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The behavioural effects of the transcranial magnetic brain stimulation (TMS) in a rat: a comparison with electroshocks [1]

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Some experimental studies suggest that stimulation of the central nervous system with strong magnetic field pulses (transcranial magnetic stimulation = TMS) evokes functional and structural changes analogous to those, which take place during electroconvulsive therapy (ECT/ECS).
The aim of our study was to compare the effects of the prolonged (long-time) repetitive rapid-rate TMS and chronic electroconvulsive shocks on rat behaviour in some tests: Open Field, Tail Flick, Apomorphine Hyperactivity and Porsolt's Forced Swim Test.
None of the animals exposed to rTMS showed symptoms of convulsive seizure, which was present in ECS. The Open Field Test showed that neither acute nor chronic rTMS or ECS disturbed general locomotor activity of animals. Chronic ECS evoked analgesia - extending the latency of tail flick (46%). Tail Flick Test showed presence of nociceptive effect after acute and chronic rTMS (respectively 24 and 21% of control values). Both rTMS (max 58% in 30 min of the stimulation for the strongest stimulation regime) and even stronger ECS (max 92%) intensified ampomorphine-induced hyperactivity of animals. Porsolt's Forced Swim Test showed the highest shortening of immobility time after ECS (up to 50% of control values) and slightly lower activity after rTMS (up to 29%). The effect depended on rTMS parameters.
The results obtained proved that rTMS and ECS evoke some antidepressant responses in behavioural tests on rats, but rTMS evokes fewer side effects.

Key words: transcranial magnetic stimulation, electroshocks, behavioural tests, rat

Introduction

In 1992 we published theoretical and model assumptions regarding the possible application of the neuro-physiological technique of transcranial magnetic stimulation (TMS) in treatment of depression [1]. As a new, physical method of depression treatment, TMS method can substitute electroconvulsive therapy, which, despite its high

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clinical effectiveness, is basically applied as a secondary choice method. The superiority of TMS consists of the fact that the antidepressant effect is obtained in a painless way not burdening the patient and it does not require evoking a convulsive seizure, which is unavoidable in the ECT method [2].

Since that year, the method has been applied in several hospitals all over the world in about 250 patients [3, 4, 5, 6]. As an experimental method of treatment, TMS was used mostly in patients with a drug-resistant form of depression. At the present moment, clinical examinations according to the protocols of the third research phase are being conducted (examinations in larger and diversified groups of patients aimed at determining the relation between safety and therapeutic effectiveness of the method). The results of clinical examinations seem satisfactory, though they undoubtedly require testing, especially in a different group than that with drug-resistant depression.

Contrary to the classical research procedures applied in testing new pharmacological means including anti-depressant drugs, TMS method was not submitted to sufficient basic tests on animals. Depending on the kind of research methods, we distinguish four types of experimental investigations: (neuro)structural investigations, neurophysiological investigations, bio-chemical methods and behavioural tests [7, 8, 9]. Only eight works have been published regarding the application of all these methods to animals, and it is a highly insufficient number in comparison to a large number of animal studies on each psychopharmacological drug [10, 11, 12, 13, 14, 15, 16]. We need not discuss the necessity of conducting experiments on animals. They not only allow for evaluation of the biological effectiveness of a new anti-depressant drug of physical method like ECT or TMS (bio-chemical and behavioural models), they also enable us to assess safety. This work presents the results of behavioural investigations, in which we performed a comparison of TMS and ECT techniques in several behavioural tests (consisting in evaluation of the animal's behaviour), which are used in classical pharmacology for evaluation of psychotropic drugs' activity.

Goal

The aim of this study was to compare the influence of repetitive prolonged rapid-rate transcranial magnetic stimulation (rTMS; this type of magnetic stimulation is ascribed the highest anti-depressant effectiveness) and electroconvulsive stimulation (ECS) in rats. In our work, we wanted to examine whether the alternative magnetic field we applied would give in behavioural tests similar results to those observed in rats after ECS or different ones.

Material and method

The experiments were carried out on 114 male Wistar rats, weighing 250-300 g, kept five rats per cage in standard conditions (temperature 22-23^{0}C; 12-12 h dark-light cycle, food and water - ad libitum). The investigations comprised three experiments, in which we applied different parameters of the magnetic field (frequency, duration of a single session, number of stimulation sessions).

Magnetic stimulation was conducted using a prototype magnetic stimulator MS-3 designed in Electro-technology Institute in Warsaw and constructed in ZDANiA at

the Academy of Mining and Metallurgy in Cracow. This stimulator generates an impulsive magnetic field with maximum induction value 1.6 T and maximum frequency f=100Hz. Due to the coil cooling system, total train time could amount to several minutes[2]. Animals submitted to magnetic stimulation were place in special cage-tubes for their immobilisation during the several minutes' stimulation. The coil was placed immediately above the animal's head (Fig 1.).

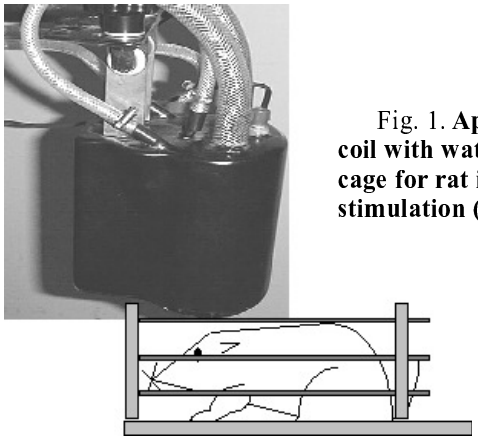

Fig. 1. **Appearance of stimulating coil (core coil with water cooling) and it location over the cage for rat immobilization rat during rTMS stimulation (real size proportion).**

The action of magnetic stimulation was compared with the action of electroshocks applied to the animals - without anaesthetisation - with the use of ear electrodes (clips). The electroshock machine ZK-2 generated electric current with the following parameters: I=150mA, f=50Hz, t=0.5s. The same parameters of electroshock stimulation were used in each experiment. TMS or ECS were applied once a day, every second day, i.e., three times a week, and their total number depended upon the routine (regime) of a given experiment.

