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An overview on clinical aspects in magnetic seizure therapy

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Abstract The aim of the presented work is to provide an overview on the clinical data of the promising convulsive brain stimulation technique, the magnetic seizure therapy (MST). We review the advantages and disadvantages of MST, focusing on rationale, development and current treatment procedure. We also provide a summary of the current literature including clinical trials and case reports found in the PubMed database. Furthermore, we consider effectiveness and side effects, emphasizing on crucial issues to be addressed for a better understanding of this potential new treatment option in treatment-resistant depression (TRD).

Keywords MST · Severe depression · Cognition · Antidepressant therapy · Magnetics

Introduction

There is a growing interest in non-pharmacological strategies to treat major depressive disorder (MDD) given the fact that a high percentage of patients do not respond sufficiently to pharmacotherapy and psychotherapy (Adli et al. 2006; Rush et al. 2006). Electroconvulsive therapy (ECT) has been used as a treatment for psychiatric disorders since the 1930s and its effectiveness in particular in severe depression has been largely investigated (Group 2003; Pagnin et al. 2004). For a long time, it has been the only established therapy for patients with severe or treatment-resistant depression (TRD). ECT has been regarded as the most effective treatment for severe depression, with remission rates ranging from 50 to 75 % (Husain et al. 2004; Sackeim et al. 2000). During ECT, an electric current is passed briefly through the brain, via electrodes applied to the scalp, to induce a generalized seizure. There exist a few theories of ECT's mechanism of action. The monoamine neurotransmitter theory suggests that it affects several targets in the CNS system restoring neuromodulating systems such as serotonergic, adrenergic, and dopaminergic systems whereas the neuroendocrine theory supports a release of hypothalamic or pituitary hormones, including prolactin, thyroid-stimulating hormone, adrenocorticotropic hormone, and endorphins and restores the dysregulation of the hypothalamic–pituitary–adrenal axis. The anticonvulsant theory postulates that ECT's efficacy is a result of the anticonvulsant nature of the treatment. The neurotrophic theory suggests that ECT may have a positive effect by inducing neurogenesis and increasing neurotrophic factors, rearranging neural networks as well as supporting cell growth (Wahlund and von Rosen 2003; Kellner et al. 2012).

While ECT is both, highly effective and commonly used, it can cause short-term disorientation immediately after treatment. This was reported in about 37 % of patients (Tzabazis et al. 2013). It can also lead to mostly short-term memory impairment for current events (anterograde amnesia) in about 41 % (Sackeim et al. 1987) and long-term memory impairment for past events (retrograde amnesia) (Sackeim 2000; Lisanby 2007). In addition, persistent deficits in autobiographical memory tests have been reported (Frasert et al. 2008). Nevertheless, little to no data exists of the exact frequency of each of these cognitive dysfunctions (Sackeim et al. 2007). Patients who reported

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persistent or permanent memory loss ranged from 29 to 55 % (Rose et al. 2003). These effects appear to be dose related and depend on electrode placement, possibly the type of electrical stimulus and patient characteristics. However, cognitive impairments have been highlighted as a particular concern by many patients, especially long-lasting retrograde amnesia for autobiographical events (Rose et al. 2003) and ECT should only be considered as a treatment option after careful evaluation of the individual risks and benefits. Additionally, there is a notable social stigma in using ECT coming from past claims of overuse or misuse in its early history, cultural fears regarding unintentional electrocution, and the electrocution punishment of state-sanctioned criminals (Payne and Prudic 2009). This may be the main reasons why ECT is so rarely used despite its great efficacy (Grundmann and Schneider 2013).

