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## Quick recovery of orientation after 100 Hz magnetic seizure therapy (MST) for major depressive disorder

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### Abstract

**Introduction**—Magnetic seizure therapy (MST), in which seizures are elicited with a high-frequency magnetic field, is under development as a new treatment for major depressive disorder. Its use may be justified if it produces the antidepressant effects of ECT, coupled with limited cognitive side effects. This pilot study reports shortened recovery times after MST compared with ECT as a preliminary step to evaluate the usefulness of a new 100Hz MST device.

**Methods**—We induced seizures with 100Hz magnetic transcranial stimulation in eleven patients with major depressive disorder during one session of a regular course of ECT. Recovery times after these MST and ECT induced seizures were compared.

**Results**—Seizures could be elicited in ten of the eleven patients. Stimulation over the vertex produced tonic-clonic activity on nine out of eleven occasions. Stimulation over the prefrontal midpoint elicited seizures on three out of seven occasions. The mean duration of magnetically induced seizures was 31.3 sec, ranging from 10–86 sec. All patients had an exceptionally quick recovery of orientation: mean of 7 min 12 sec (SD = 2 min 7 sec, range 4 min 20 sec – 9 min 41 sec). The recovery times were on average 15 min 35 sec shorter with MST than with ECT in the same patients (paired-samples t-test:  $p = 0.00009$ ). Patients reported feeling less confused after MST. Side effects were confined to myoclonic movements, associated with the use of etomidate.

**Conclusions**—The new 100 Hz magnetic stimulator elicits seizures in the majority of patients when administered over the vertex. MST was associated with shorter recovery times and less confusion following treatment. Subsequent work will be required to assess the safety and effectiveness of MST in the treatment of depression.

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## Introduction

Electroconvulsive therapy (ECT) is the most effective treatment for major depressive disorder (1,2). However, its use is restricted, mostly due to concerns about cognitive side effects (3). Modifications to the treatment procedure that could reduce the cognitive side effect burden are therefore of great clinical interest. Since the introduction of repetitive transcranial magnetic stimulation (rTMS), it was noticed that a rare side effect of this treatment was the induction of seizures, when rTMS was used at high frequencies, high intensities, or with long train durations. The possibility and safety of deliberately inducing seizures with repetitive magnetic fields was first tested in nonhuman primates (4-8). The first human subject received a course of four magnetic seizure therapy (MST) sessions in 2000, using 40 Hz at 100% intensity of the rTMS equipment available at that time (9). A second patient was successfully treated with a full course of MST with similar parameters (10). Both patients tolerated the treatments well and their depressions responded. Following this, ten depressed patients received two MST sessions each during a course of ECT, in a blinded, randomized within-subject cross-over trial. This time a custom-modified device capable of producing 50 Hz stimulation at a peak magnetic field of 1.2 Tesla was used. Acute side effects of MST were milder compared with ECT (11,12). Although seizures were induced in all patients, it was observed that in three patients the seizure threshold was at the maximum output of the device, highlighting the need for technological improvements in the equipment. Twenty depressed patients were treated with a full course of MST using the same 50 Hz MST device in 2003 (13). MST improved depression scores and patients demonstrated remarkably rapid reorientation with few side effects, though improvements were smaller than those seen in the simultaneously treated group of ECT patients (14). However, the maximum stimulation of 400 pulses per session was estimated to be on average only 1.3 times the magnetic seizure threshold, perhaps contributing to the suboptimal antidepressant efficacy, similar to some modes of ECT which are highly sensitive to dosage relative to seizure threshold (15). These early trials were a proof of principle that MST could induce therapeutic seizures in a clinical setting, but they also indicated the need for improved MST devices (as discussed in (16)). Since then, available MST technology has significantly advanced. A new prototype MST device (Magstim Company Limited) capable of stimulating continuously at 100 Hz at maximum stimulator output (1.2 Tesla at the coil surface) for up to 10 seconds became available for animal use in 2004. This device was used for the first time in 2004 in a study of rhesus monkeys (16). Since then, 275 MST sessions have been successfully performed in 11 rhesus monkeys. Seizures have been induced in all sessions, and 100 Hz MST still demonstrates fewer cognitive side effects in the monkey model than conventional electroconvulsive shock (17). A version of the 100 Hz MST device designed specifically for human use (called the Magstim Theta) became available in the middle of 2006. The current study was designed as a pilot to examine the feasibility of MST at 100Hz in patients, its safety and side effects, and MST recovery times compared with ECT.

