4.92$	0.007	0.511	
RVDLT total learning	0.941 (11)	1.011 (13)	−3.396	14	0.004				0.6
RVDLT recall	0.900 (13)	0.949 (13)	−2.693	16	0.016				0.3
RVDLT recognition	1.010 (14)	1.053 (14)	−1.180	15	0.256				0.3
ROCF recall immediately	0.933 (10)	1.019 (10)	−3.087	14	0.008				0.8
ROCF recall delayed	0.924 (11)	1.008 (13)	−2.588	15	0.021				0.7
ROCF recognition	1.010 (14)	1.053 (14)	−1.180	15	0.617				
Working memory						$F_{1,38} = 0.55$	0.464	0.014	
WMS digits backwards	0.994 (10)	0.971 (8)	0.787	18	0.442				0.2
WMS block span backwards	0.968 (11)	0.971 (10)	−0.095	18	0.925				0.1
Language						$F_{1,14} = 0.62$	0.805	0.002	
HAWIE lexis test	1.036 (11)	1.046 (12)	0.743	15	0.469				0.1
HAWIE finding similarities	1.024 (10)	1.017 (10)	−0.542	15	0.595				0.1
Attention						$F_{1,38} = 1.12$	0.298	0.030	
d2 total corrected (minus errors)	0.912 (8)	0.937 (10)	−1.874	17	0.078				0.2
Visual perception						$F_{1,38} = 0.75$	0.394	0.020	
VOT	1.035 (8)	1.056 (8)	−2.291	17	0.035				0.2
Executive function						$F_{1,34} = 0.49$	0.490	0.014	
Phonological tasks						$F_{1,33} = 57.17$	< 0.001	0.839	0.3
Stroop interference	0.834 (7)	0.854 (8)	−3.662	18	0.002				
FPT non-verbal fluency	1.011 (7)	1.025 (7)	−0.578	18	0.571				0.1
TMT-A	0.924 (8)	0.913 (8)	1.043	18	0.311				0.1
TMT-B	0.969 (8)	1.000 (9)	−2.089	17	0.052				0.5

Visuospatial tasks					$F_{1,39} = 2.69$	0.109	0.065	0.2
RWT formal-lexical-verbal fluency	0.958 (8)	0.930 (9)	2.647	19	0.016			
RWT semantic-categorical-verbal fluency	0.938 (12)	0.901 (12)	1.311	19	0.206			0.3

MWT-B, German-language Multiple Choice Verbal Intelligence Test-B; MMSE, Mini-Mental State Examination; VLMT, Verbal Learning and Memory Test; RVDLT, Rey Visual Design Learning Test; ROCF, Rey–Osterrieth Complex Figure Test; WMS, Wechsler Memory Scale; HAWIE, Hamburg-Wechsler Intelligence Test for Adults; d2, Attention and Burden Test; VOT, Hooper Visual Organization Test; FPT; Five-Point Test; TMT, Trail Making Test; RWT, Regensburger Wortflüssigkeits-Test; df, degrees of freedom; S.D., standard deviation.
The analysis involved 20 magnetic seizure therapy (MST)-treated patients with treatment-resistant depression (TRD).
Two-tailed paired *t* tests with scores at baseline and post-treatment within each test as dependent variables.
[a] Bonferroni adjusted.
ANOVAs for repeated measures with the factor time (baseline in comparison to post-treatment) separate for cognitive functions.
Effect sizes were measured using Cohen's *d*.
z scores are presented as mean (S.D.); *z* scores of neuropsychological tests were based on published normative data.
Level of significance was set at $p < 0.05$.

associated with greater levels of treatment resistance (Schlaepfer *et al.* 2012) and 'anxious depression' (Trivedi *et al.* 2006). However, the current response rates were similar to response rates following BL-ECT as treatment for the usual resistance forms of depression (Sackeim *et al.* 1993; Husain *et al.* 2004). Both methods elicited secondary generalized seizure activity, which is thought to be responsible for the antidepressant efficacy (Sackeim, 1999). MST reliably induced generalized seizures in all treatments. Furthermore, the response rate in this study is of particular importance compared to other treatments for TRD (e.g. antidepressant medication, which has moderate rates of response of approximately 22–30%; Trivedi *et al.* 2006). Thus, a safe and highly effective alternative treatment strategy to usual treatments would be relevant for severely depressed patients. Moreover, of great clinical importance is the observation that in our patient sample anxiety occurred in the context of depression. In clinical practice, reducing anxiety is important because it correlates with patients' perceptions and quality of life (Mendlowicz & Stein, 2000). This was also reflected in patients' subjective reports in our study. The high relapse rates during the long observational period (6 months of follow-up) are in line with the ECT literature (Sackeim *et al.* 2001; Prudic *et al.* 2004). However, these relapse rates are lower compared with other treatments such as psychotherapy or pharmacotherapy in TRD, which are associated with relapse rates of up to 60% for first-episode patients and 90% for third-episode patients (APA, 2001). Given the experience in the field of maintenance ECT and our experience with MST, we suggest that maintenance MST could be as helpful in preventing relapses as maintenance ECT (Kimball *et al.* 2009). A further point of interest is that our non-responder, who subsequently underwent ECT treatments after MST, also did not benefit from the ECT treatments. To date, there are few studies that have focused on possible predictors for worse outcome to a single treatment in TRD patients. It is also not clear why some patients respond to a treatment, while others do not (Fava *et al.* 2001). Variables such as the number of previous episodes, duration of current depressive episode or severity of depression maintain TRD (Fava *et al.* 2001; Warden *et al.* 2007, 2009; Paykel, 2008; Fekadu *et al.* 2009; Schlaepfer *et al.* 2012). Thus, our sample fulfilled all of the above-mentioned criteria. However, the question remains regarding why patients respond neither to MST nor to subsequent ECT with the assumption that both MST and ECT are convulsive stimulation methods with similar clinical outcomes, as we have demonstrated in our results. Thus, response (or not) to a treatment could be based