Magnetic seizure therapy (MST) was developed to be a more focal stimulation form of convulsive therapy in contrast to widespread stimulation in ECT (Lisanby et al. 2001b). Like ECT, MST is able to induce therapeutic seizures, but through the use of high frequency repetitive transcranial magnetic stimulation (rTMS) rather than a direct electrical current producing highly focal induced seizures (Hoy and Fitzgerald 2010). It targets a seizure induction in the prefrontal cortex and spares medial temporal structures (i.e., hippocampus), which are thought to be most involved in the development of cognitive side effects in ECT (Kosel et al. 2003; Lisanby et al. 2003a; Lisanby 2002; Moscrip et al. 2006). While rTMS has been investigated in its own right as an antidepressant technique, it has not yet shown equivalent efficacy in treating depression when compared to ECT, but its cognitive safety has been demonstrated (Lam et al. 2008; Eranti et al. 2007). Thus, MST probably is a novel therapeutic intervention combining the efficacy of ECT and the minimal cognitive side effect profile of rTMS (McClintock et al. 2011).

Rationale and development

Despite the great efficacy of ECT, negative cognitive side effects were common (Lisanby et al. 2000), so the research in the field of TRD focused on a treatment option with a better risk to benefit ratio (Lisanby 2007). Led by the aspects of ECT seizure induction that are believed to be therapeutic (focal frontal seizures) and those assumed to be related to cognitive side effects (medial temporal structures), the MST device was designed to reach a more specific therapeutic target. Based on the features of rTMS, MST was developed to use longer durations of stimulation with higher intensity and more frequency, resulting in a larger dose of magnetic stimulation that can produce therapeutic seizures resembling ECT (Lisanby et al. 2001b). Other than ECT's widespread electrical stimulation to the entire brain, magnetic stimulation avoids the impedance of the scalp and skull and is able to stimulate more localized regions of the superficial cerebral cortex (Rowny et al. 2009). It is therefore possible to control the induced electrical field and the resultant seizures more precisely in targeted regions of the brain.

In 1998, MST was introduced in non-human primates (Lisanby et al. 2001a), human studies started in 2000 (Lisanby et al. 2001b). In the course of the first human proof-of concept trial, one patient received a course of two MST treatments within a course of ECT (Lisanby et al. 2001b). The same group treated another patient successfully with a full course of 12 MST sessions (Kosel et al. 2003). MST was applied at 40–50 Hz at 100 % of machine output, because of the rTMS equipment available at that time. After this 50 Hz device did not induce seizures reliably, the MST technology advanced substantially in the late 2000s when two companies developed high-dose MST (HD-MST) devices capable of stimulating continuously at 100 Hz for up to 10 s. Those devices induced seizures more reliably (Spellman et al. 2008).

Current treatment procedure

Like ECT, a treatment course usually comprises a series of 8–12 sessions during 3–4 weeks. Patients are placed under general anesthetic and muscle relaxants are given to prevent muscle contractions (White et al. 2006). The use of a bite block, which is mandatory for patients receiving ECT, may not be necessary since there is no direct stimulation of the masseter muscle by shunted electric current, but is used nevertheless in most of the patients (Cretaz et al. 2015; White et al. 2006). Usage of earplugs is recommended by some study groups, because of the device's loud clicking noise (Cretaz et al. 2015).

The duration of motor seizure activity is commonly assessed using the standard cuff lower-limb technique. Electroencephalograms (EEGs) are obtained bilaterally with left and right frontal (Fp1 and Fp2) leads. EEG seizure duration is recorded and ictal and peri-ictal EEG parameters are used to rate (among other seizure characteristics) the postictal suppression as a marker that correlates with therapeutic efficacy (Perera et al. 2004; Krystal et al. 1995; Luber et al. 2000).

Outcome

Up to now, only about nine clinical trials and four case reports have been published since the first application of MST in the year 2000. Due to the small sample size, there

often was no stratification for medication, some authors did not mention the patient's medication and complementary therapies at all. The results given in the studies and the within-subject crossover design did not allow for calculations of effect sizes. Given the fact that MST is a new technique in a still experimental state, there is substantial variance in the study designs and protocols. Most of the trials used open-label study designs, no prospective randomization or compared to ECT in a within-subject crossover scheme. A summary of all the studies is given in Table 1.