The third group consisted of control animals, not submitted to any kind of stimulation, but remaining in the same room as the other two groups. Thus, all groups of animals were exposed to acoustic artefacts generated by the magnetic stimulator while it was on. Each group consisted of eight (experiment No 1; see below) or nine (experiments No 2 and 3) animals. In some experiments (No 2 and 3), in which different parameters of magnetic stimulation TMS were examined, we used several of third groups (TMS1, TMS2, TMS3).

We used the following behavioural tests to estimate stimulation effects: "open field" and "tail-flick" tests (both in the experiment No. 1); apomorphine stereotypy test (experiment No. 2); and Porsolt's forced swimming test (experiment No. 3). Conducting of three separate experiments was connected with the necessity of examining different

[2] Antidepressant activity is seen mostly in a prolonged, i.e. longer than one minute, magnetic stimulation. The presently accessible standard magnetic stimulators ensure constant stimulation lasting 10-15 sec. In clinical investigations, this short train duration is overcome by application of several 10-sec trains divided by several minute long intervals needed for cooling the coil e.g. in a container filled with ice.

parameters of stimulation as well as with the high sensitivity of behavioural tests and the possibility of their interference if more than one were conducted the same day. Behavioural tests were carried out the day after that when the magnetic stimulation procedure was performed.

Examination of motor activity in the "open field" test

The test consists in observing the activity of an animal placed in a special experiment chamber - "an open field". Both the general motor activity (e.g., the distance covered in a given time) and other elements of behaviour like standing on hind legs, defaecations, urinations, scratching, etc., are evaluated.

Initially, the animal, which is placed in a new environment for the first time, examines actively the area of the "open field". This activity may be connected with certain cognitive needs of the animal, and it may correspond to cognitive activity, curiosity or interest of a man, who has come to a new place formerly unknown to him. After a time, when the animal gets acquainted with the place, the interest lessens and the motor activity usually decreases. The activity level achieves a stable value, which is more or less constant for a given individual and is connected with its basic motor activity (temper) [17, 18, 19, 20].

In the experiment, we used a chamber consisting of four neighbouring "open fields" (arenas) 50x50x50 cm in size. A video camera placed above the "open fields" recorded simultaneously motor activity of four animals. We performed evaluation of their motor activity during the first ten minutes after their being placed in the chamber. The "open field" test was carried out after the first and the ninth Tm and EC stimulation. The rats were stimulated with the magnetic field of the following parameters:

B = 1.6 T; f = 30 Hz; t = 330 s; n = 9; N = 89100 impulses = 90 Kimp (kilo-impulses).

Video-recording was analysed with "EYE" software, which allows for tracking of a white spot (the rat) on the background of the dark arena of the "open field", through registering of the animal's co-ordinates. Later, "TRACK-ANALYZER" software measured automatically the distance covered by the animal in the watch-time (it was the only aspect of motor activity that was taken into account in our experiment).

Analgesic effects in the "tail-flick" test

Tests evaluating the influence of the examined drug on the pain threshold are used in psycho-neuro-pharmacological research. "Tail-flick" test is one of these. This test consists in measuring the latency of pain reaction, i.e., duration of pain stimulus applied to the skin of the animal's tail, till the reaction of its removal (flick) beyond the area of the stimulus action. Special instruments are used to generate pain stimulus of changeable strength. In our experiment, the stimulus was generated by a beam of intensive light (like sunrays converged by a lens) applied from an ANALGESIA METER APPARATUS (mod. 33 IITC, Inc.) Landing, N.I. The start of the stimulus turns on a time meter, which is stopped by a photocell impulse at the moment of the tail flick [19, 21, 22, 23, 24].

The "tail-flick" test, like the "open field" test was performed after the first EC and TM stimulations. Due to its much greater invasiveness (application of a pain stimulus), it was performed at least 3-4 hours after the examination of spontaneous motor activity. Since we performed the "tail-flick" test within the frames of the same experiment, the magnetic field used in stimulation had the same parameters as those given above:

B = 1.6 T; f = 30 Hz; t = 330 s; n = 9; N = 89100 impulses = 90 Kimp.

Motor hyperactivity after apomorphine

Psychopharmacological studies indicate that application of apomorphine (in 1-16 mg/kg doses) - leading to stimulation of dopaminergic receptors - triggers off a set of stereotypical behaviours like licking, biting, climbing cage walls as well as hypothermia. In lower doses (<1 mg/kg) apomorphine intensifies locomotor activity without evoking stereotypical symptoms. The effects of motor action of apomorphine are neutralised by neuroleptics. On the other hand, antidepressant drugs as well as ECS sessions intensify stereotypy and motor hyperactivity induced by apomorphine. Certain differences in the influence of antidepressant drugs and ECS on apomorphine induced hypothermia allow for application of a test to detect those antidepressants, which intensify noradrenergic neurotransmission [7, 9, 12, 25, 26, 27].

The animals' motor activity was examined in special photo-mechanic actometers [28], 15 minutes after a dose of 0.5 mg/kg of apomorphine was hypodermically injected. We investigated motor activity for 30 minutes, recording the activity after 10, 20 and 30 minutes of examination. In the test we applied magnetic stimulation according to two regimes that differed in the number of stimulations:

TMS 1: B = 1.6 T; f = 20 Hz; t = 300 s; n = 9; N = 54 Kimp.
TMS 2: B = 1.6 T; f = 20 Hz; t = 300 s; n = 18; N = 108 Kimp.

The regime that included 18 stimulation sessions was the only one in which stimulations were conducted every day and not every second day. Besides, two control groups took part in the experiment: 1) animals not submitted to any stimulation, which received a dose of apomorphine (called control proper), and 2) animals (conventionally called naive), which were not stimulated with EC or TM either, and which received saline injections. The described selection of control groups is a standard procedure used in pharmacological tests.