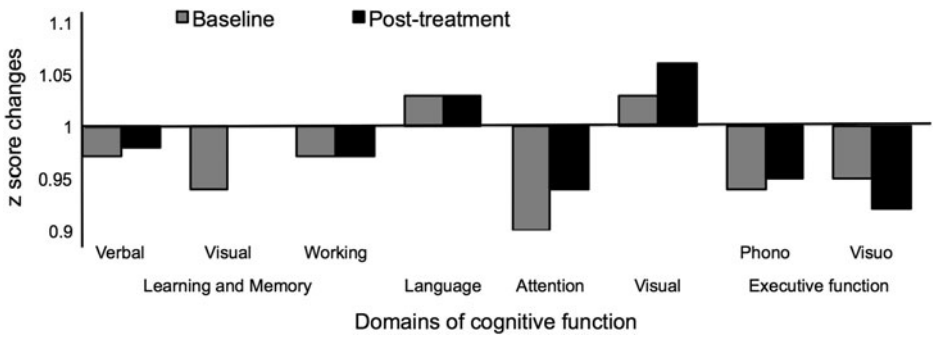

Fig. 4. Changes in cognitive domains. Mean *z* scores of the cognitive domains are presented at baseline and post-treatment including learning and memory [verbal learning and memory (Verbal), visual spatial learning and memory (Visual) and working memory (Working)], language, visual perception, attention and executive functions [phonological (Phono) and visuospatial (Visuo) tasks]. S.D., Standard deviation. Repeated-measures ANOVAs with the factor time (at baseline in comparison to post-treatment) separate for cognitive domains were used. **p* value < 0.05.

on similar mechanisms of action for both convulsive treatment methods.

In addition to efficacy, tolerability and cognitive safety were further focuses in this study. Using a large comprehensive battery of neuropsychological tests, essentially no negative effect on cognition following MST was found, except for a slight decline in performance in verbal fluency; the latter remained within the norm. We found a trend towards improvement in most cognitive functions, which may resemble reversal of baseline deficits in depressed patients (Austin *et al.* 2001). This is remarkable because we found no influence of improvement in depression to positive cognitive changes in analogy to prior studies (Rush *et al.* 1983; McNeely *et al.* 2008). Thus, MST did not result in a lack of cognitive impairment but rather in an improvement. Following ECT, autobiographical retrograde amnesia has been reported as a major concern (Rose *et al.* 2003; Sackeim *et al.* 2007), but its objective quantification remains problematic (Fraser *et al.* 2008; Kirwan *et al.* 2008; Semkovska & McLoughlin, 2010). In a recent study no impairment in autobiographical memory following MST was indicated (Fitzgerald *et al.* 2013). However, we used a hippocampal-dependent measure. The VLMT enables specific examination of hippocampal-dependent declarative memory including learning performance, in addition to more frontal lobe-associated encoding recall and recognition tasks, and in the neuropsychological tests assessing hippocampal function, no impairment was detected after MST. Moreover, frontal lobe dysfunction is currently thought to be involved in prevalent, persistent retrograde memory impairments following ECT (Sackeim, 2000; Sackeim *et al.* 2000*a*). These retrograde memory impairments following ECT might be related more to frontal lobe impairment than to medial temporal lobe activation changes, which is largely consistent with previous research proposing a limbic-cortical dysregulation model of depression (Mayberg, 2003). In line with these findings, we found an improvement in executive function across several tests that were associated with frontal lobe function, although our conclusions are limited because of the small sample size and trend-level findings. According to a systematic review from the British ECT Review Group (2003), differences in ECT modalities may explain variations in cognitive impairment; thus, BL-ECT produced the greatest impairments, along with treatment at least three times a week, and high-dose rather than low-dose ECT. However, BL-ECT is the most effective treatment in severe depression, with response rates varying from 65% (Sackeim & George, 2008) to 79% (Husain *et al.* 2004). By contrast, the current MST application was bilateral and the most effective stimulation parameters were high dose (HD-MST), but these led to no cognitive impairment (Kirov *et al.* 2008; Kayser *et al.* 2011). Given the present positive results for cognition and the robust antidepressant effect of MST, it would be appropriate to conduct MST without titration of the seizure threshold at the first treatment by immediately using HD-MST. Therefore, improvement in depression symptoms may occur earlier by applying MST more than two or three times a week. These characteristics of MST are reported to lead to high patient adherence to MST, which was also demonstrated in the current study.

Structural changes in major depression have been suggested in the prefrontal cortex (PFC), subgenual cingulate cortex (Cg25) (Ressler & Mayberg, 2007), amygdala, divisions of the thalamus, and striatum (Drevets, 2001). In particular, an increase in frontal activity in depression as found here has been reported frequently in ECT studies (Silfverskiold *et al.* 1986; Guze *et al.* 1991; Drevets, 2001; Nobler *et al.* 2001;

Table 4. *Number needed to treat (NNT) analyses*

Variable	Actual sample	Sackeim *et al.* (2000*b*)
Age (years), mean (S.D.)	47.7 (10.0)	55.0 (15.6)
Sex, *n* (% female)	50 (1.0)	13 (65.0)
Treatment method	BL-MST	BL-ECT
Duration of current episode (weeks), mean (S.D.)	257.9 (304.5)	42.1 (33.6)
Suicide ideation before treatment, *n* (%)	10 (1.0)[a]	5 (25.0)[a]
Suicide attempts before treatment, *n* (%)	25 (1.3)[a]	6 (30.0)
Number of included patients	20	20
Number of past medical treatment courses	15.3 (7.0)	6.5 (7.8)
HAMD-24 baseline, mean (S.D.)	24.5 (6.0)	29.2 (7.4)
Response rate (%)	65	65
Neuropsychological subtest	VLMT	SRT
Total learning, mean (S.D.)	−2.0 (12.5)[b]	−17.6 (22.5)[b]*
Recall, mean (S.D.)	+2.5 (10.8)[b]	−22.1 (32.9)[b]*
Recognition, mean (S.D.)	+1.0 (16.0)[b]	−15.0 (24.8)[b]*
Therapy defined for NNT analysis	New	Control
NNT total learning		
Risk of outcome	0	0.2
Absolute risk reduction	0.2	
Relative risk	0	
Relative risk reduction	1	
NNT	5 (95% CI 2.6 to 78.3)	
NNT recall		
Risk of outcome	0	0.2
Absolute risk reduction	0.2	
Relative risk	0	
Relative risk reduction	1	
NNT	5 (95% CI 1.28 to 38.72)	
NNT recognition		
Risk of outcome	0	0.15
Absolute risk reduction	0.15	
Relative risk	0	
Relative risk reduction	1	
NNT	6.7 (95% CI − 2.22 to 32.22)	

HAMD-24, 24-Item Hamilton Depression Rating Scale; BL-MST; bilateral magnetic seizure therapy; BL-ECT, bilateral electroconvulsive therapy; VLMT, Verbal Learning and Memory Test; SRT, Buschke Selective Reminding Test (VLMT and SRT count among the cognitive domains 'verbal learning and memory'); S.D., standard deviation; CI, confidence interval.