Neurophysiological and seizure characteristics

Postictal suppression is a measure reported to predict response to ECT (Abbott et al. 2014; Sackeim 1999). Former studies suggested that greater ictal power and/or the presence of postictal EEG suppression are associated with superior antidepressant effects. In previous animal studies and some clinical studies in humans, MST showed less postictal suppression and less EEG amplitude compared to ECT-induced seizures.

In 2001 and 2003, Lisanby et al. found different patterns of EEG activity following ECT and MST (Lisanby et al. 2001a, b). They hypothesized that in MST, the electric fields induced within the brain were less intense and more confined to the superficial cortex so that the electric field and resultant seizures were more focal. They also found MST-induced seizures to be less robust, less propagated to deep brain structures (i.e., hippocampus), and had less postictal suppression. In 2006, the group of White et al. described lower amplitude and relative absence of postictal suppression after suprathreshold MST stimulation (White et al. 2006). Kirov et al. confirmed these differences after stimulation at 100 Hz. EEG characteristics during ECT were markedly different from the EEG recorded after MST (Kirov et al. 2008). In 2013, Fitzgerald et al. reported shorter motor seizures, a lesser amplitude in the ictal activity and much less postictal suppression. In some patients, ictal activity was not always apparent on the EEG despite a clear motor seizure (Fitzgerald et al. 2013).

In contrast to previous studies, two studies described similar EEG characteristics for the ECT and the MST group (Kayser et al. 2011, 2013). In the study of 2011, Kayser et al. reported that EEG characteristics were similar in both treatment groups, consisting of high-amplitude synchronized theta activity and equal postictal suppression. Nevertheless, in the MST group some patients showed delayed ictal EEG activity and shorter duration of motor and ictal activity (Kayser et al. 2011). In 2013, the authors found no significant differences in visible motor seizures and EEG activities between the two treatment groups, including postictal suppression (Kayser et al. 2013). Again, seizures lasted longer in patients receiving ECT as shown in another study (Soehle et al. 2014).

Antidepressant efficacy

Preliminary studies suggested that MST possesses clear antidepressant efficacy. White et al. compared the effectiveness of MST to that of ECT using the Hamilton Depression Rating Scale (HDRS). They reported a decrease in depression scores in both groups with ECT being more effective (mean reduction of 24 points vs. 18 points in MST, $p < 0.05$). In 2011, Kayser et al. reported the first randomized trial using a block design in 20 patients either treated with MST or ECT (TRD and bipolar depression) (Kayser et al. 2011). They found no significant difference in symptom reduction between the MST and the ECT group. Mean symptom reduction in ECT was 11.9 whereas mean reduction in MST was 12.4 in the HDRS ($p < 0.001$ for the whole group). Six patients out of ten in the MST group responded to the treatment (meaning a 50 % reduction of depressive symptom severity) and three achieved remission (HDRS <10). Four out of ten patients treated with ECT responded to the treatment and achieved remission, respectively.

Since then, a few open-label clinical trials have suggested a good antidepressant effect in about 40 more patients (Fitzgerald et al. 2013; Hoy et al. 2013; Kayser et al. 2015). In the study of Fitzgerald et al. in 2013, HDRS decreased from 26.7 to 19.2. Out of 13 patients, five patients met response criteria, of which two achieved remission at the end of the trial (Fitzgerald et al. 2013).

Cognitive effects

Research on the neurocognitive effects of MST has primarily focused on reorientation after treatment, global cognitive function, and anterograde and retrograde memory.