Porsolt's forced swimming test

The forced swimming test developed by Porsolt is a highly predictive method used in the studies on antidepressant drugs [29]. An animal is forced to swim in a container (for a rat it is a cylindrical glass jar: h = 40 cm; 2r = 18 cm and water level at 15 cm above bottom; water temperature = 25^0C), which it cannot leave. Initially, it manifests high motor activity. After a time, however, it assumes a characteristic posture of immobility, executing only minimum movement necessary to keep its head above water surface. The test is conducted on two subsequent days. On the fist day the animal in placed in the water container for fifteen minutes to adopt to the test. On the second day, it is placed in water again, and its swimming time is measured during five minutes. The examination itself consists in measuring the active swimming period during a several minutes log observation.

It is known that drugs with antidepressant potential decrease the immobility period [20, 30, 31, 32].

In our experiment, Porsolt's test was executed after the 9^{th} or 18^{th} TMS session and after 9 ECS sessions. We applied different stimulation frequencies and stimulation times.

Finally, due to different parameters of stimulation, TMS technique was used in three groups of animals, as shown in the list below:

TMS I: B = 1.6 T; f = 20 Hz; t = 300 s; n = 9; N = 54 Kimp.
TMS II; B = 1.6 T; f = 20 Hz; t = 300 s; n = 18; N =108 Kimp.
TMS III: B = 1.6 T; f = 30 Hz; t = 330 s; n = 9; N = 90 Kimp.

The investigations were conducted in the Institute of Pharmacology of the Polish Academy of Sciences in Cracow. Statistical significance of the results was estimated on the basis of the unifactor variance analysis and t-Student test for independent variables.

Results

"Open field" test

Figure one shows the mean distance covered by animals from all groups during the ten minutes when their motor activity was recorded. The "open field" test showed that neither ECS nor TMS influenced effectively the animals' motor activity. Both after the first and the ninth stimulation session, the motor activity of the stimulated rats increased, but this phenomenon was not statistically significant. A particularly marked motor activation was registered after the first stimulation session (by 48% for ECS and by 60% for TMS; $p \geq 0.05$). This can be explained with the animals' reaction to a completely new and rather stressing situation of the newly started experiment. After nine stimulation sessions, the animals were well adjusted to the three-week-long ex-

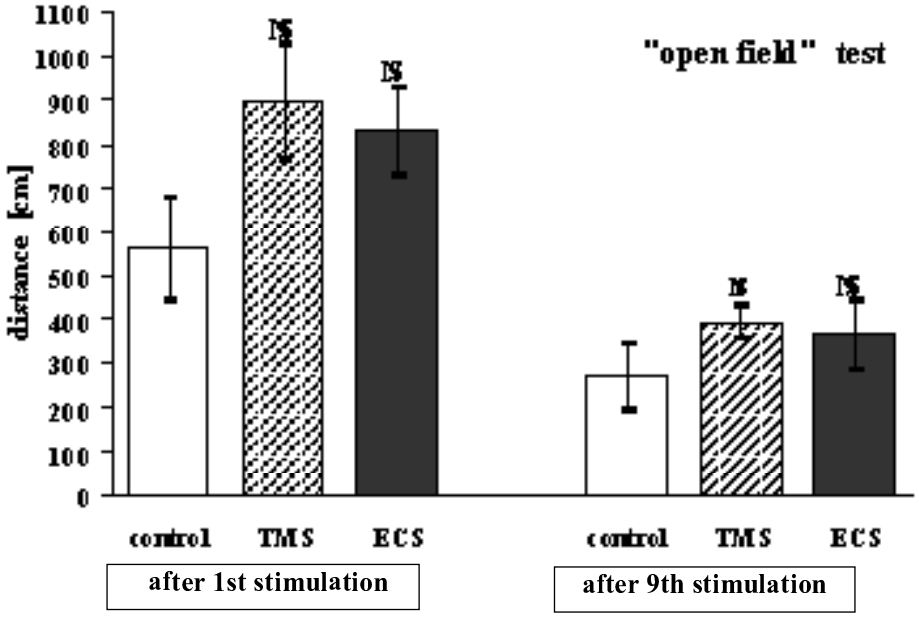

Fig. 2 **Rats' motor activity in the "open field" test after a single and prolonged electroconvulsive shocks (ECS) and transcranial magnetic stimulation (TMS);** each column represents x ± SEM; groups are equal in number, n = 8; NS = no statistical signifi-

periment, hence their motor activity was not connected with the stimulating procedure (activity increased by 36% and 46% respectively; $p \geq 0.05$). This explanation seems to be confirmed by the activity of the control group animals, whose activity after the first day of the experiment was nearly twice as high as after the experiment termination. Execution of the test 24 hours after stimulation showed that, e.g., the particularly high increase of the rats' activity after magnetic stimulation was not connected with the rebound effect after the 5.5 minutes long immobilisation (Fig. 2).

The "open field" test proved that neither ECS nor TMS - while preserving the same tendency (increase of the animals' motor activity) - disturbed the rats' locomotor activity. Thus, none of the techniques manifested tachythymoleptic action, which, in clinical conditions, can be an undesirable side effect of antidepressant drugs.