NNT analyses were performed to calculate the risk of side-effects of MST as a new therapy compared to ECT as treatment as usual.

[a] Indicates a score of ≥3 on the HAMD suicidal item.

[b] Mean (S.D.) for the percentage change from baseline to post-treatment.

Level of significance was set at 0.05 (*$p < 0.05$).

Awata *et al.* 2002; Takano *et al.* 2007) and in a recently published imaging study using MST (Hoy *et al.* 2013). Thus, our results are in line with these reported data and are also concordant with the hypothesis that depression arises from limbic-cortical dysregulation (Mayberg, 2003), showing relative regional changes in limbic areas (e.g. pallidum and striatum) and in cortical/subcortical areas (e.g. the frontal cortex and Cg25). Thus, the FDG-PET results were in line with our robust clinical findings.

As mentioned, MST is still in an early phase of clinical testing. Therefore, current application of MST can only be justified as a method of last resort in severely compromised patients under non-randomized and non-blinded conditions, both of which limit the generalizability of our results. Larger randomized and blinded clinical trials validating the efficacy of MST are warranted. An optimal study design would be a double-blind, cross-over design involving a comparison of treatments for severe depression in

Table 5. *Seizure characteristics as assessed with EEGs of responders, non-responders and relapsed patients*

Variable	All patients ($n = 26$)	Responders ($n = 18$)	Non-responders ($n = 8$)	p value (responder *v.* non-responder)	Relapse ($n = 9$)	p value (non-responder *v.* relapse)
Polyspike phase						
Duration (s)	13.4 (6)	0.9	13.2 (4)	0.72	12.8 (6)	0.90
Amplitude (μV)	3549 (1258)	0.43	3712 (1000)	0.12	3379 (965)	0.43
Slow wave phase						
Duration (s)	6.3 (4)	0.91	6.1 (3)	0.72	5.9 (3)	0.91
Amplitude (μV)	1923 (585)	0.57	2106 (679)	0.30	1722 (397)	0.57
Global pattern						
Total seizure duration (s)	19.95 (9)	20.17 (10)	19.33 (7)	0.72	21.98 (12)	0.52
Regularity (0–6)	3.6 (1)	0.68	3.7 (1)	0.96	3.7 (1)	0.68
Stereotypy (0–3)	1.7 (1)	0.94	1.7 (1)	0.65	1.8 (0)	0.94
Post-ictal suppression (0–3)	2.2 (0)	2.4 (1)	2.1 (0)	0.35	2.1 (0)	0.99

EEG, Electroencephalogram.

Ictal and peri-ictal EEG parameters were compared using a paired t test and manually rated in each patient and each treatment. Polyspike phase duration was defined as time from end of stimulation to beginning of slow wave activity; slow wave phase duration occurred until seizure termination; amplitudes were maximum amplitudes. Global seizure pattern was rated with respect to stereotypy: highest stereotypy (3) was rated when activity proceeded from low amplitude chaotic polyspike activity to high amplitude slow wave without a major change in amplitude; regularity describes slow wave activity; post-ictal suppression was rated from 0 (minimally suppressed) to 3 (very flat with sudden ending).

Data are presented as mean (standard deviation).

pharmacologically treated and ECT-treated groups. In addition, new studies should consider whether including a sham condition is ethically justified, as the lack of a sham-controlled group is a major limitation of this study, as with other published studies. However, we consider that placebo effects did not play a major role in these truly depressed patients as it is known that the probability of eliciting a placebo response decreases with treatment resistance at baseline (Schatzberg & Kraemer, 2000).

Identifying markers to predict response to MST may result in better selection of patients and enable such patients to benefit from MST at an earlier stage. In addition, in future research the influence of different classes of medication at different doses should be included. In cases of a relapse, maintenance MST could be helpful, as has been shown for ECT (Kimball *et al.* 2009). Appropriate funding in large multi-centre studies may be useful to replicate clinical efficacy and to identify further characteristics of MST, including more imaging results, cognition studies, EEGs and modes of action. It is also important to improve MST devices for use in physicians' offices and hospitals. Finally, the problematic history of ECT in terms of public opinion should not be forgotten. In our 10 years' experience with applying MST in a framework of clinical studies, we had the impression that MST is associated with a far lower degree of stigma than is ECT. Thus, standardized use of MST would allow TRD patients to receive an effective treatment at an earlier phase of the disease.

Furthermore, potential practice effects, which alone can improve performance, should be excluded by using alternate forms of any of the neuropsychological tests. A sham-controlled group could also be implemented. Thus, practice effects could be limited if neuropsychological tests were used at two different time points within weeks (baseline and post-treatment) (McCaffrey *et al.* 2000). Although we did not measure improvement on all neuropsychological tests, improvements should be equal if repeated testing results in practice effects (Parsons *et al.* 2006). Several tests applied have been found to have negligible practice effects (e.g. measuring language, working memory, executive functions and attention) (Dikmen *et al.* 1999; Wilson *et al.* 2000). Certain characteristics of patients are thought to be potential factors in advancing the incidence of practice effects, such as younger participants (< 39 years), as indicated by better baseline