In 2003, Lisanby et al. were the first to focus on cognitive side effects of MST in contrast to ECT (Lisanby et al. 2003a). The 10 treated patients had fewer subjective side effects and recovered and oriented more quickly after MST relative to ECT. MST was also superior to ECT on measures of attention, retrograde amnesia, and category fluency. In a case report by Kosel et al. 2003, recovery time was found to be considerably shorter relative to unilateral low, moderate and high dosage ECT reported in the literature (Kosel et al. 2003). White et al. too, found lesser cognitive side effects and shorter recovery time in the group treated with MST (White et al. 2006).

After the development of high-dose MST (HD-MST) with higher frequencies at 100 Hz, Kirov and colleagues published the first report on shorter reorientation time after

Table 1 Summary of previously published clinical MST trials and case reports

References	Objective	Subjects	Study design	Medication/ psychotherapy	Sessions
Lisanby et al. (2003a)	Safety and feasibility of MST	$n = 10$ (MDD)	Randomized, within-subject crossover, double-masked trial MST vs. ECT	5/10 stable medication: 2 AD, 2 AP, 1 MS; psychotherapy: N/A	Two of the first four sessions MST, followed by ECT
Kosel et al. (2003)	Case report	$n = 1$ (TRD)	Open label	Stable medication: 0.5–1 mg risperidone, 100 mg carbamazepine; stable psychotherapy	12 treatments
White et al. (2006)	Anesthetic considerations for MST	$n = 20$ (MDD)	Double-blind, randomized trial MST vs. ECT	N/A	10–12 treatments during 3–4 weeks either MST or ECT
Kirov et al. (2008)	Reorientation time after MST	$n = 11$ (TRD or SZA)	Open label, crossover MST vs. ECT	Stable medication: 11 AD, 6 AP, 2 MS; psychotherapy: N/A	$n = 8$ already receiving ECT, one session substituted with MST; $n = 3$ MST before ECT
Hoy and Fitzgerald (2010)	First patient treated in Australia	$n = 1$ (TRD)	Open label	N/A	8 treatments
Kayser et al. (2011)	Antidepressant effect of MST in TRD	$n = 20$ (16 MDD, 3 BP-II, 1 BP-I)	Block design randomized MST vs. ECT	Stable medication: AD (number unknown); 18/20 stable psychotherapy	12 treatments, twice weekly, either MST or ECT
Fitzgerald et al. (2013) and Hoy et al. (2013)	Clinical and cognitive effects of MST and effect of MST on regional brain glucose metabolism	$n = 13$ (MDD)	Open label	12/13 stable medication: 3 TCA, 5 SSRNI, 1 SSRI, 3 AGO: psychotherapy: N/A	Mean of 12 treatments, maximum of 18 treatments; FDG-PET in $n = 10$ at baseline and 3-4 days after completion of the treatment
Kayser et al. (2013)	Cognition and seizure characteristics	$n = 7$ (6 MDD, 1 BP-II)	Open label, within-subject controlled crossover	Stable medication: AD (number unknown); 7/7 stable psychotherapy	12 sessions, ECT follow-up after non-response to MST
Noda et al. (2014)	Case report (adolescent)	$n = 1$ (BP-II)	Open label	No medication; psychotherapy: N/A	21 treatments
Soehle et al. (2014)	Recovery times in MST compared to ECT	$n = 20$ (TRD)	Open label, random allocation of patients to the ECT and MST groups	20/20 stable medication: AD; psychotherapy: N/A	10–12 sessions MST or ECT
Noda et al. (2015)	Case reports	$n = 2$ (BP-I)	Open label	N/A	6 and 23 treatments
Polster et al. (2015)	Acute memory retrieval after MST compared to ECT	$n = 30$ (20 MDD, 10 controls)	Open label	Stable medication: AD (number unknown); psychotherapy: N/A	10–12 sessions MST or ECT
Kayser et al. (2015)	Clinical, neuropsychological and metabolic effects of MST	$n = 26$ (TRD)	10 patients in the randomized trial (Kayser et al. 2011); 16 patients open label, 6-month follow-up FDG-PET of 12 patients	Stable medication: (number unknown); 24/26 stable psychotherapy	12 treatments