"Tail-flick" test

Figure 2 shows the results of the "tail-flick" test. The test manifested that both a single TMS stimulation and a whole series of such stimulations (9) led to a consider-

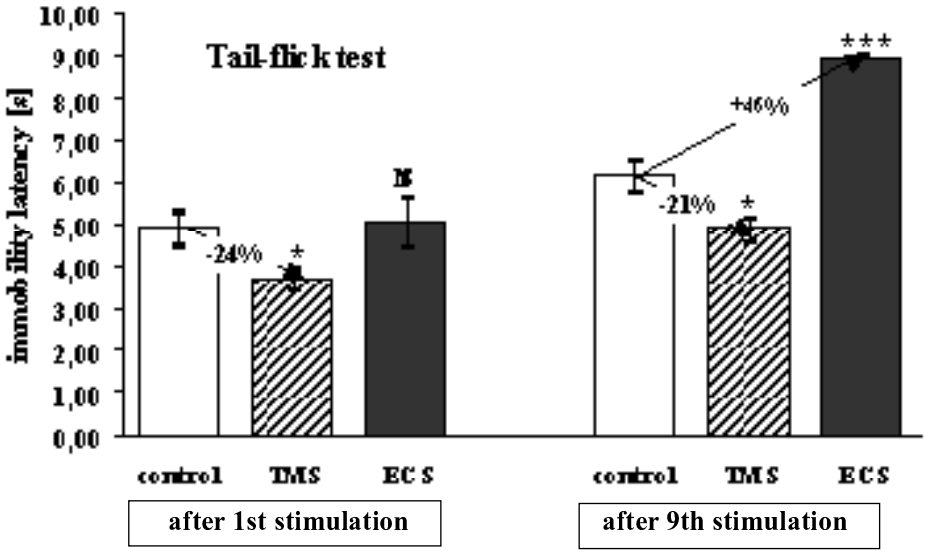

Fig. 3 **Pain threshold in rats measured in the "tail-flick" test after single and prolonged electroconvulsive shocks (ECS) and transcranial magnetic stimulation (TMS);** each column represents x ± SEM; groups are equal in number, n = 8; *=p<0.05; ***=p <0.001; NS = no statistical significance.

able decrease of the tail-flick latency. This effect (hyperalgesia; lowering of the pain threshold) seemed to persist during the whole experiment, since it decreased the latency of pain reaction after the first and the ninth magnetic stimulation session by 24% and 21% respectively ($p<0.05$). A reverse effect was observed after ECT stimulation, but statistical significance was attained only after a series of stimulations. Statistical calculations show that nine ECS sessions evoked analgesia, considerably prolonging

the tail-flick latency by ca. 46% ($p<0.01$) (Fig. 3).

The analgesic action of the ECT series, i.e., disturbance (disappearance) of pain reaction can be interpreted as an undesirable phenomenon resulting from - at least - functional deterioration of the central nervous system. The reverse effect observed after magnetic stimulation, i.e., acceleration of the reaction to a pain stimulus - important, among others, for self-defence - seems a beneficial phenomenon, but its clinical implications require further consideration.

Apomorphine induced hyperactivity

Figure 3 shows the results of influence of TMS and ECS on motor hyperactivity after apomorphine (cumulative diagram). The animals from the "naive" group manifested the lowest motor activity; apomorphine injection in the control proper evoked more than twice as high locomotor activity. The latter group was a control for the groups subjected to stimulation procedures. Statistical analysis showed that electroshocks considerably intensifies the apomorphine induced motor hyperactivity. The activity intensification after ECS was significant at each of the three time points in the test (by 62, 75 and 92% respectively for the 10th, 20th and 30th minute of the test). The influence of TMS

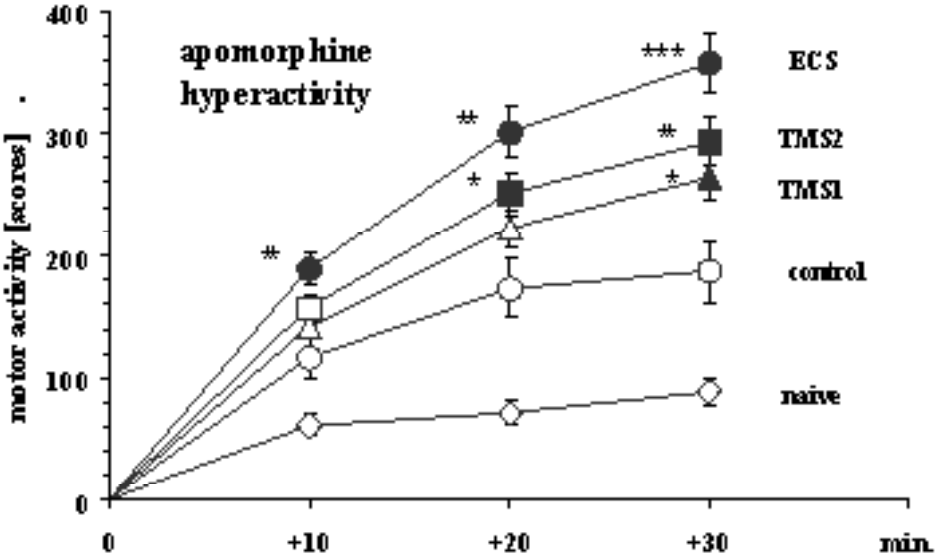

Fig. 4 **Influence of repeated electroconvulsive shocks (ECS) and transcranial magnetic stimulation (TMS) on rats' motor activity after administration of apomorphine - cumulative diagram;** each point represents x ± SEM; groups are equal in number, n = 8; black marker = statistical significance on the level: *= $p<0.05$; **= $p<0.01$; ***= $p<0.001$; white marker = NS = no statistical significance. Legend: TMS 1: b = 1.6 T; f = 20 Hz; t = 300 s; n = 9; N = 54 Kimp.; TMS 2: B = 1.6 T; f = 20 Hz; t = 300 s; n = 18; N

was slightly weaker and clearly dependent upon the number of stimulation sessions. When we applied only 9 stimulation sessions, statistically significant intensification of motor activity (41%; $p<0.05$) was achieved as late as the 30th minute of the test. The more intensive magnetic stimulation procedure (twice as high number of stimulation sessions, stimulation applied every day) allowed us to achieve statistical significance after 20 minutes of the test (45%; $p<0.0$) After the subsequent ten minutes of the test, this effect was even stronger (58%; $p<0.01$) (Fig. 4).

Thus, in the test of motor hyperactivity after apomorphine, TMS manifested action similar to that of ECT; it was dependent upon the dose of the applied magnetic field.