Table 6. *FDG-PET imaging: results of VOI-based analysis*

Region	rCMRGlc			% Change		
	Baseline ($n = 12$)	Post-treatment ($n = 12$)	p value[a]	Short-term ($n = 3$)	Long-term ($n = 9$)	p value[b]
Left superior frontal gyrus (F1)	32.7 (1.1)	32.6 (1.2)	0.05	−1.8	0.3	0.03
Right superior frontal gyrus (F1)	32.7 (1.1)	32.7 (1.1)	0.8	−1.4	0.3	0.04
Left medial frontal gyrus (F2)	35.3 (1.4)	35.4 (1.3)	0.8	−1.8	0.9	0.04
Right medial frontal gyrus (F2)	34.2 (1.4)	34.3 (1.5)	0.7	−1.8	1.1	0.04
Left orbital prefrontal cortex	31.7 (1.0)	31.8 (1.0)	0.7	−1.8	0.9	0.04
Right orbital prefrontal cortex	31.6 (1.2)	31.6 (0.9)	0.9	−1.8	1.1	0.04
Left inferior frontal gyrus (F3)-pt	35.6 (1.4)	35.3 (1.3)	0.3	−2.1	1.1	N.S.
Right inferior frontal gyrus (F3)-pt	36.1 (1.9)	35.8 (1.9)	0.3	−1.2	0.2	N.S.
Left inferior frontal gyrus (F3)-pop	35.8 (1.8)	35.9 (1.5)	0.9	−2.1	1.1	N.S.
Right inferior frontal gyrus (F3)-pop	35.6 (2.2)	35.5 (2.0)	0.8	−1.2	0.2	N.S.
Left anterior cingulate cortex	34.2 (1.3)	34.3 (1.2)	0.8	−0.5	0.5	N.S.
Right anterior cingulate cortex	34.7 (1.7)	34.5 (1.3)	0.5	−1.9	0.0	N.S.
Left subgenual cingulate cortex	30.8 (1.6)	30.2 (1.8)	0.06	−2.0	−1.9	N.S.
Right subgenual cingulate cortex	30.9 (1.8)	31.0 (1.9)	0.8	0.6	0.4	N.S.
Left lateral parietal cortex	33.5 (1.2)	33.5 (1.1)	1.0	−1.2	0.4	N.S.
Right lateral parietal cortex	33.7 (1.4)	33.8 (1.3)	0.8	−0.3	0.4	N.S.
Left lateral temporal cortex	33.0 (1.2)	32.9 (1.2)	1.0	−0.9	0.2	N.S.
Right lateral temporal cortex	32.9 (1.4)	32.9 (1.2)	0.9	−0.3	0.0	N.S.
Left occipital cortex	36.1 (2.5)	36.1 (1.8)	0.9	1.7	0.0	N.S.
Right occipital cortex	36.4 (2.6)	36.6 (2.7)	0.7	2.5	0.3	N.S.
Left hippocampus	30.1 (0.8)	29.8 (1.3)	0.2	−2.2	−1.5	N.S.
Right hippocampus	30.2 (1.1)	30.0 (1.0)	0.5	−1.2	−1.8	N.S.
Left putamen	39.7 (3.5)	39.0 (3.3)	0.04	−2.2	−1.5	N.S.
Right putamen	39.6 (3.8)	38.8 (3.2)	0.08	−1.2	−1.8	N.S.
Left caudate nucleus	34.8 (2.9)	34.2 (2.5)	0.04	−0.5	−2.0	N.S.
Right caudate nucleus	34.6 (3.0)	34.2 (2.8)	0.08	−0.5	−1.2	N.S.
Left accumbens nucleus	36.5 (3.1)	35.8 (2.9)	0.03	0.5	−0.9	−2.0
Right accumbens nucleus	35.8 (2.9)	35.6 (2.8)	0.5	2.7	−0.2	−0.8
Left amygdala	27.2 (1.5)	27.0 (1.2)	0.4	0.5	−1.0	N.S.
Right amygdala	27.3 (1.8)	27.5 (1.5)	0.3	2.7	0.4	N.S.
Left thalamus	32.5 (2.1)	32.1 (2.3)	0.1	−1.3	−1.3	N.S.
Right thalamus	31.8 (2.0)	31.7 (2.3)	0.6	0.4	−0.7	N.S.

FDG-PET, [^{18}F]-Fluorodeoxyglucose positron emission tomography; rCMRGlc, regional cerebral metabolic rate of glucose consumption; VOI, volume of interest; pt, pars triangularis; pop, pars opercularis; N.S., non-significant.

The average radioactivity concentration of the entire brain was normalized to 30 ml/min/100 g tissue.

[a] Significance levels resulting from a two-sided paired t test.

[b] Significance levels resulting from a one-sided two-sample t test.

Bonferroni–Holmes correction for multiple comparisons were conducted.

Data are given as mean (± standard deviation).

performance (Dikmen *et al.* 1999). However, our sample was composed of higher-aged patients who mostly perform below average at baseline, with the result that, in general, practice effects did not occur. Finally, we cannot ignore the possibility of the involvement of practice effects in some neuropsychological tests. However, for the above-mentioned reasons, we assume that the influence is subsidiary. Thus, practice effects alone do not explain our results. Despite these limitations, this current study is an important step towards demonstrating the efficacy and cognitive safety of MST.

Overall, we were able to confirm the data of MST published by others (Lisanby *et al.* 2003; Fitzgerald *et al.* 2013) and reported previously by our group (Kayser *et al.* 2009; Kayser *et al.* 2011). The results of this study indicate once again that MST is an effective and safe (cognitively) alternative treatment method for TRD.

(*a*)

