Curr Neurobiol 2017; 8 (3): 78-88 *ISSN 0975-9042*

The Effects of External Pico-Tesla TMS in Epilepsy Patients MEG Study

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Abstract

Magnetoencephalographic (MEG) recordings were obtained in order to look for possible effects of external pico-Tesla Transcranial Magnetic stimulation (pT-TMS). All subjects were 20 epilepsy patients (11 male, 9 female) ranging from 18-42 years of age (mean:32.2±9.1). The pT-TMS was applied to the above patients with proper field characteristics (magnetic field amplitude:1-7.5pT, frequency: the alpha-rhythm of the patient: 8-13Hz)

We found a significant effect of an increase in the 2-7Hz frequencies in most of the subjects. In addition, patients responded to the pT-TMS with a feeling of relaxation from their seizures and their high MEG abnormal activity followed by an increase in the number of the low frequency components toward their alpha-rhythm. The results were statistically significant at 14 of 20 patients (70%). This method of the pT-TMS has some potential effects to be considered as a non-invasive safe and efficient modality in the managing of epilepsy symptoms.

Keywords: MEG, Epilepsy, pT-TMS, Brain frequencies.

Accepted August 08, 2017

Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive and easy to perform method without direct contact with the underlying skin and has been used to investigate a variety of clinical conditions [1]. Its magnetic field strength is about 1.5 to 2 Tesla at the surface of the coil, and drops off exponentially with distance from it. A review article [2] suggested that TMS has provided important insight into the pathophysiological substrate of human epilepsies and it is a valuable tool for diagnostic, prognostic and therapeutic purposes. Magnetoencephalographic (MEG) recordings is a well-established non-invasive method, for investigating human brain activity with whole head neurophysiological measurements. It measures weak magnetic fields generated at the scalp surface by the underlying electrical activity in the brain and it is significant to the diagnosis, classification, and further understanding of epilepsy [3].

To our knowledge there are only a few reports in the literature investigating epilepsy with MEG and TMS. In a study [4] with MEG and TMS , suggested that the cortical excitability alteration in focal epilepsy is widely distributed beyond the epileptic focus and the profiles of excitability change correlate with clinical severity in terms of seizure frequency. It was suggested by [5] that navigated TMS may reveal the functional plasticity and shifts of motor cortical function, and epileptic foci may modify cortical inhibition and the navigated TMS results. It is also seen in reviews [6] methodological aspects, clinical applications, and future directions of TMS-based mapping. They concluded that noninvasive brain stimulation is an important investigative tool and has potential therapeutic applications in cognitive neuroscience, neurophysiology, psychiatry, and neurology. TMS is particularly useful to establish and map causal brain-behavior relations in motor and non-motor cortical areas. It was suggested [7] that MEG, data fusion models (EEG-fMRI-BOLD), TMS, evoked potentials, intracranial electrophysiology, and EEG complemented by fMRI and PET would certainly help in further understanding the broader association between brain and behavior. It was investigated by [8] neurophysiologic correlates of psychiatric disorders and potential applications in epilepsy.There is an increasing interest in psychiatric evaluation using neurophysiologic tools such as EEG, MEG, and TMS.

In a number of studies by [9] suggested that pico-Tesla (pT) (1pT=10-12 Tesla) external transcranial magnetic stimulation (pT-TMS) to patients has some quantifiable benefit, demonstrated that MEG recordings in patients with seizures disorders showed significant abnormal MEG activity often in the absence of EEG abnormalities. Thus, using external weak pT-TMS we were able successfully to attenuate seizure activity in a cohort of over 100 patients with various forms of epilepsy. Specifically, using the electronic

device invented by [10] we were able to increase the abnormal (2-7Hz) frequencies of the brain activity towards frequencies of less than or equal to those frequencies of the alpha frequency range (8-13Hz) of each patient [11-17]. One possible electrophysiological explanation for the efficacy of pT-TMS has been provided by the proposed "Neural Net Model" [18] that suggests that pT-TMS causes a temporally modulated neuronal inhibition in regions exhibiting abnormal activity in the frequency range of 2-7Hz. This hypothesis is in concordance with data presented by other investigators [19-21]. Clinically, this technique was used in our General University Hospital, Laboratory of Medical Physics in the School of Medicine of Democritus University in Greece [10-17,22] .All patients treated in the above references were referred from Neurologists from Greece , Europe,England and USA .

The aim of this research was to identify any change in the state of the brain consistent with our predictions that the pT helmet electronic device should increase the mean peak frequency difference (MPFD) within the 2-7Hz band towards frequencies ≤ 8-13Hz for each epilepsy patient [10-16,22].

Methods

Biomagnetic measurements were performed using a whole-head 122-channel MEG device (Neuromag-122, Neuromag Ltd. Helsinki, Finland). Recordings were taken in an electromagnetically shielded room in order to avoid extraneous electromagnetic noise. The spontaneous MEG recordings were taken with sampling frequency rate of 256Hz and associated Nyquist frequency of 128Hz, which was well above constituent frequency components of interest in our MEG recordings and avoid interfering artifacts. The MEG signals were filtered with cut-off frequencies at 0.3 and 40Hz.