Porsolt's test

Porsolt's test confirmed that EC stimulation led to the greatest decrease of immobility latency (by 50%; $p<0.001$). This means that animals subjected to electroconvulsive stimulation remained active on the water surface for the longest time. This carries simple and understandable clinical implications. The decrease of immobility latency in Porsolt's "forced swimming" test was also observed after application of a series of

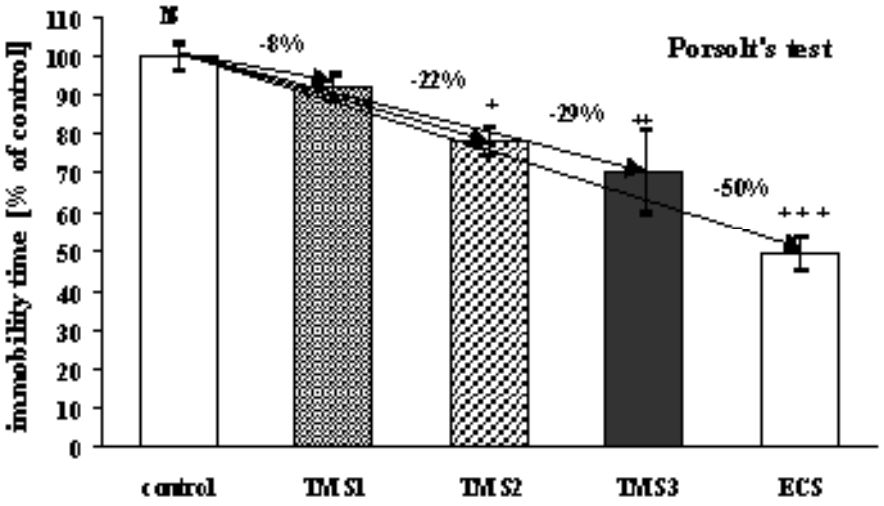

Fig. 5 **Shortening of rats' immobility time in Porsolt's "forced swimming" test after prolonged electroconvulsive stimulation (ECS) and transcranial magnetic stimulation (TMS);** each column represents x ± SEM; groups are equal in number, n= 8; *= $p<0.05$; **=$p<0.01$; ***=$p<0.001$; NS = no statistical significance. Legend: TMS I: B = 1.6 T, f = 20 Hz, t = 300 s, n = 9, N = 54 Kimp.; TMS II: B = 1.6 T, f = 20 Hz, t = 300 s, n = 18, N = 108 Kimp.; TMS III: B = 1.6 T, f = 30 Hz, t = 330 s, n = 9, N = 90 Kimp.; ECS: I = 150 mA, f = 50 Hz, t = 0.5 s, n = 9

magnetic stimulations. The action of TMS was slightly weaker than that of ECS, though it was also statistically significant. The decrease of immobility time after TMS depended upon the frequency and time of stimulation, and the frequency parameter seemed to be more important. So, as compared with the control group, immobility latency was

shortened by 8%, 22% ($p<0.05$) and 29% ($p<0.01$) respectively after magnetic stimulation according to the procedures TMS I, TMS II and TMS III (Fig. 5).

Thus, we showed that the transcranial stiulation technique (TMS) evokes effects similar to those achieved after ECS in the test highly correlated with clinical action of antidepressant drugs. Besides, we proved a correlation between the dose of the applied magnetic field expressed by parameters like frequency and stimulation time, and the value of the obtained biological result (response). Our second observation seems to confirm the existence of correlation between the dose and the result, which was also observed in the test of motor hyperactivity after apomorphine.

Discussion

The influence of magnetic fields (or the so-called magnetic component of electromagnetic fields – EM) on humans and animals has been studied for several decades. The aim of these studies was to prove – or disprove – the influence of artificial, industrial EM fields on behaviour of living organisms, their motor activity and cognitive functions included. The obtained results, however, were neither consistent nor univocal.

The researchers most often observed an increase of motor activity in animals under the influence of magnetic stimulation. As early as in 1960, Barnothy and Barnothy detected over 50% locomotor activation in mice after stimulation with the field of intensity amounting to hundredth parts of tesla [after 33]. The increase of motor activation in animals was detected with the use the "open field" test [34, 35, 36, 37, 38]. Numerous works, however, claimed no influence of a magnetic field on a 24-hour model of animal motor activity [34, 36]. With the use of Nakamura and Thoenen's test allowing for evaluation of animals' irritability on a conventional scale, Mrowiec et al. [40] were not able to detect differences between rats subjected to magnetic stimulation and control rats. Despite a relatively long time of exposure (up to 72 hours) and a strong field (1.5 T), Davis et al. [39] were not able to obtain changes of locomotor activity in mice. Some authors also reported an inhibiting influence of magnetic stimulation. To estimate activity, Mrowiec et al. [40] used the "open field' test and the "hole" test, in which episodes of a rat's crossing over, looking into, climbing up, washing and defecating were counted during three minutes in a special experimental container. In the "open field" test, the authors showed that the activity of rats subjected to magnetic stimulation of 0.01 T and 40Hz decreased. This decrease was observed both after the first stimulation and after 7 days of exposition. The activity of the stimulated animals became equal to that of control animals in the second week of the experiment. Observations made in the first and second week after termination of a 14 days long stimulation procedure did not show any difference in locomotor activity of the two groups of animals. In turn, Norekian et al. [41] detected a prolonged reaction time in rats subjected to stimulation, but this effect persisted for less than one hour after exposition.

The hitherto conducted studies on the influence of magnetic field on memory, attention and generally understood cognitive functions in animals are not univocal either. Experimental works indicate both improvement and deterioration of cognitive functions under the influence of exposition to magnetic field. Using the field of

induction = 10 mT and frequency = 40 Hz, Mrowiec et al. [40] reported a considerable improvement of spatial memory evaluated in the "water labyrinth" test. Innis et al. [after 33] found that the applied magnetic field did not influence significantly the process of memorisation. The results of Levine's and Bluni's works [42] even indicated a considerably decreased ability to learn distinguish the left side from right one in mice after their being exposed to magnetic field. Cieslar et al. [43] detected a change in rats' reactivity to a pain stimulus, in the form of a mild analgesic effect. Other behavioural symptoms in animals, connected with their exposure to magnetic field, were also described [44, 45].