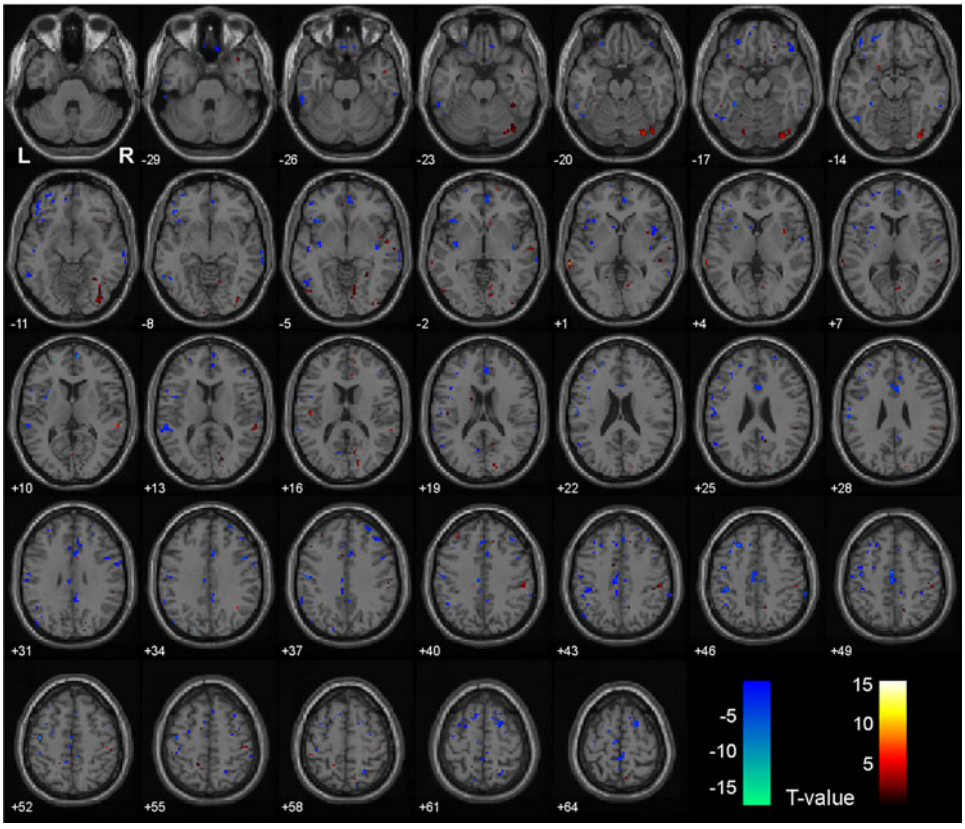

Fig. 5. [^{18}F]-Fluorodeoxyglucose positron emission tomography (FDG-PET) analysis of (*a*) short-term (<7 days) and (*b*) long-term (⩾7 days) metabolic changes. Shown are series of axial sections demonstrating the SPM5 analyses of voxel-wise paired *t* tests ($p = 0.05$) comparing FDG-PET images performed before the start of magnetic seizure therapy (MST) treatment (baseline) and after the MST treatment course was completed (post-treatment). Increases are displayed in the red and yellow portions of the colour scales and decreases in the blue portions. L and R denote the first planes left and right respectively. Images underwent proportional scaling to the global mean and correction for non-sphericity.

Acknowledgements

This investigator-initiated study was funded in part (funding of the MST device) by a grant from MagVenture A/S Inc. to T.E.S. The sponsor had no influence on the design or conduct of the study, on the collection, management, analysis and interpretation of the data, or on the preparation, review or approval of the manuscript. T.E.S. has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. We thank the patients and their relatives for participating in this study.

Declaration of Interest

S.K. has received support for lectures and a grant from MagVenture A/S Inc. R.H. has received support from a German Research Foundation (DFG) grant (HU1302/2-2) and a Starting Independent Researcher Grant provided jointly by the Ministry of Innovation, Science, Research and Technology of the German State of North Rhine-Westphalia (MIWFT) and the University of Bonn. M.S. has received honoraria for lectures from Covidien Germany (Neustadt/Donau, Germany). The rest of the authors report no conflicts of interest.

References

APA (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association: Washington, DC.

APA (2000). *Handbook of Psychiatric Measures*. American Psychiatric Association: Washington, DC.

APA (2001). *The Practice of ECT: Recommendations for Treatment, Training and Privileging*. American Psychiatric Association: Washington, DC.

Aschenbrenner A, Tucha O, Lange K (eds) (2000). *RWT Regensburger Wortflüssigkeits-Test. Handanweisung*. Hogrefe: Göttingen.

(*b*)

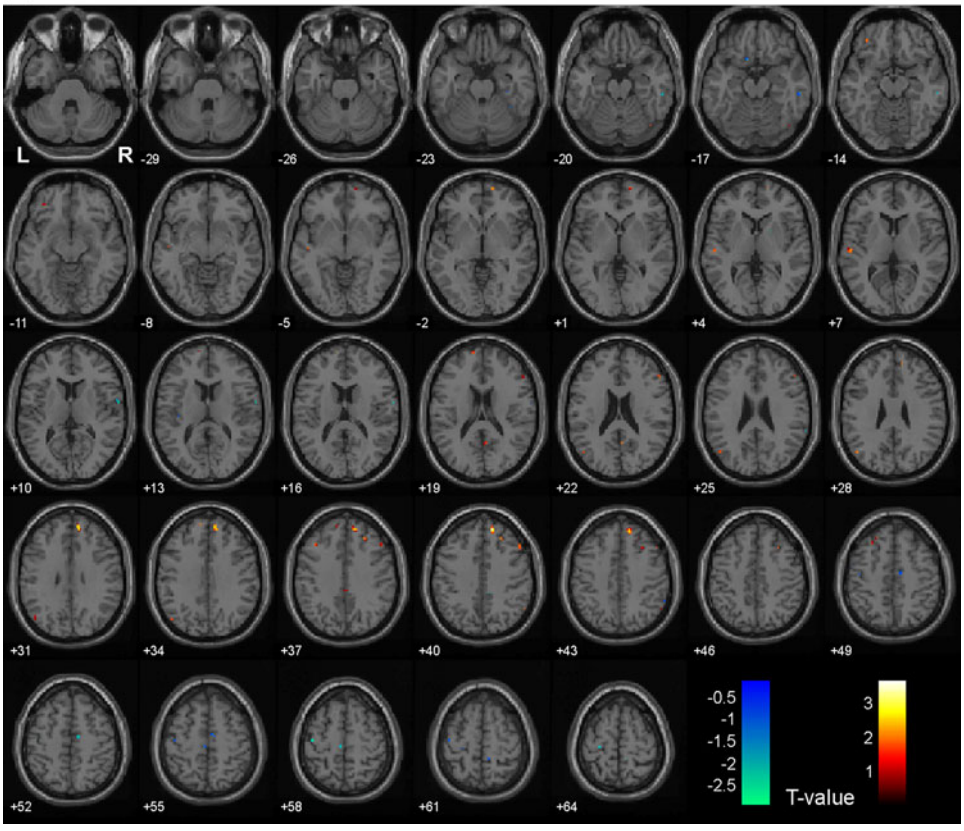

Fig. 5. (continued)

Austin MP, Mitchell P, Goodwin GM (2001). Cognitive deficits in depression: possible implications for functional neuropathology. *British Journal of Psychiatry* **178**, 200–206.