Patients

The subjects were 20 epilepsy patients (11 male, 9 female) ranging from 18-42 years of age (mean:32.2 ± 9.1). The research was approved by the Research Committee of the Democritus University of Thrace by a decision with the project number 80347. Informed consent was obtained from all individual participants included in the study.

All patients were referred to our Laboratory of Medical Physics in Alexandroupoli, Greece, by practicing neurologists. In this study, we set out to show the effect of pT-TMS in epilepsy patients using MEG recording protocols and a double-blind experimental design. In our study, we haven't included healthy subjects as controls because this research was already published by [23] in which we have used a double-blind experimental design with our pico-Tesla electronic device [10] in order to look for an effect of pT-TMS on healthy subjects.

The pT-TMS electronic device is a modified helmet containing up to 122 coils which are arranged in 5 array groups, so as to cover the 7 brain regions (frontal, vertex, right and left temporal, right and left parietal and occipital) of the subject. It is designed to create pT-TMS range modulations of magnetic flux (intensity: 1-7.5 pT), in the alpha frequency range (8-13Hz) of each epilepsy patient. The pT-TMS device was configured for each individual to generate a square wave (so as to resemble the firing activity of neurons in the brain) modulated magnetic field at the individual's mean peak alpha frequency - generated in the subject's occipital lobe [10,24]. The electronic device has an extra hidden switch to disable current flow to the helmet coils. This switch, controlling real or sham stimulation, was operated by a member of the technical support team, so that neither the subject nor the experimenter were aware of whether sham or real stimulation was applied (double blind design).

The time frame of our clinical investigations was as follows:

1st Day: MEG measurements in our lab (baseline run1). Application of sham stimulation and MEG recordings afterwards (run2). We have found no significant differences in patients' MEG spectrum.

2nd Day: Interview by clinicians after sham stimulation.

Application of real pT-TMS and MEG recordings afterwards (run3). The patients' MEG spectrum was almost like normal in the majority of them with absence most of the abnormal frequencies.

3rd Day: Interview by the same clinicians after real stimulation. They confirmed our findings of our MEG recordings.

10th Day: MEG recording and evaluation again by the same clinicians.

The patient's medication stopped from the 1st day up to the end of the 3rd day. The subjects were at rest with eyes closed in order to avoid artifacts and to enhance alpha rhythm during the MEG recordings. In order to have high sensitivity recordings, the head was stabilized within the MEG helmet with plastic patches so that to reach maximal stabilization. In addition, four indicator coils were attached to the head of each individual patient in order to determine the exact position of the head with respect to the MEG sensors. The exact positions of the coils were determined using a three-dimensional head position indicator (HPI) digitizer. All MEG tracings were visually inspected carefully off-line for movement artifacts and periods contaminated with movement artifacts were cut off.

Experimental Protocol

The time taken for each recording was 2min in order to ensure alertness for each subject. Each patient was scanned in two separate sessions. During each MEG scan the subject had no task and was asked to sit comfortably in the MEG chair.

The 1st session (session 1) consisted of a 2min resting state MEG. These MEG data were subsequently used to establish the subject's alpha frequency in the range of (8-13 Hz), for calibration of the pT-TMS electronic device. In the 2nd session (session 2), the protocol was as follows:

At all times the pT-TMS electronic device, which was connected to the helmet, was set to real or sham pT-TMS by a third party. Neither the researcher nor the participant were aware of the state of the device. In session 2, 2 min of pre-stimulus baseline MEG data were recorded (run 1) in the 1st day. In the 2nd day, 2min of real or sham pT-TMS stimulation were administered with the subject sitting comfortably just outside the scanner room. Following these 2min of stimulation, a further 2min of resting state MEG data were acquired (run 2). This was followed by another 2min of stimulation- in this case the device was switched from sham to real or vice versa (by the third party) and 2 more min of MEG scanning data were carried out (run 3) in the 3rd day.

A software program was developed in our lab in order to detect the amplitude of the primary dominant frequency of the power spectra of the MEG recordings obtained from each epilepsy patient and channel after the application of Fast Fourier Transform (FFT). Then, we were interested in the alpha rhythm of the patient in order to calibrate the electronic device and in the primary dominant frequency of his/her MEG power spectra in the (2-7Hz) band. In order to explain the primary dominant frequency, we used the Matlab program in order to magnify the spectrum (Figure 2).

Data Analysis

We performed our analysis as follows: firstly, we have tried to blindly identify real from sham runs based on the predicted frequency increase due to pT-TMS.

As we have indicated before in (session 2) there are 3 data sets (run1, run2, run3) and the task is to identify where the sham stimulation was delivered (before recording run2 or before recording run3). Based on the frequency differences across all channel groups we were able to make a prediction of the likely stage (run2 sham or run3 sham) of pT -TMS in each of the 20 recording MEG.

