Magnetic Seizure Therapy (MST) – a safer method for evoking seizure activity than current therapy with a confirmed antidepressant efficacy

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Abstract

Since 1999, attempts have been made in the application of a new technique called magnetic seizure therapy (MST) or magnetic convulsion therapy (MCT) in the treatment of depressive disorder – as an alternative to electroconvulsive treatment. The technique of rapid rate transcranial magnetic stimulation (rTMS) is used to evoke intentional and repeated magnetoconvulsive seizures, though it requires the use of stimulation parameters practically inaccessible in commercially available rTMS magnetic stimulators. Magnetic convulsion therapy has been tested on monkeys as well as humans. A decisive majority of studies carried out both on animals and humans addressed the issue of safety of the MST method and confirmed that the side-effects (mostly of a cognitive nature) which occurred after magnetic seizures were weaker than those observed after electroconvulsive seizures. An analysis of available sources, however, does not confirm any proven antidepressant action of the MST technique. No experimental investigations have been carried out on animal models of depression. Clinical effectiveness had been confirmed in merely a few (perhaps three) patients with depression. The authors submit the results of the hitherto conducted studies on MST to critical analysis, particularly in the aspect of their antidepressant efficacy.

INTRODUCTION

Since 1992, several new, physical techniques attributed with certain therapeutic, antidepressant action have been subject to experimental and clinical studies (Higgins & George 2009; Lisanby 2004; Zyss 2007a). These techniques include: transcranial magnetic stimulation TSM (Padeberg *et al.* 2007a), vagus nerve stimulation VNS (Rush 2003; Eschweiler 2003a), deep brain stimulation DBS (Greenberg 2008), transcranial direct current stimulation tDCS (Fregni *et al.* 2006) and magnetic seizure/convulsive therapy MST/MCT (Lisanby & Peterchev 2007). The first and the last of the above mentioned techniques use a strong, alternating, impulse magnetic field; the remaining

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three methods make use of electric current to evoke the desired therapeutic changes. The present work deals with magnetic seizure/convulsive therapy. The starting point to the research into the new MST technique was comprised of the following three assumptions:

- high clinical effectiveness of electroconvulsive therapy (ECT);
- relatively low therapeutic effectiveness of transcranial magnetic stimulation (TMS);
- specific seizure-inducing potential of the repetitive rapid-rate stimulation rTMS.

Numerous clinical works as well as clinical practice testify to the high antidepressant efficiency of electroconvulsive therapy (Fink 2000; Gábor & László 2005; Sienaert & Peuskens 2006). Despite the low number of experimental studies and a much higher number of clinical investigations which confirm the antidepressant effect of transcranial magnetic stimulation (TMS) – its actual effectiveness is not particularly high (Loo 2008; Padeberg *et al.* 2007b). An analysis of the effectiveness of TMS basically confirms the observations derived from much older studies on electroconvulsive therapy; namely that a repeated convulsive seizure, specifically seizure activity of an appropriate duration (minimum 20–30 sec) and of a general (and not local) nature is a necessary condition to achieve a strong antidepressant effect. Seizures of an inadequate length (abortive) or partial seizures do not result in the occurrence of an appropriate, satisfactory clinical effect (d'Elia *et al.* 1983; Strömgren *et al.* 1980; Weiner *et al.* 2001).

Hence, attempts have been made to make intentional use of specific seizure-inducing actions of magnetic stimulation (rTMS). Seizure activity in EEG or a clinical epileptic seizure is usually recognized as a complication or an undesirable side-effect application of the rTMS technique – particularly those which generate magnetic impulses at high frequencies (Huber 2007; Wassermann *et al.* 1996). In turn, rTMS with a low frequency of stimulation is supposed to inhibit convulsive activity – up to quenching type action (Joo *et al.* 20070. There have been attempts made to utilize this effect in the treatment of drug-resistant epilepsy (Tergau & Werhahn 2007).

The method which consists of the eliciting of seizure activity within the patient's cortex with the use of magnetic stimulation (instead of electric stimulation applied in ECT) has been named magnetic seizure therapy (MST), magnetic convulsive therapy (MCT) or magnetoictal therapy (MIT).

From a historical standpoint, it is Ollendorf who should be recognized as the forerunner of the MST technique. In theory published in 1964, he performed a mathematical analysis of the possible triggering of electroshock with the use of inductive (i.e. magnetic) stimulation. However, clinical and experimental studies on the MST technique are mostly associated with Sarah H. Lisanby from the Institute of Psychiatry in New York.

EXPERIMENTAL INVESTIGATIONS ON ANIMALS

Then first experiments with the aim of evoking seizure activity in EEG with the use of rTMS stimulation were conducted on rats. It remains difficult to explain why it has proven impossible to trigger seizure activity with magnetic stimulation in this species (even in animals which were not under general anesthesia). Moreover, it should be noted that in the case of rats – due to the much smaller anatomical dimensions of the head (and therefore, smaller distance between the head surface and the brain) – the parameters of stimulation must result in the generation of a much stronger magnetic and electric field in the animal's brain than evoked in, for example, a human brain. Nevertheless, it still proved ineffective in evoking convulsive activity. An opposing explanation, namely the impossibility of evoking an adequately strong electric field in the brain of a rat, can be found in work by Lisanby and Peterchev (2007).

On the other hand, it has proven possible to evoke magnetic shock in the macaques (rhesus) – primate genus of monkeys (Lisanby 2004). The results of these experiments were first presented at the meeting of the Biological Psychiatry Association that took place in May 1999. It was two years later that the results of these experiments were published in the form of a letter to the editor (Lisanby *et al.* 2001a).