Awata S, Konno M, Kawashima R, Suzuki K, Sato T, Matsuoka H, Fukuda H, Sato M (2002). Changes in regional cerebral blood flow abnormalities in late-life depression following response to electroconvulsive therapy. *Psychiatry and Clinical Neurosciences* **56**, 31–40.

Azuma H, Fujita A, Otsuki K, Nakano Y, Kamao T, Nakamura C, Fujioi J, Otake H, Nishigaki M, Suzuki M, Kataoka M, Matsuzawa T, Sonoda M, Nakaaki S, Murata Y, Akechi T, Furukawa TA (2007*a*). Ictal electroencephalographic correlates of posttreatment neuropsychological changes in electroconvulsive therapy: a hypothesis-generation study. *Journal of ECT* **23**, 163–168.

Azuma H, Fujita A, Sato K, Arahata K, Otsuki K, Hori M, Mochida Y, Uchida M, Yamada T, Akechi T, Furukawa TA (2007*b*). Postictal suppression correlates with therapeutic efficacy for depression in bilateral sine and pulse wave electroconvulsive therapy. *Psychiatry and Clinical Neurosciences* **61**, 168–173.

Baddeley AD (1990). *Human Memory: Theory and Practice*. Lawrence Erlbaum Associates: London.

Baeumler G (ed.) (1985). *Farbe-Wort-Interferenztest* (*FWIT*) *nach J.R. Stroop*. Hogrefe: Göttingen.

Bartenstein P, Asenbaum S, Catafau A, Halldin C, Pilowski L, Pupi A, Tatsch K; European Association of Nuclear Medicine (2002). European Association of Nuclear Medicine procedure guidelines for brain imaging using [(18)F]FDG. *European Journal of Nuclear Medicine and Molecular Imaging* **29**, 43–48.

Beck A (ed.) (1987). *Beck Depression Inventory: Manual*. Psychological Corporation: San Antonio, TX.

Benedict RH, Zgaljardic DJ (1998). Practice effects during repeated administrations of memory tests with and without alternate forms. *Journal of Clinical and Experimental Neuropsychology* **20**, 339–352.

Bernstein HJ, Beale MD, Berns C, Kellner CH (1998). Patients attitude about ECT after treatment. *Annals of General Psychiatry* **28**, 524–527.

Bernstein JH, Waber DP (1996). *Developmental Scoring System for the Rey-Osterrieth Complex Figure: Professional Manual*. Psychological Assessment Resources: Odessa, FL.

Bertolote JM, Fleischmann A, De Leo D, Wasserman D (2004). Psychiatric diagnoses and suicide: revisiting the evidence. *Crisis* **25**, 147–155.

Brickenkamp R (ed.) (1962). *d2. Aufmerksamkeits-Belastungs-Test*. Hogrefe: Göttingen.

Buschke H (1973). Selective reminding for analysis of memory and learning. *Journal of Verbal Learning and Verbal Behavior* **12**, 543–550.

Cockrell JR, Folstein MF (1988). Mini-Mental State Examination (MMSE). *Psychopharmacology Bulletin* **24**, 689–692.

Cohen J (1988). *Statistical Power Analysis for the Behavioral Sciences*. Lawrence Erlbaum Associates: Hillsdale, NJ.

Des Jarlais DC, Lyles C, Crepaz N (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. *American Journal of Public Health* **94**, 361–366.

Devanand DP, Fitzsimons L, Prudic J, Sackeim HA (1995). Subjective side effects during electroconvulsive therapy. *Convulsive Therapy* **11**, 232–240.

Dikmen SS, Heaton RK, Grant I, Temkin NR (1999). Test-retest reliability and practice effects of expanded Halstead-Reitan Neuropsychological Test Battery. *Journal of the International Neuropsychological Society* **5**, 346–356.

Drevets WC (2001). Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Current Opinion in Neurobiology* **11**, 240–249.

Fava GA, Ruini C, Mangelli L (2001). Patients with depression can be taught how to improve recovery. *British Medical Journal* **322**, 1428.

Fekadu A, Wooderson SC, Markopoulo K, Donaldson C, Papadopoulos A, Cleare AJ (2009). What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. *Journal of Affective Disorders* **116**, 4–11.

Fink M (2001). Convulsive therapy: a review of the first 55 years. *Journal of Affective Disorders* **63**, 1–15.

Fitzgerald PB, Hoy KE, Herring SE, Clinton AM, Downey G, Daskalakis ZJ (2013). Pilot study of the clinical and cognitive effects of high-frequency magnetic seizure therapy in major depressive disorder. *Depression and Anxiety* **30**, 129–136.

Franke G (1995). *SCL-90-R. The Symptom Checklist of Derogatis Revised. German Version* [in German]. Beltz: Göttingen.

Fraser LM, O'Carroll RE, Ebmeier KP (2008). The effect of electroconvulsive therapy on autobiographical memory: a systematic review. *Journal of ECT* **24**, 10–17.

Grunhaus L, Hirschman S, Dolberg OT, Schreiber S, Dannon PN (2001). Coadministration of melatonin and fluoxetine does not improve the 3-month outcome following ECT. *Journal of ECT* **17**, 124–128.

Guze BH, Baxter Jr. LR, Schwartz JM, Szuba MP, Liston EH (1991). Electroconvulsive therapy and brain glucose metabolism. *Convulsive Therapy* **7**, 15–19.

Haerting C, Markowitsch HJ, Neufeld H, Calabrese P, Deisinger K, Kessler J (eds) (2000). *WMS-R. Wechsler Memory Scale – Revised* [German adaptation]. Huber: Bern.

Hamilton M (1967). Development of a rating scale for primary depressive illness. *British Journal of Social Psychology* **6**, 278–296.

Hamilton M (ed.) (1976). *HAMA. Hamilton Anxiety Scale*. National Institute of Mental Health: Rockville, MD.

Helmstaedter C, Lendt M, Lux S (eds) (2001). *VLMT. Verbaler Lern- und Merkfähigkeitstest*. Beltz: Göttingen.