In order to blindly identify real from sham stimulation we have to predict the frequency increase due to pT-TMS from all recorded MEG channels. For this purpose, we have to calculate the increase in primary dominant frequency from sham to real stimulation under two conditions. Having this in mind then we can estimate either the average frequency difference for each brain channel by calculating the differences between each average frequency (run1+run3) / 2 from run2 using the relation of run2- (run1+run3) / 2 if run3 is the sham and run2 is the real stimulation or the average frequency difference of (run1+run2) / 2 from the run3 using the relation of run3- (run1+run2) / 2 if the run2 is the sham and run3 is the real stimulation for the same epilepsy patient in each brain channel as it is seen in the following equations 1 and 2.

$$\Delta f(2) = run2 - (run1+run3)/2 \quad \textbf{(1)}$$

$$\Delta f(3) = run3 - (run1+run2)/2 \quad \textbf{(2)}$$

In these equations run1 is considered as the baseline MEG recordings, being the same for both calculations. We have blindly attempted to determine the order of stimulation (run2 sham or run3 sham) based on the mean peak frequency difference (MPFD).

If after all these calculations we have a MPFD to be greater for a particular epilepsy patient then run2 will be the real stimulation and run3 the sham stimulation or the run2 will be the sham stimulation and the run3 will be the real stimulation.

We used students' t-test for the statistical analysis of our results.

Results

We observed that at the 2nd day, after real pT-TMS, most of the patients had MEG spectrum with the majority of the high abnormal frequencies in the 2-7Hz frequency band to be absent. At the 10th day and with no real pT-TMS we observed that most of the patients reported a progressive deterioration to their pretreatment status.

Figure 1A shows the 122- channel MEG and a patient during the recordings. Figure 1B illustrates the configuration of the stimulation coils within the helmet of the pT-TMS device, whereas Figure1C exhibits the frequency output from the device which is 9Hz. Figure 2 shows an MEG raw data and a magnified spectrum after FFT application and in order to explain the primary dominant frequency we used the Matlab program in order to magnify the spectrum, the primary dominant frequency is 3.3Hz.

Figure 1: *A) The 122 channel MEG system inside the shielded room and a patient during MEG recording (small photo). B) The configuration of the stimulation coils within the helmet of the electronic device. C) The frequency output from the electronic device which has calibrated to 9Hz.*

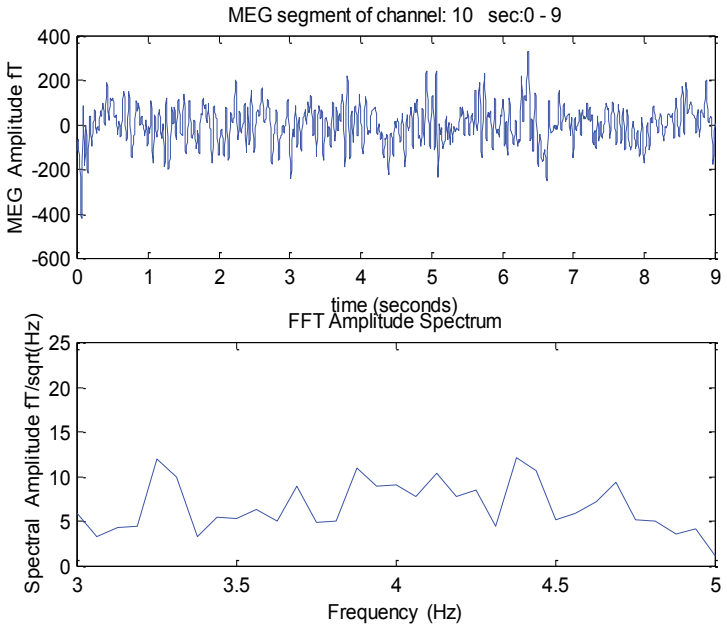

Figure 2: *A MEG record of 9 sec obtained from a patient and its primary dominant frequency after FFT application which is 3.3 Hz.*

A. Patients	**RUN2(REAL) MPFD (Hz)**	**RUN3(SHAM) MPFD (Hz)**
1	0.627	-0.018
3	0.116	-0.158
5	0.305	-0.599
7	0.877	-1.586
9	1.47	-1.24
10	Not clear	
11	1.151	-0.308
12	-0.097	-1.014
17	0.738	-0.107
18	1.18	-0.623
B. Patients	**RUN3(REAL) MPFD (Hz)**	**RUN2(SHAM) MPFD (Hz)**
2	1.417	-0.853
4	0.729	-0.126
6	0.387	-0.385
8	1.39	0.423
13	1.093	0.06
14	1.498	-0.492
15	0.476	-0.584
16	0.128	-0.623
19	0.513	-1.78
20	-1.04	2.189

Table 1. *This table shows the prediction to determine the order of stimulation (run2 sham or run3 sham) based on the on the mean peak frequency (MPFD) in all brain channels in each patient in band 1 (2-7Hz) as is described by equations 2 and 3. On each of the 20 epilepsy patients the prediction was based (run2 sham or run3 sham) on whichever order gave rise to the largest change in MPFD from all MEG recorded channels. In patient 10, the MPFD was not clear because the difference between the two MPFD was too small to discriminate..*

In Table 1, after unbliding based on the knowledge of the true stimulation sequence, we can show the true effect of the pT-TMS. It was found that correctly predicted the order of stimulation in 19 out of 20 patients (95%). In patient 10, the average of all MPFD was not clear because the difference between the two MPFD values was too small to discriminate. Figure 3 shows the MPFD values versus the number of patients according to the data of Table 1.