References	MST device/parameters	ECT device/parameters	Clinical effectiveness	Cognitive outcome	Neurophysiological outcome	Imaging
Lisanby et al. (2003a)	50 Hz modified Magstim; first session titration for ST, followed by sessions of 60 Hz at	Mecta 5000 Q, 0.5 ms PW; RUL 6× ST ($n = 9$); BL	N/A	Fewer cognitive side effects in MST	Shorter seizures in MST	N/A

Table 1 continued

References	MST device/parameters	ECT device/parameters	Clinical effectiveness	Cognitive outcome	Neurophysiological outcome	Imaging
	100 % output 0.5–8.0 s stimulus	2.5× ST ($n = 1$)				
Kosel et al. (2003)	50 Hz Magstim Super Rapid (custom-modified magnetic stimulator)	–	Remission	No cognitive side effects	Fast reorientation	SPECT: higher perfusion of the fronto-parietal cortex and the basal ganglia after the treatment compared to baseline
White et al. (2006)	50 Hz modified Magstim; titration for ST, followed by sessions at 1.3× ST (suprathreshold)	Mecta 5000 Q; 0.5 ms PW; BF 2.5× ST	Response[a] MST: 58 %	Faster reorientation in MST	Faster recovery in MST, compared to ECT	N/A
Kirov et al. (2008)	100 Hz modified Magstim; 0.34–0.4 ms PW; 10 s stimulus	Device: N/A; UL ($n = 3$); BL ($n = 7$); $n = 1$ no ECT	N/A	Faster reorientation after MST (7, 12 min) vs. ECT (26,35 min); $p < 0.005$	N/A	N/A
Hoy and Fitzgerald (2010)	100 Hz MagVenture MST MagPro	–	Response	No cognitive side effects	No disorientation	N/A
Kayser et al. (2011)	100 Hz MagVenture MST MagPro; 0.37 ms PW at 4–6 × ST	Thymatron IV; 0.5 ms PW; RUL 3× ST	MST: 60 % response, 30 % remission; ect: 40 % response	No cognitive side effects in both groups	N/A	N/A
Fitzgerald et al. (2013) and Hoy et al. (2013)	100 Hz MagVenture MST MagPro, 400 pulses above ST	N/A	38 % response, 15 % remission	Shorter reorientation after MST	N/A	FDG-PET: increased relative metabolism in the basal ganglia, orbitofrontal cortex, medial frontal cortex and dorsolateral prefrontal cortex
Kayser et al. (2013)	100 Hz MagVenture MST MagPro, 6× ST	Thymatron IV; 0.5 ms PW; RUL ($n = 5$) 6× ST; BL ($n = 2$) 3× ST	No patients fulfilled response or remission criteria	Faster reorientation after MST	Similar but shorter seizures in MST	N/A
Noda et al. (2014)	100 Hz MagVenture	–	Remission after 18 sessions	Minimal subjective cognitive impairment	Faster reorientation	N/A
Soehle et al. (2014)	100 Hz MagVenture MST MagPro	Thymatron IV, 0.5 ms PW; RUL ($n = 9$); BL ($n = 1$)	N/A	N/A	Shorter recovery time ($p < 0.5$) in MST	N/A
Noda et al. (2015)	100 Hz MagVenture	–	Switch to mania	N/A	N/A	N/A

Table 1 continued

References	MST device/parameters	ECT device/parameters	Clinical effectiveness	Cognitive outcome	Neurophysiological outcome	Imaging
Polster et al. (2015)	100 Hz MagVenture MST MagPro; 6 × ST	Thymatron IV, 0.5 PW; RUL ($n = 10$) 5× ST	N/A	Absence of disturbed delayed recall after MST compared to ECT	N/A	N/A
Kayser et al. (2015)	100 Hz MagVenture MST MagPro; 0.2 PW; 6 × ST	N/A	69 % response, 46 % remission; 50 % relapse in the follow-up	No cognitive side effects	N/A	Metabolic increase in the frontal cortex bilaterally and a decrease in the left striatum