Holm S (1979). A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics* **6**, 65–70.

Hooper HE (ed.) (1958). *The Hooper Visual Organization Test*. Western Psychological Services: Beverly Hills, CA.

Hoy KE, Thomson RH, Cherk M, Yap KS, Daskalakis ZJ, Fitzgerald PB (2013). Effect of magnetic seizure therapy on regional brain glucose metabolism in major depression. *Journal of Psychiatric Research* **211**, 169–175.

Husain MM, Rush AJ, Fink M, Knapp R, Petrides G, Rummans T, Biggs MM, O'Connor K, Rasmussen K, Litle M, Zhao W, Bernstein HJ, Smith G, Mueller M, McClintock SM, Bailine SH, Kellner CH (2004). Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for Research in ECT (CORE) report. *Journal of Clinical Psychiatry* **65**, 485–491.

Jones SH, Thornicroft G, Coffey M, Dunn G (1995). A brief mental health outcome scale: reliability and validity of the Global Assessment of Functioning (GAF). *British Journal of Psychiatry* **166**, 654–659.

Kayser S, Bewernick B, Axmacher N, Schlaepfer TE (2009). Magnetic seizure therapy of treatment-resistant depression in a patient with bipolar disorder. *Journal of ECT* **25**, 137–140.

Kayser S, Bewernick BH, Grubert C, Hadrysiewicz BL, Axmacher N, Schlaepfer TE (2011). Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression. *Journal of Psychiatric Research* **45**, 569–576.

Kimball JN, Rosenquist PB, Dunn A, McCall V (2009). Prediction of antidepressant response in both 2.25 × threshold RUL and fixed high dose RUL ECT. *Journal of Affective Disorders* **112**, 85–91.

Kirov G, Ebmeier KP, Scott AI, Atkins M, Khalid N, Carrick L, Stanfield A, O'Carroll RE, Husain MM, Lisanby SH (2008). Quick recovery of orientation after magnetic seizure therapy for major depressive disorder. *British Journal of Psychiatry* **193**, 152–155.

Kirwan CB, Bayley PJ, Galvan VV, Squire LR (2008). Detailed recollection of remote autobiographical memory after damage to the medial temporal lobe. *Proceedings of the National Academy of Sciences USA* **105**, 2676–2680.

Kosel M, Frick C, Lisanby SH, Fisch HU, Schlaepfer TE (2003). Magnetic seizure therapy improves mood in refractory major depression. *Neuropsychopharmacology* **28**, 2045–2048.

Krystal AD, Weiner RD, Coffey CE, Smith P, Arias R, Moffett E (1992). EEG evidence of more 'intense' seizure activity with bilateral ECT. *Biological Psychiatry* **31**, 617–621.

Krystal AD, Weiner RD, McCall WV, Shelp FE, Arias R, Smith P (1993). The effects of ECT stimulus dose and electrode placement on the ictal electroencephalogram: an intraindividual crossover study. *Biological Psychiatry* **34**, 759–767.

Krystal AD, West M, Prado R, Greenside H, Zoldi S, Weiner RD (2000). EEG effects of ECT: implications for rTMS. *Depression and Anxiety* **12**, 157–165.

Laupacis A, Sackett DL, Roberts RS (1988). An assessment of clinically useful measures of the consequences of treatment. *New England Journal of Medicine* **318**, 1728–1733.

Lehrl S (2005). *MWT-B. Mehrfachwahl-Wortschatz-Intelligenztest*. Spitta Verlag: Balingen.

Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, Gilmer W, Marangell LB, Aaronson S, Daskalakis ZJ, Canterbury R, Richelson E, Sackeim HA, George MS (2009). Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology* **34**, 522–534.

Lisanby SH, Luber B, Schlaepfer TE, Sackeim HA (2003). Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy. *Neuropsychopharmacology* **28**, 1852–1865.

Lisanby SH, Maddox JH, Prudic J, Devanand DP, Sackeim HA (2000). The effects of electroconvulsive therapy on memory of autobiographical and public events. *Archives of General Psychiatry* **57**, 581–590.

Lisanby SH, Schlaepfer TE, Fisch HU, Sackeim HA (2001). Magnetic seizure therapy of major depression. *Archives of General Psychiatry* **58**, 303–305.

Mayberg HS (2003). Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *British Medical Bulletin* **65**, 193–207.

McCaffrey RJ, Duff K, Westervelt HJ (2000). *Practitioner's Guide to Evaluating Change with Intellectual Assessment Instruments*. Kluwer Academic/Plenum Press: New York.

McCall WV, Robinette GD, Hardesty D (1996). Relationship of seizure morphology to the convulsive threshold. *Convulsive Therapy* **12**, 147–151.

McNeely HE, Mayberg HS, Lozano AM, Kennedy SH (2008). Neuropsychological impact of Cg25 deep brain stimulation for treatment-resistant depression: preliminary results over 12 months. *Journal of Nervous and Mental Disease* **196**, 405–410.

Mendlowicz MV, Stein MB (2000). Quality of life in individuals with anxiety disorders. *American Journal of Psychiatry* **157**, 669–682.

Montgomery Jr. EB, Gale JT (2008). Mechanisms of action of deep brain stimulation (DBS). *Neuroscience and Biobehavioral Reviews* **32**, 388–407.

Montgomery SA, Åsberg M (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* **134**, 382–389.

Nobler MS, Oquendo MA, Kegeles LS, Malone KM, Campbell CC, Sackeim HA, Mann JJ (2001). Decreased regional brain metabolism after ECT. *American Journal of Psychiatry* **158**, 305–308.

Nobler MS, Sackeim HA, Solomou M, Luber B, Devanand DP, Prudic J (1993). EEG manifestations during ECT: effects of electrode placement and stimulus intensity. *Biological Psychiatry* **34**, 321–330.

Ottosson JO, Max Fink M (eds) (2004). *Ethics in Electroconvulsive Therapy*. Brunner-Routledge: New York.

Parsons TD, Tucker KA, Hall CD, Robertson WT, Eron JJ, Fried MW, Robertson KR (2006). Neurocognitive functioning and HAART in HIV and hepatitis C virus co-infection. *Acquired Immune Deficiency Syndrome* **20**, 1591–1595.