Figure 4 shows the channels in stereographic projection seen from above. The arrows indicate the direction of the gradient at which the sensor is sensitive. (Neuromag-122 User's Manual: System Hardware). Table 2 shows the symptoms in each of the 20 patients as were evaluated in the interviews by clinicians the 2nd day after sham stimulation and the 3rd day after real pT-TMS application.

In order to determine the maximum effect of stimulation for each of the 7 brain regions we based our results to the maximum on the MPFD for all patients. Thus, Tables 3,4 shown the maximum MPFD values from Real (run2 in $\Delta f(2)$) to Sham (run3 in $\Delta f(3)$) and Real (run3 in $\Delta f(3)$) to Sham (run2 in $\Delta f(2)$) stimulation respectively for each of the 7 brain regions. We have used the maximum values from the Table 3 and Table 4, t-test for the statistical analysis of our results. The statistical significance was evaluated at the level of 0.05. Table 5 shows the statistical analysis for the 10 epilepsy patients of Table 3. We observed a statistical significance difference at 6 patients (60%). Table 6 exhibits the statistical analysis for the 10 epilepsy patients of Table 4. The results are statistical significant at 8 patients (80%). In conclusion, for the 20 epilepsy patients the results were statistically significant at 14 ones (70%).

Discussion

The therapeutic effects of TMS (1.5-2 Tesla) have been

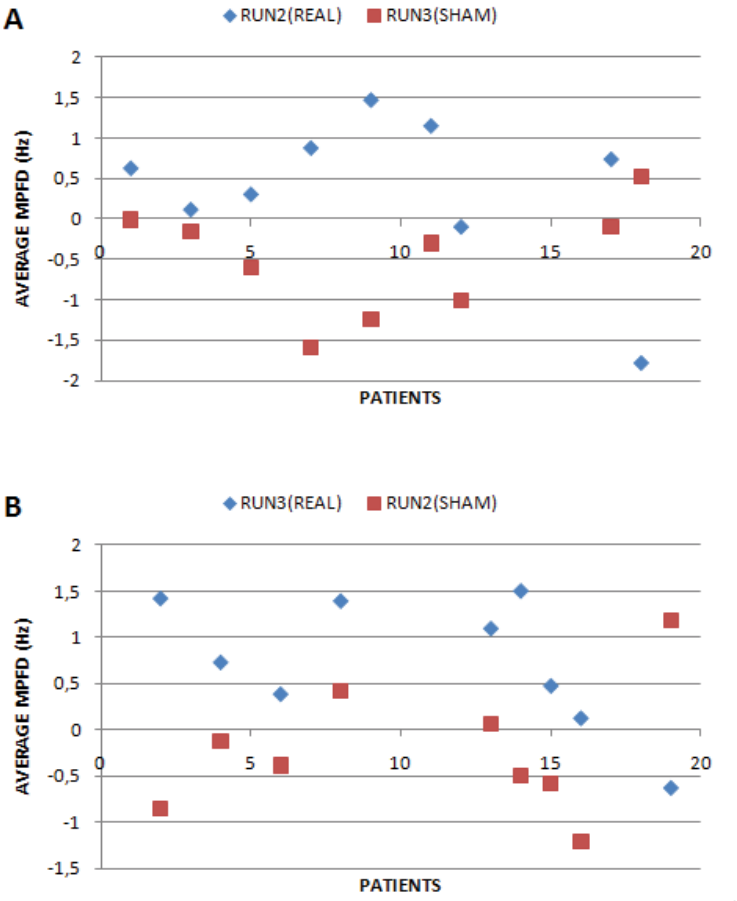

Figure 3: *The average MPFD versus the number of patients according to the data of Table 1.*

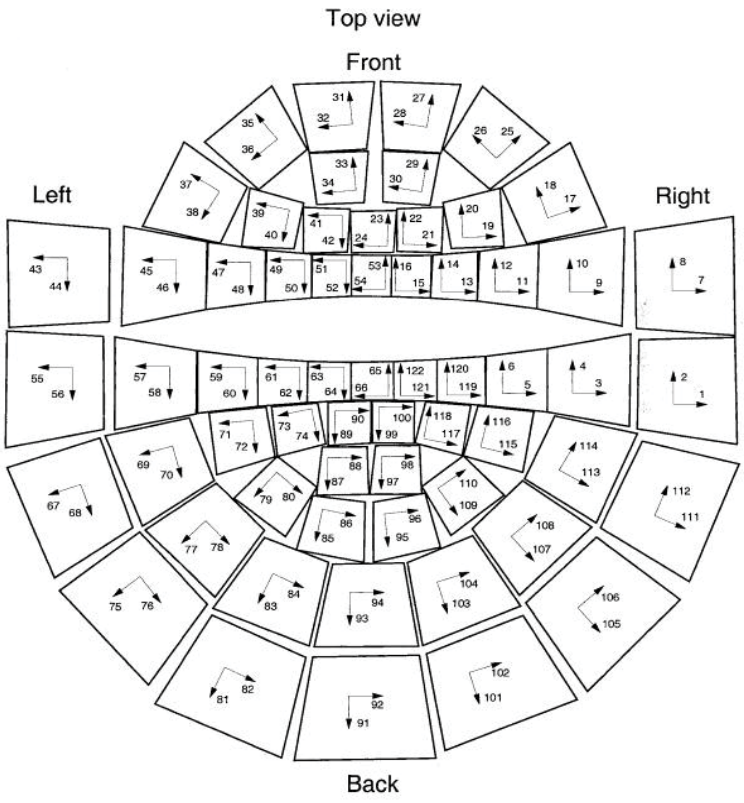

Figure 4: *Scan order of the channel. (Neuromag-122 User's Manual: System Hardware).*