## Patients and Methods

Eleven patients diagnosed with treatment resistant major depressive episodes in the context of either recurrent Major Depression, or Schizoaffective Disorders according to DSM-IV criteria, who had been referred for ECT, were enrolled in this pilot study. Demographic details are presented in Table 1. Patients were treated in Whitchurch Hospital, Cardiff, and the Royal Edinburgh Hospital. Eight of the patients were already receiving ECT, and one of their regular (twice weekly sessions) was substituted with MST. The remaining three patients received MST before ECT; two of these continued with ECT, the third decided against it. Local Research Ethics Committee approval was obtained at both centres and patients gave written informed consent following the approved protocols. In accordance with usual clinical practice of ECT delivery in the UK, antidepressant medication was not stopped during the treatment. Every

patient received at least one antidepressant, six were also taking one or more antipsychotics, and two patients (patients 5 and 10 in the table) were also taking sodium valproate.

### **Magnetic Seizure Therapy**

We used two custom-built Magstim Theta devices (Magstim Ltd, Whitland, Wales). This stimulator is capable of producing 100 Hz magnetic stimuli at 1.2 Tesla (at the centre of the coil) with a biphasic waveform with a pulse width of 340-400 $\mu$ s for up to 10 sec duration (i.e. a maximum of 1000 pulses). We used a round coil with an 80 mm average diameter (47 mm inside diameter, 115 mm outside diameter). For positioning of the coil we used standard 10-20 EEG positions. The middle of the coil was applied firmly to the head of the patients, and positioned over Cz for vertical, and Fz for frontal stimulation for up to 10 seconds. The direction of current induced in the brain was counter-clockwise. The inside of coils heats from 20 C $^{\circ}$  to 130 C $^{\circ}$  after 1000 pulses at 100% output stimulation; therefore coils were cooled down to 5-10 C $^{\circ}$  in a refrigerator prior to stimulation and were changed if a patient required re-stimulation. All treatments were given at 100 Hz frequency and at maximum stimulator output. When a patient was re-stimulated, we allowed at least 20 seconds between stimulations. Staff and patients wore ear protectors during MST.

### **Anaesthesia**

For anaesthesia we used intravenous (i.v.) etomidate (0.15 to 0.3 mg / kg) as it does not cause an increase in the seizure threshold and might even reduce it, reviewed in (18). Muscle relaxation was achieved with i.v. succinylcholine generally at a lower dose than that routinely used in ECT (0.5 to 1.0 mg/kg), as recommended for MST due to the faster recovery of patients (14).

### **Seizure monitoring**

Seizure duration during MST was measured from the start of MST stimulation to the termination of the observed seizure, cf. (12). EEG seizure expression was monitored via bilateral fronto-mastoid EEG using MRI-compatible plastic electrodes to prevent electrode heating during MST.

### **Orientation Assessment**

Recovery of orientation after MST/ECT was assessed by asking the patient for their name, date of birth, age, place, and day of the week. The point of orientation recovery was defined as the time when a patient was able to recall four of these five items.

## **Results**

The first treatment session with the new device took place in Cardiff in June 2006. The patient was a 35 year old female, who had already received 5 bi-temporal ECT treatments, administered at 195.8 mC. For MST, the coil was positioned over the vertex (C<sub>z</sub>). Stimulation with 250 pulses produced no seizure. She was re-stimulated 52 sec later with 500 pulses and had a visible motor seizure of 25 sec, EEG duration was approximately 21sec, but the endpoint was difficult to estimate as there was no post-ictal suppression (EEG trace available from the authors on request).