The first experiments in which a standard Super Rapid commercial stimulator, manufactured by Magstim (Magstim Company Ltd; using 100% maximal output, a frequency of 25 Hz, stimulation time of 10 sec, impulse width 300 μsec, bipolar course), was used proved ineffective. The magnetic field generated with the use of a 4cm round coil, which was placed over the vertex of the head, could not evoke a seizure in a monkey anesthetized with methohexital (Lisanby *et al.* 2001a).

The first successful magnetic seizure was evoked with the help of a modified Magstim Super Rapid magnetic stimulator, which eight power modules (or boosters) as opposed to the standard number of four. The augmented power supply of the stimulator enabled the stimulation frequency to be increased to 40 Hz. The parameters of the stimulation amounted to ca. 400% of the motor threshold and allowed for the triggering of repeated seizures in the monkeys subjected to stimulation. Magnetic stimulation evoked typical tonic-clonic seizures lasting ca. 10–15 sec. The mode of general anesthesia influenced neither the duration of a seizure nor its morphology (Lisanby *et al.* 2001a).

The duration of a seizure could be influenced by a gradual prolongation of the stimulation time with the help of the titration method. A typical tonic-clonic seizure could be triggered only with the help of impulses amounting to 90% of output power of the stimulator that were generated with the frequency of 40 Hz within the time of 4–5 sec (Lisanby *et al.* 1999; Lisanby *et al.* 2001).

In the subsequent years it was Tammy Moscrip, a doctoral student in The Laboratory of Magnetic Stimulation of The Brain directed by Lisanby, who studied magnetoconvulsive stimulation of monkeys (Moscrip 2005). For this project, a set of research tests which examined cognitive functions in monkeys was developed. After ECT procedures the monkeys were less precise and slower – as compared to the animals subjected to magnetic stimulation or simulated ECT. In regards to their cognitive abilities, the monkeys subjected to magnetic convulsion stimulation did not differ from those of the control group. On the basis of the results, Moscrip concluded that MST stimulation (50Hz, 100% of output power, 120 or 240 impulses) is less invasive to cognitive functions than ECT (Moscrip 2005; Moscrip *et al.* 2006).

During the course of their work in 2003, the researchers dealing with magnetic convulsion techniques conducted on primates listed the similarities and differences between magnetic stimulation MST and electroconvulsive therapy (Lisanby *et al.* 2003a).

Using deep electrodes implanted for a longer period of time, Lisanby *et al.* (2003a) showed that the electric field generated in brain structures during MST procedures was much weaker than that generated during ECT. Also, the value of the electrical discharge to the head was lower in the magnetic method. The nature of the forced current flow in these two techniques shows that the current flow in electric stimulation leading to electroconvulsive seizure is transverse (the current flow is perpendicular to the brain surface) while it is longitudinal (parallel to the brain surface) in the magnetic method. The distribution of voltage measurements at different points of the brain showed that electric stimulation which triggers electric convulsions propagates and reaches distant areas of the hemispheres. When stimulation was conducted over the right frontal area, excitation reached the contralateral frontal area as well as the distant parietooccipital areas and the deep structures of the brain. During the process of magnetic stimulation, the excitation was both weaker and limited to the stimulated area – it was of a local nature. The results of these investigations were also presented by Lisanby *et al.* (2003b) during the Second International Symposium devoted, among others, to Transcranial Magnetic Stimulation TMS, which took place in 2003 in Göttingen.

Lisanby *et al.* (2003b) as well as Lisanby herself (2004) expressed the opinion that MCT/MST magnetic stimulation facilitated more precise control of spatial propagation of the stimulus in the neural tissue of the brain than did electric stimulation ECT. Electroshock causes the triggering of generalized seizure activity within the entire brain – in the frontal lobes as well as in the hippocampus. On the other hand, seizure activity during a magnetic shock is limited mostly to the stimulated area, e.g., frontal cortex, and therefore the further it is from the stimulated area, the weaker its result due to the superficial and spatially limited location. As a result, the seizure activity either does not reach the hippocampus or reaches it with little intensity – which is theorized to result in lesser disturbances of cognitive functions, e.g., memory, than those which occur after ECT.

Proof of weaker penetration of magnetic shock to the deeper cerebral structures was provided by an experiment, conducted by Morales *et al.* (2003), in which they measured plasma levels of prolactin as an indicator of hypothalamic-pituitary axis excitation. While ECT usually evokes a significant increase in the plasma levels of prolactin, magnetic shocks revealed only a slight increase in the concentration of this hormone.

As the penetration of the physical stimulus into deeper brain structures is weaker in magnetic seizure technique than it is in ECT, it should be expected that MCT/MST stimulation would have lesser impact on the phenomena of hippocampus plasticity like mossy-fiber sprouting or neurogenesis than those observed after ECT procedures (or electroshocks) in experiments on rodents. The above research hypothesis was confirmed by subsequent experiments carried out by Lisanby's team (Lisanby *et al.* 2003c; d).

Lisanby's team also performed experiments in which they tried to explain what structural effect can be potentially evoked by MCT/MST stimulation. Twelve macaques were subjected to magnetic convulsion procedures every day for six weeks. Neither MCT/MST nor ECT procedures performed on the control group led to the manifestation of any symptoms of brain tissue damage. However, in the ECT group the GFAP reaction (Anti-Glial Fibrillary Acidic Protein – the marker of astrocyte damage) was more intensive (Dwork *et al.* 2004).

A serious shortcoming of the studies on MST technique (both those conducted before 2004 and those which followed) is that they lack any research into the actual effects of magnetic seizures in the behavioral or biochemical models of depression in animals (actually, in the later period there have been hardly any publications related to further experiments on animals). In the end, MST was not to be a safer or better tool for brain stimulation but a physical technique to evoke a biological and clinical antidepressant effect. This situation seems to resemble certain research experience of the first author of this work. What is the importance of a given method (here: MCT/MST, in the first author's work: rTMS) being safer in regards to cognitive functions or structural aspects if it does not satisfy (or prove) the basic requirement, namely (sufficiently high) therapeutic (antidepressant) efficacy (Zyss *et al.* 2006a).