Table 2: *This Table shows the symptoms of 20 epilepsy patients as were evaluated by interview by clinicians after sham stimulation (2nd day in our lab) and after pT-TMS (3rd day in our lab) (F:Female; M:Male).*

Patients	Sex	Symptoms before pT-TMS	Symptoms after Sham TMS	Symptoms after pT-TMS
1	M	He experienced epileptic seizures since the age of 18. His age now is 39 years-old. He received carbamazepine (400-600mg/day) and diazepam (15mg/day). She experienced seizures about one per week. His MEG was characterized abnormal	No change	After pT-TMS his MEG has a reduction of the average emitted power and his seizures.
2	F	She is a 40-year-old female patient suffering from idiopathic petit-mal epilepsy since the age of 11. She was experienced with 5-10 seizures/day with loss of consciousness, without falling down. The anticonvulsant drug therapy was carbamazepine (1200mg/day) and valproid acid (1500mg/day). Her MEG taken prior to magnetic treatment was abnormal.	No change	After pT-TMS her MEG has a reduction of the abnormal emitted power spectrum and her seizures.
3	M	He is 40-year-old man with petit mal seizures since the age of 5. At the age 16 experienced daily tonic-clonic generalized seizures occurred usually at night, but occasionally in the morning upon awakening.His medication included phenytoin (300mg/day), carbamazepine (1200 mg/day). His MEG taken prior to magnetic treatment was abnormal.	No change	After pT-TMS his MEG has a reduction of the abnormal emitted power spectrum with less seizures.
4	F	She is 20-year-old female patient suffering daily from tonic-clonic generalized seizures since the age of 10. The seizures occur with frequency of about 2/day. The anticonvulsant drug therapy was carbamazepine (1200mg/day) and valproid acid (1500mg/day). An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities	No change	After pT-TMS her MEG was characterized with a reduction in the abnormal power spectrum and without daily seizures.
5	M	He is a 36-year-old man with absence (petit mal) seizures since the age of 3. Starting at age 7 he had daily tonic-clonic generalized seizures with a frequency of about 2/day. The seizures occurred usually during sleep but at times in the morning after awakening. His anticonvulsant drug therapy was carbamazepine (1200mg/day) and valproid acid (1500mg/day). An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities.	No change	After pT-TMS his MEG was characterized with a reduction in the abnormal power spectrum and without daily seizures
6	M	He is 42-year-old man with epileptic seizures since the age 20. His patient's mother had a history of seizure disorder. His anticonvulsant drug therapy was carbamazepine (400mg/day) and valproid acid (1500mg/day). An MEG taken prior to magnetic stimulation revealed a background of alpha rhythm activity which was interrupted by brief series of theta and delta waves.	No change	After pT-TMS his MEG was characterized with a reduction in the abnormal power spectrum and without daily seizures.
7	M	He is a 42-year-old man with epileptic seizures since the age of 15. These seizures often preceded by a visual aura. His seizures occurred usually at night, but occasionally in the morning upon awakening. His anticonvulsant drug therapy was carbamazepine (1200mg/day) and valproid acid (1500mg/day). An MEG taken prior to magnetic stimulation revealed a background of alpha rhythm activity which was interrupted by brief series of theta and delta waves.	No change	After pT-TMS his MEG was characterized with a reduction in the abnormal power spectrum and less daily seizures
8	M	He is a 39-year-old male patient suffrering from idiopathic petit-mal epilepsy since the age of 10. He was experienced with 5-8 seizures/day with loss of consciousness, without falling down. The anticonvulsant drug therapy was carbamazepine (1200mg/day) and valproid acid (1500mg/day. His MEG taken prior to magnetic stimulation revealed a background of alpha rhythm activity which was interrupted by brief series of theta and delta waves.	No change	After pT-TMS his MEG taken is shown a reduction of the abnormal emitted power spectrum with less seizures.