Orientation was recovered after 4 minutes 36 seconds. Immediately upon awakening, the patient achieved a Mini Mental State Examination score of 27/30 points. On the next day, the patient's score was at the pre-ECT level of 30 points. A battery of further cognitive tests that included tests for verbal and visual memory, verbal fluency and executive speed was also

administered and no relevant changes in performance from baseline were found (results not presented).

We have since treated ten further patients. In order to explore optimal parameters of stimulation for this new procedure, we applied different numbers of pulses and changed the positioning of the coil between  $C_z$  and  $F_z$ . The results for each patient and the corresponding settings for their ECTs are presented in Table 1.

Seizures were elicited in ten of the 11 patients. The one who did not fit was stimulated with only 600 pulses. Vertex stimulation appeared to be more effective in inducing seizure activity (Table 1; see patients number 3, 4, 6 and 8). The mean duration of successful seizures was 31.3 sec, range 9.5-86 sec.

Orientation was recovered much faster after MST than after ECT. The mean time to recovery after successful seizures was 7 min 12 sec (SD = 2 min 7 sec, range 4 min 20 sec-9 min 41 sec). We compared these results with the recovery times of the same patients during their nearest ECT session(s) taking care that the order of ECT and MST sessions used for the calculation was approximately balanced. The mean recovery time after ECT was 26min 35sec. When the recovery times of the nine patients who had both ECT and MST were compared in a paired-samples t-test, MST was shown to result in 15 min 35 sec quicker recovery, and despite the small numbers, this result was highly significant at  $p = 0.00009$ .

Patients uniformly commented that they felt less confused after MST. Side effects of 100 Hz MST were restricted to the usual myotonic movements observed after etomidate anaesthesia. No serious immediate adverse events resulted from the use of MST.

## Discussion

We report the first use of a new MST device capable of sustaining maximum stimulator output for 10 seconds at 100 Hz (1000 pulses). We treated 11 patients with a total of 18 stimulations. To explore the range of seizure thresholds, we used a different number of pulses and two positions of the coil: over vertex ( $C_z$ ) or pre-frontally ( $F_z$ ). Seizures were elicited in 10 of the 11 patients. The one who did not fit received only 600 pulses over the vertex. This was a 70-year old woman who was on valproate, both age and anticonvulsant medication could account for the difficulty to elicit a seizure. Eight more patients received stimulation over the vertex of between 250 and 1000 pulses. One of these patients (our first patient) did not have a seizure when we used 250 pulses, but she fitted when re-stimulated at 500 pulses. These findings correspond to the previous observations that the mean seizure threshold with 50Hz MST was at 268 (12) or 320 pulses (14).

We also tested if stimulation at 100 Hz was capable of inducing seizures over the pre-frontal cortex, which had been difficult to achieve at lower frequencies (9,12,13). We attempted seven prefrontal cortex stimulations in six patients. Of those, three were successful (one at 500 and two at 1000 pulses) and four were not successful (one at 500, one at 600, and two at 1000 pulses). Patients who did not fit with prefrontal stimulation, fitted when stimulated over vertex (Table 1). We conclude that even at the maximum setting of the machine, some patients will only fit if the coil is positioned over the vertex (i.e. closest to the motor cortex, which has a lower seizure threshold than pre-frontal or pre-central cortex).

We measured seizure duration during MST starting from the onset of stimulation. This is because we observed that the seizures in MST start during the stimulation train. In contrast, the convulsion typically does not start during electrical stimulation in ECT and a latent phase is usually seen immediately after stimulation (19).

The mean duration of successful MST seizures was 31.3 sec, range 10-86 sec. Four patients had short seizures of 10, 18, 15 and 11sec (Table 1), which would not be considered therapeutic if evoked by ECT. Two of these patients were stimulated with only 600 pulses, raising the possibility that they may have had adequate seizures if stimulated at the maximum duration output (10 sec) of the device.

In line with previous results (12), the recovery of orientation after MST was much faster than after ECT. Despite the small sample size, this difference was highly statistically significant, and more importantly, clinically meaningful. The ability to combine antidepressant efficacy with low neuro-cognitive adverse effects would be invaluable for patients who require neuro-stimulation therapies (20). All patients felt less confused after MST. Many patients felt as if they had received no treatment and remembered details of what had happened immediately prior to MST. For instance, patients were able to continue conversations after recovery that had begun just prior to MST.