Moreover, almost identical safety results can also be achieved in ECT. The technique involves applying lower parameters of the electric current, which would not lead to generalized seizure activity but keep it locally limited. This effect could be reinforced by the application of electrodes placed close to one another on the surface of the head. The location and arrangement of electrodes in this case would force the current flow to

be perpendicular rather than parallel to the head/brain surface; the current would not penetrate the deeper cerebral structures but would "bend" very quickly, mostly in the superficial layers, and flow back between the electrodes.

CLINICAL INVESTIGATIONS

Soon after their first publication regarding experimental investigations, Lisanby *et al.* (2001b) published a work in which they reported conducting the first successful magnetic convulsion procedures on a human. The MCT/MST stimulation procedure was carried out in 2000 on a 20 year old woman, a patient of the Psychiatric Clinic of the University Hospital in Bern, with a depressive episode lasting three years. During this period, the patient had been subjected to therapies with a drug from the SSRI group, two tricyclic antidepressants, two drugs from the MAOI group and several other new antidepressants. Also, augmentation with lithium, triiodothyronine and methylphenidate was administered. However, all therapies proved unsuccessful.

The patient was subjected to four MCT/MST trial procedures – conducted at the rate of three procedures per week. During the procedures the patient herself was under general anesthesia – during the first two stimulations she was administered ethomidate while for the latter two she received thiopental. Muscle relaxation was induced with succinylcholine.

MCT/MST was performed with a modified Magstim Super Rapid magnetic stimulator with eight power modules.

Only one stimulation was performed during each of the first two procedures; later, two stimulations were performed during each procedure. The magnetic field was generated by a double cone coil, it was only during the second stimulation in the third procedure that a butterfly coil was used. Before stimulation the coils were cooled so that they could be used longer (in 2000 no manufacturers of commercial rTMS magnetic stimulators offered fluid or air cooled coils). The double cone coil was placed on the vertex of the patient's head while the butterfly coil was placed on the head over the right dorsolateral prefrontal cortex.

During the majority of stimulations, magnetic impulses were generated at a frequency of 40 Hz and at 100% of the output power of the stimulator, which made it possible to achieve ca. 240% of the threshold of motor excitation. A single stimulation lasted from 2.0 to 6.3 sec (which corresponds with the duration of the electric impulses generated in ECT). In the third and fourth procedures, the interval between the two subsequent stimulations lasted 28 seconds and 136 seconds respectively.

Magnetic stimulation with the parameters described above led to the triggering of convulsive seizures lasting from 30 to 250 seconds (confirmed by the EEG records and observation of motor symptoms with the help of the cuff technique). The work by Lisanby *et al.* (2001b) states that from the second procedure, the threshold of magnetic seizure was determined with the titration method.

The magnetic convulsion procedures themselves were well tolerated by the patient and brought about a reduction of her score on the Hamilton Rating Scale for Depression from the initial 20 to 12 points.

Due to unknown reasons – despite the initiate improvement – after the initial four procedures, MST was terminated in the patient. Furthermore, a series of 8 classical unilateral ECT procedures was conducted bringing about further improvement (a reduction to 8 points on the Hamilton scale).

The authors concluded that the experiment confirmed the ability to evoke seizure activity with the help of magnetic stimulation even in subjects under general anesthesia (significantly increasing the excitability threshold). The authors posed the thesis that one of the advantages of MST would be the possible limitation of seizure activity to definite areas of the brain and the prevention of the spread of a seizure over the entire area of the cortex – and this, while allowing for the occurrence of a therapeutic effect, would reduce the risk of the occurrence of undesirable side-effects.

An in-depth analysis of the study, however, does not reveal the premises on the basis of which Lisanby *et al.* (2001b) could have drawn the presented conclusions. The recording of EEG activity was performed with the use of the standard two channels and the location of the recording electrodes was standard for ECT procedures (frontomastoid placement of electrodes). In regards to the registered seizure activity – considering the distant location of the recording electrodes – it is possible to infer that the seizure was not of a local or focal nature but of a generalized one. If no larger number of registering electrodes is applied, it is impossible to assess the qualitative and quantitative parameters of seizure activity in different areas of the brain. Moreover, clinical examinations of ECT clearly confirm that the efficacy of generalized seizures is higher than that of local ones.

Soon after the above-described clinical experiments first confirmed the possibility of evoking seizure activity with the help of magnetic stimulation, further studies were carried out on a larger number of patients (Lisanby *et al.* 2001c; 2003e). These were clinical studies of the first phase aimed at the assessment of the safety of magnetic convulsions – mostly in the area of cognitive functions and bioelectric brain activity. These convulsive therapy studies involved ten patients (3 males and 7 females) with a diagnosis of major depression. During the first two to four procedures, convulsions were elicited by magnetic stimulation. Subsequent procedures were classical ECT. Magnetic stimulation was performed with the use of a modified Super Rapid stimulator with sixteen power modules that allowed for stimulation at 100% of initial output power of the apparatus for 6.6 sec at a frequency of 60 Hz. Magnetic impulses (100 to 400 impulses on the average) were generated with the use of three types of coils: (a round

coil 8 cm in diameter, a butterfly coil with each winding 7 cm in diameter, and a double-cone coil with windings of 9 and 12 cm in diameter), where the magnetic field induction amounted to 2 T. Three locations of the coils were examined corresponding with the 10–20 system designations: F6, Fz and Cz.