9	F	She is 20-year-old female patient suffering daily from tonic-clonic generalized seizures since the age of 10. The seizures occur with frequency of about 2/day. The anticonvulsant drug therapy was carbamazepine (1200mg/day) and valproid acid (1500mg/day). An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities	No change	After pT-TMS her MEG taken after was characterized with a reduction in the abnormal power spectrum, appearance of alpha rhythm and without daily seizures.
10	M	He is 35-year-old building construction worker with absence (petit mal) seizures since the age 10. His anticonvulsant drug therapy was carbamazepine (1200mg/day) and valproid acid (1500mg/day). An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities	No change	After pT-TMS his MEG taken is shown a reduction of the abnormal emitted power spectrum with less seizures.
11	M	He is 42-year-old who experienced seizures since the age of 6. At the age 16 he experienced seizures 1-2/day. His anticonvulsant drug therapy was carbamazepine (1200mg/day) and valproid acid (1500mg/day). An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities	No change	After pT-TMS his MEG taken is shown a reduction of the abnormal emitted power spectrum with less seizures.
12	F	She is 34-year-old female who experienced seizures since the age of 4. She is continued to have seizures usually at sleep. Her anticonvulsant drug therapy was carbamazepine (1200mg/day) and valproid acid (1500mg/day). An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities	No change	After pT-TMS her MEG taken is shown a reduction of the abnormal emitted power spectrum with less seizures.
13	F	She is 18-year-old female with abnormal birth and she experienced seizures since the age 4. Her anticonvulsant drug therapy was carbamazepine (1200mg/day) and valproid acid (1500mg/day). An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities	No change	After pT-TMS her MEG taken is shown a reduction of the abnormal emitted power spectrum with less seizures.
14	F	She is 20-year-old female patient suffering daily from tonic-clonic generalized seizures since the age of 10. The seizures occur with frequency of about 3-4/day. The anticonvulsant drug therapy was carbamazepine (1200mg/day) and valproid acid (1500mg/day). An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities	No change	After pT-TMS her MEG taken is shown a reduction of the abnormal emitted power spectrum with less seizures.
15	F	She is a 21-year-old woman experienced her first tonic-clinic seizure at the age of 18 months. She was the product of a normal pregnancy and delivery and was seizure free until, at the age of 3 years, and tonic-clonic seizures recurred and she was placed on phenytoin. The regimen controlled her seizures until the age of 8 years when she was experienced an exacerbation of seizures. She then was placed on clonazepam (2mg/day) and diazepam (10mg/day) and when she failed to respond she subsequently received sodium valproate (1500mg/day) and carbamazepine (600mg/day). An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities with seizures up to 10 per night	No change	After pT-TMS her MEG taken was shown a reduction of the abnormal emitted power spectrum with less seizures.
16	F	She was 28-year-old women experienced daily tonic-clonic generalized seizures since the age of 10. The seizures occur with frequency of about 3/day. The anticonvulsant drug was carbamazepine (600mg/day) and valproid acid (1500mg/day). An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities.	No change	After pT-TMS her MEG taken was shown a reduction of the abnormal emitted power spectrum with less seizures.

17	M	He was a 22-year-old man experienced chronic grand mal epilepsy and he is intractable to anticonvulsant medication. He has akinetic seizures where he was admitted for evaluation to the program. An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities.	No change	After pT-TMS his MEG taken was shown a reduction of the abnormal emitted power spectrum with less seizures.
18	F	She was 27-year-old women experienced daily chronic grand mal and petit mal seizures since the age 14. The anticonvulsant drug was carbamazepine (600mg/day and valproid acid (1500mg/day). An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities and absence of alpha activity.	No change	After pT-TMS her MEG taken was shown a reduction of the abnormal emitted power spectrum with no seizures.
19	M	He is a 37-year-old man experienced chronic grand mal epilepsy since the age 17. The anticonvulsant drug was Phenobarbital (2gr/day) and Dilantin (200mg/day). An MEG taken prior to magnetic treatment showed diffuse abnormalities with high amplitudes of theta and delta activities and absence of alpha activity.	No change	After pT-TMS his MEG taken was shown a reduction of the abnormal emitted power spectrum with no seizures and the appearance of alpha activity.
20	M	He is a 42-year-old man with a history of grand mal seizure activities with auras. The age of onset is 7. The anticonvulsant drug was Dilantin (300mg/day): Phenobarbital (200mg/day). An MEG taken prior to magnetic stimulation treatment documented with high amplitudes of theta and delta abnormalities with absence of alpha activity.	No change	After pT-TMS his MEG taken was shown a reduction of the abnormal emitted power spectrum with less seizures and the appearance of alpha activity.

Table 3: *This Table shows the effect of the maximum MPFD value from Real (run2 in Δf(2)) to Sham (run3 in Δ((3)) stimulations for each of the 1,3,5,7,9-12,17,21-according to the order of stimulation(run2 sham or run3 sham) in Table 1.*