All the studies mentioned above described behavioural action of magnetic field whose parameters (induction, increase rate) did not allow for a specific stimulation of the central nervous system neurons. This field was not able to bring about depolarisation of nervous cell membrane, subsequently evoking its stimulation. This became possible as late as the 1980s. In 1982, Polson et al. performed an effective magnetic stimulation of brain in experimental animals [after 2], and in 1985, Barker at al. executed first clinical experiments on humans. Thus, the new neuro-physiological technique called transcranial magnetic stimulation (TMS) was worked out. Its first and major application was neurological diagnostics. In 1992, a hypothesis was formulated, which described a possibility to apply TMS in psychiatry, as a therapeutic method in treatment of depression - alternative to electroconvulsive therapy [1]. Merely a few clinical centres started research on using TMS in the depressive syndrome therapy. Also, several experiments on animals were performed. The number of hitherto conducted and published behavioural on TMS activity in animals - as contrasted with the number of basic studies on newly synthesised chemical substances with probable antidepressant action - is limited to a mere three [12, 25, 46].

In 1994, Fleischmann et al. were the first to conduct a behavioural experimental study on animals. They performed a comparison of effects of TMS and ECS in rats - in the test of apomorphine evoked stereotypy [12]. In their research, they applied two kinds of magnetic stimulation: a) with the use of a "slow" stimulator Magstim 200: f= 0.2 Hz, 2x25 impulses with a ten minutes' break, for ten days ("single pulse" TMS = spTMS) and b) with the use of a "rapid" stimulator Cadwell Rapid Rate Stimulator: f = 25 Hz, 50 impulses (2 s) for seven days ("repetitive rapid rate" TMS = rTMS). To evoke motor stereotypy they administered 0.25 and 0.5 mg of apomorphine per kg of body weight. They observed an increase of apomorphine induced motor stereotypy when magnetic stimulation of 25 Hz frequency was applied (results on the threshold of statistical significance). TMS stimulation with 0.2 Hz frequency did not give significant results. These results confirmed that magnetic stimulation of the brain can evoke behavioural effects similar to those, which occur after electroconvulsive stimulation, but without a convulsive effect. TMS stimulation with frequencies amounting to several tens of Hz (rTMS) was more effective than that with the frequency < 1 Hz (spTMS).

One year later (1995), Fleishmann's group presented further results of their studies [15]. This time they used exclusively the rTMS stimulator (Cadwell Rapid Rate Stimulator; B = 2.3 T; f = 25 Hz; t = 2 s; n = 50 impulses daily; N = 7-10 days). To evaluate the action of TMS they used apomorphine stereotypy test and Porsolt's forced

swimming test. Magnetic stimulation increased the animals' stereotypical activity (measured in special points) for each dose of apomorphie (0.25, 0.5 and 1 mg/kg of body weight) though it was only after the smallest dose that the difference between TMS stimulated animals and control ones was statistically significant. Porsolt's test confirmed that TMS, like electroconvulsive stimulation, shortened the immobility period. The antidepressant-like effect after TMS was only slightly weaker that that, which was achieved after ECS.

During the international congress on transcranial magnetic stimulation that took palce in Göttingen in 1998, Keck et al. [46] presented the results of their behavioural and endocrinological research conducted on rats. Using another stimulator, also working in rTMS routine (Dantec Mag Pro; B = ?; f = ?; t = ?; n = 300 impulses daily; N = 6 weeks), they found shortening of immobility period in Porsolt's test. On the other hand, they did not detect - after a series of TMS - disturbances in the animals' learning and cognitive functions (Morris's water labyrinth) or emotional sphere (social interaction tests).

In 1997 our team also published the results of comparative research on the TMS and ECS techniques, in which we used several behavioural tests [16]. Then we used a prototype stimulator MS2 (B = 0.1 T; f = 50 Hz; t = 5 min). We found that in the forced swimming test, immobility time was shortened after TMS and even stronger so after ECS. Both TMS and ECS decreased the basic motor activity. EC stimulation diminished cognitive activity and TMS did not. Only electroconvulsive stimulation induced analgesia, prolonging tail flick latency.

Our present studies have confirmed our earlier observations and broadened our knowledge of TMS action in behavioural experiments on rats. In general, we could recognise high safety of the TMS technique. During none of the experiments, i.e., at none of the applied stimulation parameters of the magnetic field, could we evoke a convulsive seizure in any of the rats while this phenomenon was observed at each case of EC stimulation. This time, neither electroconvulsive stimulation nor magnetic stimulation, applied once or repeatedly, disturbed the animals' basic motor activity "open field". Repeated EC stimulation disturbed pain excitability threshold, leading to prolonged latency of pain reaction (tail flick test). This can be explained, i.a., with after shock functional disturbances of the central nervous system (connected with the opioid /?/ system) and seems to be clinically disadvantageous. An opposite effect was observed after one as well as several transcranial magnetic stimulations. Clinical importance and implications of hyperalgesia after TMS require further study and explanation. The apomorphine induced motor hyperactivity test and Porsolt's test showed that TMS worked in a similar way as ECS did: it intensified apomorphine stimulated motor activity and shortened the immobility time during the forced swimming. The effect after TMS was slightly weaker than after ECS. The latest two tests revealed a correlation between the parameters of magnetic stimulation (generally understood dose) and its effect. The conducted experiments showed that TMS, like ECS, evokes in rats certain responses, which suggest its antidepressant action, but brings less undesirable side effects. Basic studies on antidepressant effects of transcranial magnetic stimulation

should be continued [47, 48]. Moreover, they should cover not only other behavioural tests corresponding with animal models of depression, but also bio-chemical examinations (receptor systems, cAMP, channels, e.g., calcium channels, etc.).