The MCT/MST procedures were better tolerated than ECT and caused fewer subjective side-effects. After MCT/MST the patients regained full orientation faster, retrograde amnesia was weaker and other cognitive functions (short-term memory, learning, fluency) were less influenced. The magnetic seizure itself was usually shorter than an electric seizure, the amplitude of the EEG seizure activity was lesser and the effect of post-seizure EEG suppression was also weaker.

The above-discussed works of Lisanby's team from the years 2001 and 2003, however, did not include any information regarding the effectiveness of the magnetic convulsion procedures which had been conducted. In this context the use of the name "magnetic convulsion therapy" remains unjustified. It would be much more correct to use the term magnetoconvulsive stimulation, treatment or procedure.

Furthermore, it is impossible to learn from these works why the researchers did not apply another method – subjecting a patient exclusively to magnetic convulsion procedures. The results discussed above carry a methodological error – the differences that occurred between the groups need not have regarded the comparison between MCT/MST and ECT, they might refer to the short-term and long-term effects of the whole series of convulsions.

In 2003 a work was published by Kosel *et al.* (2003) documenting the positive clinical effect of MCT/MST on a 66 year old female patient who had suffered from recurrent depressive disorders since the age of 17. However, the clinical picture was hardly consistent due to additional diagnoses of anorexia nervosa and OCD as well as several other somatic disorders. In the period directly before getting included in the investigations, the patient was treated with several drugs including olanzapine, risperidone and St John's-wort (Hypericum) extract.

The patient was administered 12 MCT/MST procedures in all (frequency 50 Hz, stimulation time 8 sec, 100% of maximal output; double cone 13 cm coil placed over the vertex).

The patient bore the period of treatment well: she did not develop the undesirable side effects typical of ECT like headaches, muscle pains or memory disturbances. It was only once, during the second session that stimulation failed to trigger seizure activity in the patient.

The original work includes a graphic record of the ninth MCT/MST procedure administered to the discussed patient, yet it was neither demonstrative nor highly convincing. For ca. 6–7 seconds EEG activity did not, in fact, differ basically in its morphology from the bioelectric activity preceding the stimulation. Later, two high voltage waves 0.5–1 Hz were registered, which could have been artifacts, and it is after these that a weakly expressed seizure activity occurred. This activity lasted slightly longer than the motor seizure registered with a special motion detector on the second channel. It was impossible, however, to precisely determine the point at which the EEG seizure activity terminated. The researchers remarked that the registered EEG activity was typical of the magnetic seizure stimulations they conducted. This might mean that in some records the EEG seizure activity – occurring as a result of MCT/MST stimulation – was even weaker or possibly totally absent.

The authors also stated that the duration of tonic-clonic motions was between 14 and 23 seconds. Thus, even if a few seconds more were added (cave: EEG seizure activity persists longer than the motor seizure observed from without), the information allows the assumption that some of the magnetic convulsion procedures could have been of an abortive nature, i.e., did nor exceed the minimum of 30 (or even 20) seconds.

Initially it would be hard to assume that such "weak" seizures could result in a statistically significant therapeutic effect; in this case an antidepressant effect. Such improvement, however, was recognized by Kosel *et al.* (2003). The symptoms of the last depressive episode had prevailed in the discussed patient for five years. Four weeks (35 days) before she was included in the experiment and subjected to MCT/MST the severity of depression amounted to 33 points on Hamilton's (21 items) Depression Scale and 33 points on Beck's Scale.

Regretfully, the next assessment of depression severity did not take place the day before the first magnetic stimulation. Due to this, it is not clearly known whether the decrease of the intensity of depression in the patient that was detected at the second examination, i.e., after the first week of stimulation, was caused mainly or basically by the procedure of magnetic stimulation or evoked by several non-specific factors such as, e.g., recruitment and qualification for the clinical experiment.

During the series of MCT/MST stimulations the intensity of depressive symptoms significantly decreased. The results on Beck's and Hamilton's Depression Scales dropped to 11 and 6 points respectively, indicating remission.

Neuropsychological examinations performed on the patient did not show that magnetic seizures would exert significant influence on cognitive functions, or else this influence was weaker than that described in studies on effects of ECT. In turn, SPECT examination confirmed improved blood flow in the area of the frontoparietal cortex.

In their final conclusions the authors suggested that the MCT/MST technique is a new, potentially effective and safe instrument in therapy of drug-resistant depressions, which, in the future, might even replace ECT.

The statement given above may be surprising as a far-reaching conclusion drawn in the context of a single case observation. Lisanby herself (a participant

in the study-publication by Kosel *et al.* (2003) stated in her 2004 paper that the antidepressant effectiveness of MCT/MST was still unknown.

In her survey of 2004, Lisanby reported conducting two-center randomized and double-blind clinical investigations aimed at the assessment of the efficacy of magnetoconvulsive stimulation (with a stimulation frequency of 50 Hz) in the therapy of depressions. During the course of the study, 20 patients were subjected to two forms of magnetoconvulsive stimulation – one with the use of a non-focal "cap" coil placed above the vertex of the head and the other with a double-cone coil located above the prefrontal cortex. Although a few years have passed since, apart from a conference report of 2003 no published results of these investigations could be found (Lisanby *et al.* 2003f).

White *et al.* (2006) presented the results of the controlled investigations conducted on 20 patients subjected to ECT or MCT/MST. The authors demonstrated that after magnetic stimulation, patients required less time to regain complete orientation; they also needed smaller doses of succinylcholine, but at the same time their clinical improvement was weaker (lesser reduction on Hamilton's Scale). Also, both of these stimulation methods were reported to have had an unclear effect on EEG activity.