P	RT Run2 Real MPFD	RT Run3 Sham MPFD	LT Run2 Real MPFD	LT Run3 Sham MPFD	RP Run2 Real MPFD	RP Run3 Sham MPFD	LP Run2 Real MPFD	LP Run3 Sham MPFD	F Run2 Real MPFD	F Run3 Sham MPFD	V Run2 Real MPFD	V Run3 Sham MPFD	O Run2 Real MPFD	O Run3 Sham MPFD
1	5.06	1.69	5.31	2.44	5.56	3.88	5.31	5.69	4.81	4.69	5.44	2.88	5.63	5.69
3	5.19	2.44	3.84	4.69	4.78	1.88	3.75	4.68	1.19	4.56	1.78	4.69	4.78	2.47
5	2.72	1.25	5.69	1.78	3.41	1.81	3.44	3.47	2.81	1.56	3.44	3.47	2.41	3.41
7	3.69	1.81	4.88	1.44	2.75	1.31	2.88	1.44	4.56	3.75	4.13	0.94	3.56	0.94
9	4.63	0.81	4.25	2.81	4.38	0.81	4.25	0.19	4.56	2.44	5	0.81	5.81	1.88
10	1.91	5.38	4.84	4.75	2.84	5.34	4.84	5.44	2.16	3.97	4.84	5.44	4.38	5.34
11	5.09	5.81	5.28	4.69	4.53	5.03	5.28	4.69	4.69	4.56	5.28	5.03	5.5	3.22
12	0.94	0.25	2.78	1.97	2.09	0.25	1.94	4.75	3.59	0.97	2.94	1.97	4.94	0.78
17	5.13	4.5	4.5	3.88	5.13	2.88	4.38	2.88	4.38	4.88	5.13	2.13	3.88	4.25
18	5.5	0.75	5.13	3.13	5.13	0.38	5.13	3.13	3.13	0.5	5.13	4.38	5.25	3.5

P: Patient number, RT: Right Temporal, LT: Left Temporal, RP: Right Parietal, LP: Left Parietal, F: Frontal, V: Vertex, O: Occipital

well established in the literature by other researchers. A review article [25], analyzed the potential mechanisms underlying the therapeutic effects of TMS. They concluded that the total therapeutic effects of repetitive TMS may be determined by their total impact on a number of processes in the brain, including long-term potentiation, long-term depression, changes in cerebral blood flow, the activity of certain enzymes, interactions between cortical and subcortical structures, and gene expression. In [26] presented a critical overview of the studies regarding the technique of paired-pulse TMS to epilepsy patients for the past 20 years. They concluded that paired-pulse TMS is a useful method for measurement of cortical excitability and provides novel information on pathophysiology and drug response of epilepsy. In [27] reviewed the role of TMS in epilepsy research. He emphasized on how human cortex excitability can be assessed by TMS and how this may improve the understanding of pathophysiological mechanisms and the method of action of antiepileptic drugs.

Our study investigated the therapeutic effects of pT-TMS (1p=10-12 Tesla).

Since epileptic foci emit coherent magnetic activity, we have attempted to influence these foci with the pT-TMS

Table 4: *This table shows the maximum MPFD value from Real (run3 in Δ(f(3)) to Sham(run2 in Δf(2)) stimulations for each of 2,4,6,8,13-16,19, 30, according to the order of stimulation (run2 sham or run3 sham) in Table 1.*

P	RT Run3 Real MPFD	RT Run2 Sham MPFD	LT Run3 Real MPFD	LT Run2 Sham MPFD	RP Run3 Real MPFD	RP Run2 Sham MPFD	LP Run3 Real MPFD	LP Run2 Sham MPFD	F Run3 Real MPFD	F Run2 Sham MPFD	V Run3 Real MPFD	V Run2 Sham MPFD	O Run3 Real MPFD	O Run2 Sham MPFD
2	5.50	2.75	5.50	3.94	5.00	4.56	5.50	0.81	5.25	2.19	5.25	4.56	5.00	3.81
4	4.56	4.56	4.81	5.19	5.00	4.25	4.81	5.00	5.00	3.19	4.8	3.1	5.00	2.69
6	5.06	2.09	3.28	2.59	4.97	2.97	4.72	2.59	1.09	1.28	4.72	2.94	4.66	1.84
8	5.75	5.31	5.16	5.09	5.66	4.69	5.16	4.03	5.16	3.53	5.16	4.69	5.66	3.91
13	5.63	5.31	5.56	5.34	5.63	5.31	5.66	4.97	3.75	4.66	5.63	4.88	5.66	4.97
14	5.28	1.53	4.81	3.16	4.97	4.84	4.78	3.16	5.16	5.09	4.84	4.50	4.50	4.38
15	4.72	5.25	5.59	3.13	5.38	5.25	5.59	4.63	4.75	3.44	5.59	4.56	5.41	5.34
16	4.38	3.75	3.63	3.78	4.63	2.50	4.25	3.38	3.25	3.25	4.25	3.38	4.88	2.50
19	5.50	1.69	3.78	2.56	5.50	1.69	3.84	2.56	3.78	3.69	3.97	1.69	4.44	2.66
20	5.88	-2.94	5.63	-3.63	5.31	-2.88	5.63	-2.63	5.31	-3.38	5.63	-2.63	5.50	-3.13

P: Patient Number, RT: Right Temporal, LT: Left Temporal, RP: Right Parietal, LP: Left Parietal, F: Frontal, V: Vertex , O: Occipital

Table 5: *Statistical analysis for the 10 epilepsy patients of Table 3.The results are statistical significant at the level of 0.05(marked bold)*

Patients	RUN2(REAL)	RUN3(SHAM)	t-test p values
1	5.30±0.29	3.85±1.58	**0.034**
3	3.62±1.56	3.63±1.29	0.985
5	3.42±1.08	2.39±1.006	0.092
7	3.89±0.68	1.66±0.97	**0.0003**
9	4.697±0.56	1.39±0.98	**0.0001**
10	3.69±1.33	5.09±0.55	**0.024**
11	5.09±0.35	4.72±0.78	0.2704
12	2.75±1.28	1.56±1.58	0.1497
17	4.65±0.49	3.63±1.01	**0.034**
18	5.20±0.14	2.25±1.66	**0.0005**