Conclusions

1. Transcranial magnetic stimulation (TMS), like ECS, does not disturb basic motor activity in animals.
2. Electroconvulsive shocks - usually after repetitive application - led to disappearance of pain reaction, while single and repetitive transcranial magnetic stimulations induced hyperalgesia.
3. Both TMS and ECS intensified motor activity in animals stimulated before with administration of apmorphine.
4. TMS and, even stronger, ECS shortened immobility time in the forced swimming test.
5. The dose of the applied field (parameters) considerably influenced the behavioural effect of stimulation measured with the apomorphine induced motor hyperactivity test and Porsolt's test.

Literature

1. Zyss T. *Czy terapia elektrowstrząsowa musi być „wstrząsowa" – hipoteza stymulacji magnetycznej mózgu jako nowej terapii psychiatrycznej.* Psychiatr. Pol. 1992, XXVI (6): 531-541.
2. Barker AT *An introduction to the basic principles of magnetic nerve stimulation.* J. Clin. Neurophysiol. 1991, 8: 26-37.
3. George MS, Wassermann E.M, Williams W.A, Callahan A, Ketter T.A, Basser P, Hallett M, Post RM: *Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression.* NeuroReport 1995, 6,:1853-1856.
4. Pascual-Leone A, Keenan J, Freund S. *Repetitive transcranial magnetic stimulation trials in depression.* Europ. Neuropsychopharmacol. 1998, 8, Suppl. 2: 123-124, S.25.05.
5. Pascual-Leone A, Rubio B, Pallardo F, Catala MD *Rapid-rate transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in drug-resistant depression.* Lancet 1996, 347: 233-237.
6. Wassermann EM. *Applications of rTMS in psychiatric disorders.* EEG Clin. Neurophysiol. 1997, 103: 49.
7. Popik P. *Metodyka przedklinicznych badań nad depresją i lekami przeciwdepresyjnymi.* In: *Przewłocka B. (ed.): Depresja i leki przeciwdepresyjne – 10 lat później.* XIII Zimowa Szkoła Instytutu Farmakologii PAN. Mogilany 1996: 27-44.
8. Vetulani J, Stawarz RJ, Dingell JV, Sulser F. *A possible common mechanism of action of antidepressant treatments.* Naunyn-Schmiedeberg's Arch. Pharmacol. 1976, 293: 109-114.
9. Weiss JM, Kilts CD. *Animal models of depression and schizophrenia.* In: Schatzberg AF, Nemeroff CB. (ed.): *Textbook of psychopharmacology.* American Psychiatric Press. Washington 1998: 89-131.
10. Belmaker RH. *The effects of transcranial magnetic stimulation on b-adrenergic receptors and brain monoamines.* Int. J. Neural Transmission 1998, 1, Suppl. 1: 29.
11. Ben-Shachar D, Belmaker RH, Grisaru N, Klein E. *Transcranial magnetic stimulation induces alterations in brain monoamines.* J. Neural Transmission 1997, 104: 191-197.
12. Fleischmann A, Steppel J, Leon J, Belmaker RH. *The effect of transcranial magnetic stimula-*

tion compared with electroconvulsive shock on rat apomorphine-induced stereotypy. Europ. Neuropsychopharmacol. 1994, 4, 3: 449-450.

13. Fujiki M, Steward O. *High frequency transcranial magnetic stimulation mimics the effects of ECS in upregulating astrogial gene expression in the murine CNS.* Mol. Brain Res. 1997, 44: 301-308.
14. Massot O, Grimaldi B, Bailly JM, Kochanek M, Deschamps F, Lambrozo J, Fillion G. *Magnetic field (MF) affects 5-HT1B receptor function in brain: molecular and cellular studies.* Europ. Neuropsychopharmacol. 1998, 8, Suppl. 2: 120, S.25.01.
15. Oliviero A, Di Lazzaro V, Restuccia D, Ferrara L, Iacono D, Della Corte F, et al. *Metabolic changes produced by repetitive magnetic brain stimulation.* EEG Clin. Neurophysiol. 1996, 99: 373, P421.
16. Zyss T, Górka Z, Kowalska M, Vetulani J. *Preliminary comparison of behavioral and biochemical effects of chronic transcranial magnetic stimulation and electroconvulsive shock in the rat.* Biol. Psychiatry 1997, 42: 920-924.
17. Ehlers CL, Indik JH, Koob GF, Bloom FE. *The effect of single and repeated electroconvulsive shock (ECS) on locomotor activity in rats.* Prog. Neuropsychopharmacol. Biol. Psychiatr. 1983, 7: 217-222.
18. Feldman RS, Net CC. *The effect of electroconvulsive shock on fixated behaviour in the rat III.* J. Comp. Physiol. Psychol. 1957, 50: 97.
19. File SE, Green AR. *Repeated electroconvulsive shock has no specific anxiolytic effect but reduces social interaction and exploration in rats.* Neuropharmacol. 1984, 23: 95-99.
20. Kostowski W, Płaźnik A, Nazar M, Jessa M. *Antagonism of behavioral effects of electroconvulsive shock but not those of desipramine by the selective 5-HT-3 receptor antagonist, ondansetron.* Pol. J. Pharmacol. 1995, 47: 193-195.
21. Antkiewicz-Michaluk L, Michaluk J, Romańska I, Vetulani J. *Effect of repetitive electroconvulsive treatment on sensitivity to pain and on [3H]nitrendipine binding sites in cortical and hippocampal membranes.* Psychopharmacol. 1990, 101: 240-243.
22. Antkiewicz-Michaluk L, Rokosz-Pelc A, Vetulani J. *Electroconvulsive treatment effect on cerebral opiod receptor in the rat: changes in d but not m receptor.* Naunyn-Schmiedeberg's Arch. Pharmacol. 1984, 328: 87-89.
23. Korzeniewska-Rybicka I, Płaźnik A. *Analgesic effect of antidepressant drugs.* Pharmacol. Biochem. Behav. 1998, 59: 331-338.
24. Vetulani J, Castellano C, Lason W, Oliverio A. *The difference in the tail-flick but not hot-plate ersponse latency between C57BL/6 and DBA/2J mice.* Pol. J. Pharmacol. Pharm. 1988, 40: 381-385.
25. Fleischmann A, Prolov K, Abarbanel J, Belmaker RH. *The effect of transcranial magnetic stimulation of rat brain on behavioral model of depression.* Brain Res. 1995, 699: 130-132.
26. Marona-Lewicka D, Vetulani J. *Stability and variability of locomotor responses of laboratory roednts. IV. The responses of rats and mice to apomorphine and amphetamine.* Pol. J. Pharmacol. Pharm. 1988, 40: 281-294.
27. Spyraki C, Papadopoulou Z, Kourkoubas A, Varonos D. *Chlorimipramine, electroconvulsive shock and combination thereof: differential effects of chronic treatment on apomorphine-induced behaviours and on striatal and mesocortical dopamine turnover.* Naunyn Schmiedebergs Arch. Pharmacol. 1985, 329: 128-134.
28. Vetulani J, Marona-Lewicka D, Michaluk J, Antkiewicz-Michaluk L, Popik P. *Stability and variability of locomotor responses of laboratory rodents. II. Native exploratory and basal locomotor activity of Wistar rats.* Pol. J. Pharmacol. Pharm. 1987, 39: 283-293.
29. Porsolt RD, LePichon M, Jalfre M. *Depression: a new animal model sensitive to depressant treatments.* Nature 1977, 266: 730-732.
30. Borsini F, Meli A. *The forced swimming tests: its contribution to the understanding of the*