Padeberg *et al.* (2007a) concluded that MCT/MST was to bring about less intensive subjective side-effects than those occurring after ECT. The patients were claimed to faster regain complete orientation and prestimulation attention efficacy; their retrograde amnesia was also expected to be weaker.

The results of the latest major clinical works dealing with comparison of magnetic seizure stimulation and ECT were presented by Kirov *et al.* (2008). The studies were carried out on 11 patients suffering from treatment-resistant major depression and the research was not aimed at the assessment of antidepressant efficacy but at the speed at which the patients recovered orientation after the procedure.

It was probably due to the weaker magnetic field generated by the Magstim Theta stimulator (1.2 T instead of 2 T) that the effectiveness of triggering magnetic seizures was worse. Eventually, the seizures were evoked in 10 out of the 11 patients. Stimulation performed in the area of the vertex resulted in a tonic-clonic seizure in ten out of 11 cases. In turn, the same stimulation executed above the prefrontal area in its midline was effective in 3 out of 7 stimulation procedures. From the reported duration of seizure activity (10 to 86 seconds, mean – 31.3 sec) it is possible to infer that a large proportion of magnetic stimulation procedures – from the perspective of ECT practice – was of an abortive nature. The investigations confirmed that the recovery of complete orientation after MCT/MST stimulation occurred earlier (after 7 min 12 sec) than after ECT (15 min 20 sec). After magnetic stimulation the patients felt less confused (Kirov *et al.* 2008).

In their 2007 paper, Lisanby and Peterchev calculated that up until that time 45 patients with a diagnosis of treatment-resistant depression had been subjected to magnetic seizure stimulation all over the world. A large proportion of these patients took part in investigations aimed at the assessment of safety of the MCT/MCT method and not of its clinical antidepressant effect.

The latest and – probably – third case description of antidepressant efficacy of magnetic stimulation was recorded by Kayser *et al.* in 2009. They reported the effective administration of MCT/MST in the course of a depressive episode in a patient with Type I Bipolar Affective Disorder. Again, a major part of the description was devoted to information regarding the nature of convulsive seizures themselves (shorter seizure duration, lower amplitude of EEG seizure activity, less intensive suppression after a seizure) than to clinical description of depression (initial and final intensity of symptoms, course of illness and applied treatment).

Apart from the investigations discussed above, in recent years several reviews have been issued regarding MCT/MST procedures (Braga & Petrides 2007; Carpenter 2006; Dumitriu *et al.* 2008; Eitan & Lerer 2006; George 2002; Holtzheimer & Nemeroff 2006a; Holtzheimer & Nemeroff 2006b; 2008; Kennedy & Giacobbe 2007; Lisanby 2002; Lisanby *et al.* 2003g; Schläpfer 2007; Tamaoki & Motohashi 2007).

FURTHER CRITICAL REMARKS CONCERNING MCT/MST TREATMENT

Although nearly ten years have passed since the first clinical experiment was carried and several further publications have been issued, hardly anything suggests the possibility or usefulness of more widespread use of MCT/MST magnetic seizure stimulation in common clinical practice. Commercial magnetic stimulators do not guarantee the parameters of stimulation that – using magnetic impulses – could evoke seizure activity in an intentional and repeatable way (and not accidental and occasional one). The 2007 launch of air and liquid cooled stimulation coils into the market failed to spur significant research into MCT/MST.

At the present moment the main factor that limits the generation of impulses with high amplitude and at a high rate is the power element, i.e., the stimulator itself. However, further investigations may be carried out with the use of the cooled coils which, being more resistant to heat overload, can withstand longer stimulation, yet, at the same time, due to a thicker encapsulation of the coil, usually generate a weaker magnetic field. These investigations might show that rTMS administered at higher frequencies than those applied today (> 40–50 Hz) would allow for the triggering of seizure activity using a lower amplitude of the stimulus. This, in turn, would make application of commercial stimulators possible.

Our own model studies (Zyss *et al.* 2005a;b; 2007b; Zyss & Sawicki 2007c) and clinical investigations (Zyss

et al. 2006a;b; 2007d) indicate that it is the variable of the rate of magnetic stimulation and not that of amplitude, which is more important in achieving a definite biological effect. For example, in order to obtain – with the use of rTMS – the values of current flow within the brain similar to those achieved in ECT, it would be necessary to use coils powered with 15–25 kA (usually, 5-8 kA current power is applied in TMS stimulators). It would hardly be possible to execute such a solution (a large coil with a power system of appropriate parameters) and ensure the patient's safety at the same time. The cost of designing, constructing and testing such a stimulator seems enormous.

The use of higher stimulation rates may be an alternative to the increase of amplitude of a magnetic field induction. In accord with observations made in electrophysiological examinations, these higher rates allow for the decrease of the sensitivity threshold of nerve cells. This is the way recognized nowadays as potentially capable of triggering seizure activity (Zyss *et al.* 2006ba). In an experiment carried out at the beginning of 2006, our research team managed to trigger the manifestation of seizure activity in EEG (without the clinical symptoms of a seizure) with the use of a one-minute stimulation with a magnetic field of 1.7 T induction and frequency of 50 Hz generated by a prototype MS-3 magnetic stimulator (Zyss *et al.* 2000a;b).

In the context of the conducted investigations, it seems hardly possible to work out simulation parameters that would, on one hand, make magnetic stimulation capable of evoking a clinical antidepressant effect and, on the other hand, make it safe, i.e., prevent it from triggering seizure activity. In a conscious patient – and a patient subjected to TMS is usually conscious – the latter is a serious undesirable side-effect with definite clinical and psychological implications. In turn, the intentional triggering of seizures with the help of magnetic stimulation implies the necessity of protecting the patient with anesthesia, and this makes the possible application of TMS even more complicated.