Table 6: *Statistical analysis for the 10 epilepsy patients of Table 4. The results are statistical significant at the level of 0.05(marked bold)*

Patients	RUN3(REAL)	RUN2(SHAM)	t-test p Values
2	5.29±0.22	3.23±1.39	**0.0022**
4	4.85±0.16	3.99±0.99	**0.0445**
6	4.07±1.44	2.33±0.62	**0.0125**
8	5.39±0.28	4.46±0.66	**0.0051**
13	5.33±0.71	5.06±0.26	0.3636
14	4.91±0.26	3.81±1.26	**0.0436**
15	5.29±0.39	4.51±0.89	0.0581
16	4.18±0.56	3.22±0.53	**0.0065**
19	4.4±0.78	2.36±0.74	**0.0003**
20	5.56±0.20	1.29±0.88	**0.0001**

electronic device. The coils of the device were constructed to emit back to the brain magnetic fields of appropriate intensities and frequencies to those emitted prior to the application of pT-TMS. This resulted to decrease the maximal magnetic power from these areas and an attenuation of the seizure activity. It is known that magnetic fields modify the activity of the pineal gland, which has been shown to control dopaminergic, and endogenous opioid functions [28,29]. In addition, exposure of an organism or biological material to magnetic fields has been reported to induce mutagenic, immunological, metabolic, endocrine, morphological, developmental, behavioral and anticonvulsant effects [30-32] On a cellular level, the consequences of magnetic fields on seizure activity may be related to alterations in properties and stability of biological

membranes and their transport characteristics including their intra- and extra cellular distributions and flux of calcium ions [21]. Another explanation for the managing of epileptic activity using pT-TMS is based on [33] hypothesis that each stimulus entering the brain is maintained for a certain period of time representing the short-term memory of the particular stimulus occurrence. If the stimulus experience persisted for an extending period of time then the short-term memory of the presented stimulus is converted to the permanent memory of the stimulus. Based on this principle from neurophysiology it may be possible to make the brains of epileptic patients change their abnormal activities to normal using pT-TMS of proper frequencies and intensities.

In [23] have used a double-blind experimental design to look for an effect of our pT-TMS electronic device [10] in healthy subjects. They measured resting state MEG brain activity. After unblinding, they found no significant effect of an increase in the frequency range (2-7 Hz) across the subject group. The fact that of the 14 healthy subjects that were involved in the above study only 8 were characterized with frequencies (2-7 Hz) and exhibited the effect of pT-TMS.

In this study was set out to reproduce the effects of the increased abnormal dominant frequencies of 2-7 Hz band due to the effect of the pT-TMS [10-17] in a group of 20 epilepsy patients. Our experimental design was double-blind and our predictions were based on the true order of stimulation and on the MPFD in the data. After unblinding it was found that correctly predicted the order of stimulation in 19 out of 20 patients (95%). This prediction was in line with what one would expect by chance. The 2nd day's examination with the MEG showed that their spectrum was almost like normal with absent most of the high abnormal frequencies in the 2-7Hz frequency band. All epilepsy patients were evaluated clinically and with the MEG the 10th day after the first application of the pT-TMS in our lab. Most of the patients reported a progressive worsening to their pretreatment status. To determine if the responses elicited in our lab were reproducible, it was advised the patients to apply the pT-TMS treatment nightly (23.00 pm) at home with the same characteristics for each patient with those used in our laboratory.

The instructions given to their relatives were as follows:

1. Place the helmet of the device on the patient head.
2. Turn the power switch on of the electronic device which is calibrated to produce pT-TMS with the characteristics of each patient for two minutes. This is indicated by a green light.
3. When the green light of the electronic device is turned off, turn the power off.
4. Remove the helmet from the head of the patient.
5. Each patient should turn off all the lights in the room and should go to bed immediately after treatment.
6. Sore the electronic device in safe dry area.

Note that all electronic devices are operated with 4x1.5V batteries and all were new at the time that have given to each patient for the above use.

After one-month, pT-TMS treatment at home all patients were evaluated again by the same clinicians and they all reported to have benefit from this treatment.

Conclusion

In conclusion, this method of the pT-TMS has some possible effects to be considered as a non-invasive safe and efficacious modality in the managing the symptoms of epilepsy patients. However, further research with more patients are required in order to estimate the potential effect of pT-TMS and its important contribution for managing the symptoms of epilepsy patients.

Funding

Funding for this work was provided by a collaboration of GGET (General Secretariat of Research and Technology, GR) and ERGO AEBE, INC, GR under the research program titled "Foundation of a Laboratories Network and purchase of a Multichannel Biomagnetometer SQUID (Superconducting Quantum Interference Device), in order to develop an expert system for automatic acquisition, analysis, evaluation and exploitation of MEG signals that are emitted from different organs of the human body" (Grant Number: 80623).

Conflict of interest

The authors declare that they have no conflict of interest.

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