mechanisms of action of antidepressants. Adv. Biosci. 1990, 77: 63-76.

31. Hawkins J, Hicks RA, Phillips N, Moore JD. *Swimming rats and human depression.* Nature 1978, 274: 512.
32. Nishimura H, Tsuda A, Oguchi M, Ida Y, Tanaka M. *Is immobility of rats in the forced swim test "behavioral despair"?* Physiol. & Behav. 1988, 42: 93-95.
33. Zyss T, Dąbrowska B, Zając K, Walczyk M, Markiewicz M, Witusik B. *Investigations on effects of time varying magnetic field stimulation on the diurnal locomotor activity and learning processes of Syrian hamster.* 4th ECNP (the European College of Neuropsychopharmacology) Regional Meeting. Kraków 1999, European Neuropsychopharmacology 1999, 9, Suppl. 1: 34, B-39.
34. Dura GY, Csorba E. *Experimental study on the influence of pulsating electromagnetic field on motor activity.* Bioelectricity 1988, 7: 133-135.
35. Rudolph K, Krauchi K, Wirz-Justice A, Feer H. *Weak 50 Hz electromagnetic fields activate rat open field behavior.* Physiol. Behav. 1985, 35, 4: 505-508
36. Smirnova NP. *"Open field" rat behavior following exposure to a magnetic field.* Z. Wyzsz. Nierw. Diejat. 1984, 32: 72-78.
37. Smith RF, Clarke RL, Justesen DR. *Behavioral sensitivity of rats to extremely-low-frequency magnetic fields.* Bioelectromagnetics 1994, 15: 411-426.
38. Smith RF, Justesen D.R. *Effects of a 60 Hz magnetic field on activity levels of mice.* Radio Sci. 1977, 12: 279-286.
39. Davis HP, Mizumori SJ, Allen H, Rosenzweig M.R, Bennett E.L, Tenforde T.S. *Behavioral studies with mice exposed to DC and 60-Hz magnetic fields.* Bioelectromagnetics 1984, 5: 147-164.
40. Mrowiec J, Cieślar G, Sieroń A, Plech A, Biniszkiewicz T. *Reakcje behawioralne u szczurów poddanych działaniu zmiennego pola magnetycznego.* Balneol. Pol. 1994, XXXVI (3-4): 17-23.
41. Norekian TP, Tishaninowa LV, Cholodow J.A. *Effect of low-frequency alternating magnetic field on the formation avoidance reflexes in the rat.* Z. Wyzsz. Nierw. Diejat. 1987, 37 (3): 485-488.
42. Levine RL, Bluni TD. *Magnetic field effects on spatial discrimination learning in mice.* Physiol. Behav. 1994, 55 (3): 465-467.
43. Cieślar G, Mrowiec J, Sieron A, Plech A, Biniszkiewicz T. *Zmiana reaktywności szczurów na termiczny bodziec bólowy pod wplywem zmiennego pola magnetycznego.* Balneol. Pol. 1994, XXXVI (3-4): 2428.
44. Thomas JR, Schrot J, Liboff AR. *Low-intensity magnetic fields alter operant behavior in rats.* Bioelectromagnetics 1986, 7: 349-357.
45. Trzeciak HI, Grzesik J, Bortel M, Kuska R, Duda D, Michnik J, et al. *Behavioral effects of long-term exposure to magnetic fields in rats.* Bioelectromagnetics 1993, 14: 287-297.
46. Keck ME, Engelmann M, Neumann ID, Landgraf R, Holsboer F, Post A. *Neuroendocrine and behavioral effects of long-term rapid-rate TMS treatment in rats. International Symposium on Transcranial Magnetic Stimulation.* Göttingen 1998, Abstract book 15-03.
47. Zyss T. *Wpływ stymulacji magnetycznej mózgu u szczura a czynność bioelektryczna mózgu - brak danych o wywoływaniu czynności napadowej. In press.*
48. Zyss T, Adamek D, Zięba A, Vetulani J, Mamczarz J, Mika J. *Przezczaszkowa stymulacja magnetyczna a zabiegi elektrowstrząsowe – badania neuroanatomiczne u szczura.* Psychiatria Polska