At the present moment it is presumably only the Magstim corporation that possesses technological solutions which allow for research into magnetic convulsion treatment. However, neither the older modified Super Rapid stimulator with 8 or 16 (instead of 4) power modules nor the so-called Theta stimulator are freely available on the market (they are available on individual order). It is hard not to mention here the enormous cost of obtaining this kind of equipment, its prototypical character and the limited area of its practical use. The above mentioned factors are chiefly responsible for the fact that there are only a few centers in the world that can carry out research into MCT/MST – and as an experimental method at that.

Moreover, in her object work of 2004 Lisanby admitted that even the MST magnetic stimulator in her possession was too weak to be used in clinical investigations. It is sufficient to generate an impulse whose value exceeds the convulsion threshold in monkeys. In regards to the ca. 20 patients with depression subjected to magnetic stimulation up to 2004, as much as 43% of the time the convulsion threshold was achieved by the use of the maximum parameters of magnetic stimulation. Thus, if the convulsion threshold had been slightly higher in these patients, seizure activity would not have been evoked in them.

In the context of the postulated superiority of locally evoked seizure activity during MCT/MST stimulation, it is difficult to fully understand the arguments of Lisanby (2004) and well as Lisanby and Peterchev (2007) when explaining the ineffectiveness of stimulation with the more focused butterfly coil. Effective seizure activity could be achieved during magnetic stimulation with the non-focused round coil. Double cone coils manifested medium effectiveness.

In the same work, Lisanby (2004) wrote that magnetic convulsions could not be evoked when the stimulating coil was placed above the prefrontal area; they were triggered only when the coil was located over the vertex of the head. This situation could be explained by the lower sensitivity threshold of the motor cortex (located in the area close to the vertex) as compared to the prefrontal cortex. However, a clinical problem involves the fact that the metabolic disturbances identified during a depressive episode more frequently involve the prefrontal cortex and not the cortex of motor areas (Nahas *et al.* 2003; Stern *et al.* 2007).

In the case of ECT with the aim of triggering generalized seizure activity which also covers metabolically disturbed brain areas, it is not absolutely important where the seizure activity is initiated. To diminish the risk of the occurrence of cognitive symptoms it is possible to place stimulating electrodes over the non-dominant hemisphere. But for the hair, in order to increase the effectiveness of ECT it would be better to locate the electrodes not in the typical frontotemporal areas, but further back and higher – closer to the motor cortex area. It would be good for this kind of stimulation to choose the points determined by Lancaster *et al.* (1958) or Krzyżowski (1991) – mostly applied bilaterally. Due to the shorter distance to the motor cortex area and the low sensitivity threshold of this area of cortex, it can be expected that the current flow parameters and therefore the electric load for the entire brain/head necessary to evoke seizure activity would be the lowest as compared to other electrode locations. Sufficiently strong seizure activity initiated in the area of the premotor cortex would not get extinguished there but would spread over the entire brain reaching the metabolically disturbed brain structures where it will exert its therapeutic influence. Thus, if the MCT/MST method can only evoke a weak, local seizure activity in a human, mostly in the motor area, and this activity cannot spread to other areas of the brain, this fact cannot confirm that magnetic convulsions in their present form could manifest a significant antidepressant efficacy, as seen in the case of abortive electroconvulsions.

Another unfavorable premise as observed by Lisanby (2004) is the increase of seizure threshold following further magnetic convulsion procedures. In monkeys this increase was ca. 31% and in humans it amounted to 66.7%. This phenomenon is also observed in ECT. However, ECT stimulators are usually constructed with a significant power (charge or energy) reserve. This means that even with the increase of convulsion threshold it is possible to increase the stimulation parameters so that in most cases the triggering of seizure activity in subsequent stimulations is possible (if necessary, in ECT stimulators it is even possible to switch to a wider range of stimulating impulse parameters, e.g. "double dose/energy").

On the other hand, according to Lisanby herself, in the case of stimulators used in MCT/MST technique (even those modified by custom order) no such power reserve is available. Unfortunately, Lisanby (2004) did not report how she solved the problem with the patients whose sensitivity threshold required the maximum parameters even during their first magnetic stimulation and increased after the first or subsequent procedures. In their case none of the available magnetic stimulators were able to evoke effective magnetic convulsions. Lisanby did not state whether such patients were excluded from the clinical investigations or whether their treatment was continued with the use of ECT.

In the case of ECT there is a certain relationship between the power of the electric stimulus and the final therapeutic effect. The stronger the stimulus (obviously, within a certain range – too large electric charges would be unfavorable in respect to the increased risk of potential side-effects), the longer the seizure activity, and its duration is one of the main prognostic parameters which highly correlates with the final therapeutic, i.e., antidepressant effect (Weiner *et al.* 1986; Weiner & Krystal 1993). Since the magnetic stimulators accessible nowadays make it possible only to achieve convulsion threshold – the relation between stimulation at suprathreshold values and the efficacy of MCT/MST is impossible to determine.

To illustrate the problems that rTMS technique has to cope with, a comparison can be presented. Stimulation in ECT is executed with electric voltage ranges from 200 to 400 V with current value not exceeding 1 A (Zyss et al. 2007e). At the same time, in order to obtain the appropriate magnetic field using the rTMS technique, the stimulating coil must be powered with voltage of 1 000–3 000 V and the current flowing through it amounts to 4 000–7 000 A. The current flows in the coil winding separated from the patient with merely a few millimeters of insulation. The whole system must be safe for the patient in regards to electricity, temperature and mechanics. The stimulators and coils currently available on the market seem to have reached the limits of the material and construction potential (Zyss *et al.* 2007a).

In his work of 2003 Eschweiler reported that the system of a magnetic stimulator used in MCT/MST techniques is subjected to such current carrying and heat load that after a few stimulations the power supply modules get damaged (Eschweiler 2003b).