Paykel ES (2008). Partial remission, residual symptoms, and relapse in depression. *Dialogues in Clinical Neuroscience* **10**, 431–437.

Petrides G, Fink M, Husain MM, Knapp RG, Rush AJ, Mueller M, Rummans TA, O'Connor KM, Rasmussen Jr. KG, Bernstein HJ, Biggs M, Bailine SH, Kellner CH (2001). ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. *Journal of ECT* **17**, 244–253.

Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA (2004). Effectiveness of electroconvulsive therapy in community settings. *Biological Psychiatry* **55**, 301–312.

Regard M, Strauss E, Knapp P (eds) (1982). *Der Fuenf-Punkt Test*. Department of Neurology, University Hospital: Zurich.

Reitan RM (ed.) (1959). *Trail Making Test*. Indiana University Medical Center: Indianapolis, IN.

Ressler KJ, Mayberg HS (2007). Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. *Nature Neuroscience* **10**, 1116–1124.

Rey A (ed.) (1964). *L'Examen Clinique en Psychologie*. Presse Universitaire de France: Paris.

Rose D, Fleischmann P, Wykes T, Leese M, Bindman J (2003). Patients' perspectives on electroconvulsive therapy: systematic review. *British Medical Journal* 326, 1363.

Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, Ritz L, Biggs MM, Warden D, Luther JF, Shores-Wilson K, Niederehe G, Fava M (2006). Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *New England Journal of Medicine* **354**, 1231–1242.

Rush AJ, Weissenburger J, Vinson DB, Giles DE (1983). Neuropsychological dysfunctions in unipolar nonpsychotic major depressions. *Journal of Affective Disorders* **5**, 281–287.

Sackeim HA (1999). The anticonvulsant hypothesis of the mechanisms of action of ECT: current status. *Journal of ECT* **15**, 5–26.

Sackeim HA (2000). Memory and ECT: from polarization to reconciliation. *Journal of ECT* **16**, 87–96.

Sackeim HA, George MS (2008). Brain stimulation – basic, translational and clinical research in neuromodulation: why a new journal? *Brain Stimulation* **1**, 4–6.

Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, Greenberg RM, Crowe RR, Cooper TB, Prudic J (2001). Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *Journal of the American Medical Association* **285**, 1299–1307.

Sackeim HA, Luber B, Moeller JR, Prudic J, Devanand DP, Nobler MS (2000*a*). Electrophysiological correlates of the adverse cognitive effects of electroconvulsive therapy. *Journal of ECT* **16**, 110–120.

Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM (1993). Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *New England Journal of Medicine* **328**, 839–846.

Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Fitzsimons L, Moody BJ, Clark J (2000*b*). A

prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Archives of General Psychiatry* **57**, 425–434.

Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M (2007). The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology* **32**, 244–254.

Schatzberg AF, Kraemer HC (2000). Use of placebo control groups in evaluating efficacy of treatment of unipolar major depression. *Biological Psychiatry* **47**, 736–744.

Schlaepfer TE, Agren H, Monteleone P, Gasto C, Pitchot W, Rouillon F, Nutt DJ, Kasper S (2012). The hidden third: improving outcome in treatment-resistant depression. *Journal of Psychopharmacology* **26**, 587–602.

Semkovska M, McLoughlin DM (2010). Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. *Biological Psychiatry* **68**, 568–577.

Silfverskiold P, Gustafson L, Risberg J, Rosen I (1986). Acute and late effects of electroconvulsive therapy. Clinical outcome, regional cerebral blood flow, and electroencephalogram. *Annals of the New York Academy of Sciences* **462**, 236–248.

Spellman T, McClintock SM, Terrace H, Luber B, Husain MM, Lisanby SH (2008). Differential effects of high-dose magnetic seizure therapy and electroconvulsive shock on cognitive function. *Biological Psychiatry* **63**, 1163–1170.

Takano H, Motohashi N, Uema T, Ogawa K, Ohnishi T, Nishikawa M, Kashima H, Matsuda H (2007). Changes in regional cerebral blood flow during acute electroconvulsive therapy in patients with depression: positron emission tomographic study. *British Journal of Psychiatry* **190**, 63–68.

Tewes U (ed.) (1991). *HAWIE-R. Hamburg-Wechsler Intelligenztest fuer Erwachsene*. Huber: Bern.

Thase ME, Rush AJ (1997). When at first you don't succeed: sequential strategies for antidepressant nonresponders. *Journal of Clinical Psychiatry* **58** (Suppl. 13), 23–29.

Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *American Journal of Psychiatry* **163**, 28–40.

UK ECT Review Group (2003). Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* **361**, 799–808.

Warden D, Rush AJ, Wisniewski SR, Lesser IM, Kornstein SG, Balasubramani GK, Thase ME, Preskorn SH, Nierenberg AA, Young EA, Shores-Wilson K, Trivedi MH (2009). What predicts attrition in second step medication treatments for depression? A STAR*D report. *International Journal of Neuropsychopharmacology* **12**, 459–473.

Warden D, Trivedi MH, Wisniewski SR, Davis L, Nierenberg AA, Gaynes BN, Zisook S, Hollon SD, Balasubramani GK, Howland R, Fava M, Stewart JW, Rush AJ (2007). Predictors of attrition during initial (citalopram) treatment for depression: a STAR*D report. *American Journal of Psychiatry* **164**, 1189–1197.

Ware Jr. JE, Sherbourne CD (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* **30**, 473–483.

Weiner RD, Krystal AD (eds) (1993*a*). *EEG Monitoring and Management of Electrically Induced Seizures*. American Psychiatric Press: Washington, DC.

Weiner RD, Krystal AD (eds) (1993*b*). *EEG Monitoring of ECT Seizures*. American Psychiatric Press: Washington, DC.

White PF, Amos Q, Zhang Y, Stool L, Husain MM, Thornton L, Downing M, McClintock S, Lisanby SH (2006). Anesthetic considerations for magnetic seizure therapy: a novel therapy for severe depression. *Anesthesia and Analgesia* **103**, 76–80.

Wilson BA, Watson PC, Baddeley AD, Emslie H, Evans JJ (2000). Improvement or simply practice? The effects of twenty repeated assessments on people with and without brain injury. *Journal of the International Neuropsychological Society* **6**, 469–479.