It has been noted that the EEG after MST differs markedly from that of ECT, with a lower amplitude and relative absence of post-ictal suppression (12,14). We confirmed these differences after stimulation at 100Hz. EEG traces during ECT showed high amplitude, synchronised EEG activity and clear post-ictal suppression which were markedly different from the EEG recorded after MST (traces available on request from the authors). The observed differences between ECT and MST ictal expression on EEG could be due to the more focal stimulation achieved with MST, which spares deeper brain regions such as the hippocampus that may be implicated in the cognitive side effects of ECT (6). Differences in patterns of seizure expression might also explain the much faster recovery after MST. Another explanation for differences in ictal EEG expression between MST and ECT may stem from the fact that we were not recording EEG from directly under the MST coil, where the induced currents and seizure expression should be at its strongest. Specifically, our scalp EEG recordings were collected from bilateral prefrontal cortex, while the most effective MST coil placement was over the vertex. We have since observed that placing the electrodes over the motor cortex during MST produces clearer seizure activity confirming our impression that these seizures are more localised (Lisanby, personal communication).

Limitations of this work include the small sample size, open design, and non-randomized nature. Nevertheless, this initial pilot study found that MST delivered with the new Magstim Theta device was well tolerated and reliably produced seizures in the majority of patients, while resulting in much less post-ictal confusion. These encouraging initial results beg the question of the efficacy of this new investigational intervention for severe major depression. Previous open studies using 40 Hz and 50 Hz MST (4,14) showed promising results, although MST did not reach the effect size of optimal ECT. The ability to provide higher dosage MST seizures relative to seizure threshold may narrow the gap in efficacy. This will be tested in the context of new trials now underway using the 100 Hz device to assess the effectiveness and safety of high dose MST relative to ECT.

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**Table 1**  
**Treatment settings, duration of seizures and recovery of orientation during ECT and MST - The duration of MST seizures is given from the time of start of magnetic stimulation. \* Subjects 3 and 8 had MST on two separate days; C=Cardiff, E=Edinburgh, BL=bilateral, UL=unilateral**

Patient	ECT			MST			
	Seizure threshold for ECT	ECT seizure duration Motor/EEG	ECT orientation time	N pulses for MST	Position of coil	MST seizure duration Motor/EEG	MST orientation time
female, aged 35 (C)	126mC BL	36"/60"	26'49"	250 500	Vertex Vertex	0"/0" 25"/21"	- 4'36"
male, aged 21 (C)	80mC BL	26"/52"	22'45"	500	Frontal	86"/83"	5'23"
female, aged 41 (C)	841mC BL	42"/49"	25'01"	250 500	Vertex Vertex	9.5"/NA 21"/NA	- 4'20"
				500* 1000*	Frontal Frontal	0/- 70"/NA	- 4'40"
female, aged 47 (E)	80mC BL	30"/42"	29'20"	1000 1000	Frontal Vertex	0"/0" 21"/21"	- 8'41"
female, aged 56 (E)	170mC BL	30"/31"	22'30"	1000	Vertex	28"/29"	5'36"
female, aged 28 (E)	80mC BL	22"/38"	21'10"	1000 1000	Frontal Vertex	0"/NA 18"/NA	- 9'00"
female, aged 48 (E)	204mC BL	33"/39"	28'00"	1000	Frontal	22"/NA	8'43"
male, aged 39 (C)	No ECT	-	-	600	Frontal	0"/0"	9'00" no seizure
				600*	Vertex	15"/NA	9'25"
male, aged 28 (C)	80mC UL	28"/28"	16'00"	600	Vertex	49"/85"	9'41"
female, aged 70 (C)	80mC UL	54"/86"	13'10"	600	Vertex	0"/0"	7'48" no seizure
female, aged 56 (E)	46mC UL	19"/NA	11'13"	1000	Vertex	11"/NA	6'35"