From a technical point of view it is significantly easier to control and modify currents of several hundred mA (as in ECT) than those of a few thousand A (as it is in magnetic convulsion stimulation). Anti-electrocution protection of the patient and the personnel in ECT is much easier than that in rTMS method. An ECT stimulator is usually a small, portable electro-medical apparatus. rTMS stimulators that can evoke magnetic convulsions must be additionally equipped with numerous elements (power units, coupling and monitoring units, conductors, coils, stands); they are heavy, barely portable integrated units, sometimes requiring a three-phase power supply whose purchase price is several times higher than that of an ECT stimulator. It is hard to recognize a medical technique as applicable when it requires the use of prototypical equipment that is constructed on individual order and owned by 2 or 4 centers in the world.

The above mentioned Magstim Theta stimulator is still a prototypical apparatus and cannot be found in the official product line of the corporation. December of 2008 MagVenture corporation presented their own piece of equipment for evoking magnetic seizures: the MagPro MST stimulator. However, no data concerning experimental or clinical investigations in which this type of stimulator might have been used are available. Therefore nothing can be said about the actual effectiveness of the stimulation parameters it offers (magnetic field induction up to 2T, stimulation frequency ranging from 100 to 250 Hz, stimulation time from 1–6 sec) (MagVenture A/S).

POSTULATES AND RESEARCH HYPOTHESES

From a cognitive point of view, research into the effectiveness of magnetic stimulation therapy and magnetic convulsive therapy (MST/MCT) will probably be continued (Rowny *et al.* 2009). The following research steps are proposed:

1. Equipment design research

1.1. Research leading to the construction of magnetic stimulators that would enable the generation of strong magnetic impulses (>2 T); most commercial coils for rTMS do not generate a sufficiently strong field with frequencies up to several dozen Hz (60–90 Hz; these are the optimum frequencies used for stimulation of the brain in the ECT technique) for a relatively long time (several to several dozen seconds; in ECT 0.5 to 6 seconds of stimulation initiates autostimulation in form of seizure activity; for weaker stimulation, namely MST/MCT, the time of stimulation should be longer);

1.2. Construction of effective and safe stimulation coils; it is extremely difficult to combine the ability to produce a strong magnetic field (which is possible only in small coils which allow a highly concentrated magnetic field) with the ability to generate and sustain a magnetic field for an extended duration and with an adequately high frequency (this requires an intensive cooling of the coils, preferably with liquid); combination of these three properties has not yet been achieved to a sufficient extent in commercially produced coils.

2. Experiments on animals

2.1. Explanation is required regarding why it has not been yet possible to evoke magnetic seizures in rodents, e.g., in rats, for which there exist well tested animal models of depression [forced swim test (Schechter & Chance 1979), chronic mild unpredictable stress (Willner *et al.* 1987)];

2.2. Since magnetic seizures can be evoked in monkeys, it is necessary to test the MST/MCT technique in relation to the models of depression developed by McKinley (1977);

3. Clinical studies

3.1. In all studies on MCT/MST it is necessary to subject patients with depression undergoing treatment not only to evaluation in regards to their safety (e.g., the evaluation of their cognitive functions), but also, and primarily, in the aspect of the effectiveness of the therapy (appropriate clinical tests: MADRAS, HAMA, Beck Inventory).

There exist, however, opposing arguments, which seem to suggest there is little reason for further studies on MST/MCT in the therapy of depressive disorders, since the effectiveness of this method can never equal the effectiveness of ECT therapy:

1. Equipment design research

1.1. Model testing confirms that the current parameters (current density) that exist during MST/MCT stimulation (which is only slightly stronger than TMS) are at least ten times as weak as those which occur during ECT stimulation just before the initiation of seizure activity (SSAD – self sustained after-discharge). Since (for the coreless air coils) there exists linear interdependence between the current generated in the MST/MCT stimulator and the generated magnetic field and, additionally, the currents generated in the tissue, it would be insufficient to generate magnetic fields amounting to 3–4 T; to obtain the conditions prevalent in a human head during an application of ECT technique it would be necessary to generate a field of 10–15 T (Nadeem *et al.* 2003; Sekino & Ueno 2004; Zyss 2009). In the case of medical stimulators, the generation of impulsive magnetic fields is extremely difficult (much stronger magnetic fields can be obtained in engineering, but the technologies applied there, e.g. Bitter magnets (Bitter 1961), can not be applied in MST/MCT technique. Moreover, the safety aspects of the application of such strong fields are unknown.
Since the above consideration referred to generalized seizure activity – recognized as therapeutically effective in the case of ECT – obtaining focal (locally limited) seizure activity would probably require application of slightly weaker fields.

1.2. As it has been shown above, the generation of such strong fields would require special coils powered with currents of amplitudes reaching several thousand amperes. The construction of a stimulating coil that could be safely applied in clinical conditions, i.e., close to the patient's head, appears to be impossible, due to inherent problems with mechanical, electric and thermal safety (Davey & Riehl 2005; Ruohonen & Ilmoniemi 2005).

2. Experiments on animals

2.1. The differences in size between a typical stimulating coil and the head of a laboratory animal, such as a rat, cause the electric conditions which occur in the head of an animal during MST/MCT stimulation to be different than those which occur in a human head during a similar stimulation procedure (due to the thickness of the surface layers the magnetic field as well as the secondary induced currents in an animal must be stronger than those in a human); furthermore, the effective stimulation area (otherwise known as the hot point – the area closest to the internal radius of the coil) must cover the entire animal brain and not a few square centimeters – as it does in the case of a human. Thus, if seizure activity can be evoked in rats for definite parameters, it will probably be of a generalized nature and not of local nature like in humans or monkeys. Therefore, in its mechanism it will not differ from the generalized seizure activity evoked during ECT procedures and this suggests that it will not have the "advantages" of MST/MCT like higher safety in regards to cognitive processes

2.2. The availability (as well as costs and bioethical aspects) of experiments on primates significantly reduces the possibilities of verification regarding how effective MST/MCT actually is in the monkey model of depression.