AD antidepressant medication, *AGO* agomelatine, *AP* antipsychotic/neuroleptic medication, *BF* bifrontal electrodes, *BL* bitemporal electrodes, *BP-I* bipolar disorder, type I, *BP-II* bipolar disorder, type II, *ECT* electroconvulsive therapy, *FDG-PET* fluoro-D-glucose positron emission tomography, *HD-MST* high-dose magnetic seizure therapy, *MDD* major depressive disorder, *MS* mood stabilizer (medication), *MST* magnetic seizure therapy, *N/A* not available, *PW* pulse width, *(R)UL* (right) unilateral electrodes, *SSRI* selective serotonin reuptake inhibitor, *SSNRI* selective serotonin noradrenaline reuptake inhibitor, *SZ* seizure threshold, *SZA* schizoaffective disorder, *TCA* tricyclic antidepressant medication, *TRD* treatment-resistant depression

[a] Response was calculated according to Furukawa et al. (2005)

MST compared to ECT and less postictal confusion (Kirov et al. 2008). Some more studies have suggested a favorable cognitive side effects profile of MST compared to ECT. They found a better overall performance on neurocognitive tests after MST (Lisanby et al. 2003a), faster postictal reorientation time (Kirov et al. 2008; Kayser et al. 2011, 2013; White et al. 2006; Fitzgerald et al. 2013) and improvements in attention deficits, anterograde and retrograde amnesia (Lisanby et al. 2003a; Kayser et al. 2011, 2015) as well as an absence of disturbed delayed recall (Polster et al. 2015). Moreover, a trend towards improvement in most cognitive functions after MST treatment, which could be a sign of reversing the initial deficits due to the depression, was found (Kayser et al. 2015; Fitzgerald et al. 2013).

Summary

The results of this overview show that MST has the potential to become a cognitively safe and effective treatment in TRD. Earlier findings show that MST is as effective as ECT in inducing therapeutic seizures. In the most recent studies, similar EEG characteristics for both groups, MST and ECT, were reported. Further research on that matter suggests that MST and ECT are different in terms of their seizure propagation and focality, which may account for their respective differential neurocognitive effects.

Regarding the preliminary findings, MST might have an advantage on its cognitive side effects profile compared to ECT. Recovery and reorientation after MST sessions were faster and other cognitive functions, such as retrograde and anterograde memory, seem to be unaffected, too. MST is an effective treatment, with response rates ranging from 40 to 70 % and remission rates ranging from 15 to 46 % and promising to become as effective as ECT with reported remission rates of 50–75 % (Husain et al. 2004; Dierckx et al. 2012; Sackeim et al. 2000).

Taken together, this may provide considerable benefits to patients, such as better tolerability of the procedure and potential acceptability to patients. Because of the new technique and the perception as a new treatment option, it could be associated with a far lower degree of social stigma than ECT and a better treatment adherence to the procedure.

Nevertheless, experience with the technique so far is limited and further research is needed to improve the assessment of its potential effectiveness and expand the current understanding of its mechanisms. In the previous studies, there was substantial variability in the methods employed, i.e., MST stimulation parameters, patient's diagnoses, little standardization of anesthetic methods, the protocol for ECT control, and cognitive assessments. Samples sizes were small, limiting the generalization of the results, because of the low statistical power. The study design of the previous studies was almost always open label; there were no sufficient blinding and randomization.

There was no stratification for antidepressant medication or control of psychotherapy or complementary therapy given during the trials. Future research should focus on randomized controlled multi-center trials with larger samples, of double-blind design, and more consistent and homogeneous treatment protocols that will allow for better statistical power and an improved understanding of the technique.

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