3. Clinical studies:

3.1. The days of studies on ECT with simulated (sham) electric stimulation as a true placebo are long gone (Lambourn & Gill 1978; Freeman 1978). Both the ethical aspects (the attitudes of the local bioethics boards included) and people's prejudices towards all kinds of electromagnetic stimulation of the head area may become a significant obstacle for further clinical studies(Rasmussen 2009; Ross 2006).

3.2. Clinical studies on ECT show that only generalized seizures lasting at least 20–30 seconds have an antidepressant effect (Beyer *et al.* 1998; Sackeim *et al.* 1991). Focal and abortive seizures as well as prematurely terminated ones are ineffective. Thus, it is unreasonable to expect that the focal seizure activity which occurs during MST/MCT should cause any significant clinical improvement in patients suffering from depression.

3.3. Since MST/MCT is, it is widely assumed, less effective than ECT and nearly as laborious of a technique (the necessity of applying anesthetics, evoking of seizure activity), there are no valid reasons to grant preference to this technique over ECT. The above mentioned aspect of safety seems to be of little importance in the face of the overall lower effectiveness of MST/MCT. The decision concerning the patient's qualification for ECT is usually made in the case of highly intense mental disturbances (including severe depression, suicidal tendencies, accompanying psychotic symptoms, drug resistance). In these situations it would be senseless and unethical to offer a patient a method that is less effective. A situation in which the administration of ECT would be ineffective while the use of MST/MCT would prove effective seems highly improbable.

3.4. Perhaps the effectiveness of MST/MCT (as well as that of the even weaker technique of TMS) could be improved if more specifically focused magnetic stimulation was applied. It would be necessary to apply functional neuroimaging (e.g. fMRI, SPECT) to identify the superficially located structures with a disturbed metabolism (deep locations are hardly accessible for magnetic stimulation) conditioning the basic disorder (depression). Presumably, magnetic stimulation precisely focused on this area with the help of neuronavigation techniques could allow for the elimination of the metabolic dysfunction (Dell'osso & Altamura 2009; Lefaucheur *et al.* 2007; Schutter & van Honk 2005). This might be one of the possible explanations for the success of the clinical experiment carried out by Mayberg *et al.* in 2005. The experiment consisted of implanting electrodes into Broadmann area 25, which was earlier identified as metabolically hyperactive and then subjected to deep brain stimulation (DBS). By stimulating the area identified as the potential substrate of depression in selected patients, it was possible to achieve a therapeutic effect by way of non-convulsive stimulation.

Most studies in which TMS was applied to the left dorsolateral prefrontal cortex – the region recognized a priori as the "seat of depression" and a good target for magnetic stimulation – caused magnetic stimulation to be applied to an undisturbed area in numerous patients. Few studies on the improvement of the effectiveness of TMS in the treatment of depression, which would describe or use the previously mentioned and complicated instrumentation, have been published so far. The lower effectiveness of the TMS technique could be explained, among other theories, by magnetic stimulation administered "at random", i.e., in the area that potentially participates in the etiopathogenesis of depression, but not in every patient. Since MST/MCT evokes only partial and not generalized seizure activity, the above remarks concerning TMS also apply to this technique to a large extent.

The outlined suggestions regarding the improvement of the effectiveness of MST/MCT make this method either user unfriendly (if all additional supporting techniques be applied) or ineffective (without these techniques). To compare: the generalized seizure activity that occurs during ECT and leads to the excitation of the entire neuronal network of the brain, including all neurotransmitter systems, allows ECT to be applied "at random", i.e., without previous neuroimaging diagnostics searching for the source of depression, and without the necessity of placing stimulating electrodes in specific areas of the head.

CONCLUSIONS

The authors of this work perceive the potential clinical benefits of magnetic convulsions as rather illusory. The prospect of the diminishment of undesirable side effects in the area of cognitive disturbances by way of MCT/MST stimulation as compared to those which occur after ECT does not seem well grounded. Even today, an appropriate selection of parameters in ECT procedures can to a large extent influence the severity of the cognitive side effects. The lower current parameters (amplitude, frequency, width, stimulation duration, charge or energy), which result in shorter seizures (30–40 seconds), are safer in regards to cognitive functions than parameters which evoke long seizure activity (1–2 minutes). Less frequent application of ECT procedures

would be more favorable for cognitive functions than more frequent one (2 versus 3 procedures per week). Also, the effect of ECT procedures conducted unilaterally, i.e., sparingly on the dominant hemisphere, is also a well known and described phenomenon (Hese 2007).

All comparisons regarding difference in safety between ECT and MCT/MST, however, are of secondary importance if all our knowledge regarding actual antidepressant efficacy is based on three (incomplete at that) case reports and there are neither any broader, controlled, randomized and double-blind performed comparative studies nor any larger number of pilot studies performed on small groups of patients. In 2007 Padeberg *et al.* (2007a) assessed the number of patients subjected to magnetic seizure stimulation procedures all over the world as 40 and, as has already been mentioned, the investigations were concerned mostly with the aspect of safety and not that of clinical efficacy.

Since MCT/MST technique still includes "convulsions" or "seizures" in its name, it would be difficult to presume that magnetic technique could evoke lesser worries and objections in a potential patient or in the general public than those referring to electroconvulsive treatment.

It appears that in the nearest future, studies on magnetic convulsions will still be of an investigational rather than an applied nature.

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