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EC NEUROLOGY
Research Article

Pico-Tesla TMS on Head Injury Patients with A Double Bind Experimental Design. A MEG study

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Received: May 17, 2018; **Published:** June 22, 2018

Abstract

Transcranial magnetic stimulation (TMS) is a noninvasive method for treating a variety of neurological disorders. The aim of this study is to identify any change in the brain state in head injuries in patients after Pico-Tesla (pT)-TMS application. Magnetoencephalographic (MEG) recordings of 5 Head Injury patients were obtained using a whole -head 122-channel MEG system in a magnetically shielded room of low magnetic noise. The subjects were 2 male and 3 female volunteers between 30 - 71 years of age. A double-blind experimental design experimental design was used in order to look for possible effects of external Pico-Tesla TMS on Head injury patients.

Keywords: *MEG; Head Injury; pT-TMS; Brain Frequencies; Double Blind*

Introduction

Transcranial magnetic stimulation (TMS) of several Tesla demonstrated by Baker., et al. [1] is being explored as a noninvasive technique for treating neurological disorders and exploring brain function [2]. Anninos and Tsagas [3] suggested an electronic device that emits pico-Tesla (pT)TMS (1 pico -Tesla=10exp(-12)Tesla) and 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 individual subject [4-9]. One possible electrophysiological explanation for the efficacy of pT-TMS has been provided by the proposed "Neural Net Model" [10] which suggests that magnetic stimulation 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 [11,12].

Aim of the Study

The aim of this study is to identify any change in the brain state of Head Injury (HI) patients with our prediction that the pT helmet electronic device [3] should increase the mean peak frequency difference (MPFD) within the 2 - 7Hz band towards frequencies of less than equal to those frequencies of the alpha frequency (8 - 13Hz) for each individual HI patient.

Material and Methods

Biomagnetic measurements were performed using a whole-head 122-channel SQUID gradiometer device (Neuromag-122, Neuromag Ltd. Helsinki, Finland) (Figure 1A). Recordings were taken in an electromagnetically shielding room in order to avoid extraneous electromagnetic noise. The spontaneous MEG recordings were taken with a sampling frequency rate of 256Hz and the associated Nyquist frequency was 128Hz, which was well above the constituent frequency components of interest in our MEG recordings, so as to avoid aliasing artifacts. The MEG signal was filtered with cut-off frequencies at 0.3 and 40Hz. The subjects were 2 male and 3 female volunteers between 30 - 71 years of age. Informed consent was obtained from all individual participants included in the study. The research was approved by the Research Committee of the Democritus University of Thrace (code number 80347). All HI patients were referred to our Laboratory of Medical Physics in Alexandroupoli, Greece, by practicing neurologists. They were off medication for 24 hours during their participation in the study. In our study we didn't include healthy subjects as controls because this research has been and published by Troebinger., *et al*. [13], in which we have used a double-blind experimental design with our pico Tesla electronic device [3] in order to look for an effect of pT-TMS in healthy subjects.

The time taken for each recording was 2 minutes 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 first session (session 1) consisted of a 2-minute resting state MEG scan. These 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 second session (session 2 scanning session), 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 stimulation by a third party. Neither the researcher nor the participant were aware of the state of the device. First, 2 minutes of pre-stimulus baseline MEG data were recorded (run 1). Next, 2 minutes of real or sham pT-TMS stimulation were administered with the subject sitting comfortably just outside the scanner room. Following these 2 minutes of stimulation, a further 2 minutes of resting state MEG data were acquired (run 2). This was followed by another 2 minutes of stimulation- in this case the device was switched from sham to real or vice versa (by the third party)- and 2 more minutes of MEG scanning data were carried out (run 3).

The pT-TMS electronic device

The pT-TMS electronic device is a modified helmet containing up to 122 coils which are arranged in five array groups, so as to cover the main 7 brain regions (frontal, vertex, right and left temporal, right and left parietal, and occipital regions) of the subject (Figure 1B). It is designed to create pT-TMS range modulations of magnetic flux in the alpha frequency range (8 - 13Hz) of each 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) [14] modulated the magnetic field at the individual's mean peak alpha frequency - generated in the subject's occipital lobe. 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).

Figure 1: *A) The 122-Channel MEG System; B) the pT-TMS Electronic Device.*

Spectral estimates

A software program was developed in our laboratory in order to detect the amplitude of the primary dominant frequency of the power spectra of the MEG recordings obtained from HI patient and channel after the application of Fast Fourier Transform (FFT). In figure 2A, 2B we explained the meaning of the primary dominant frequency.

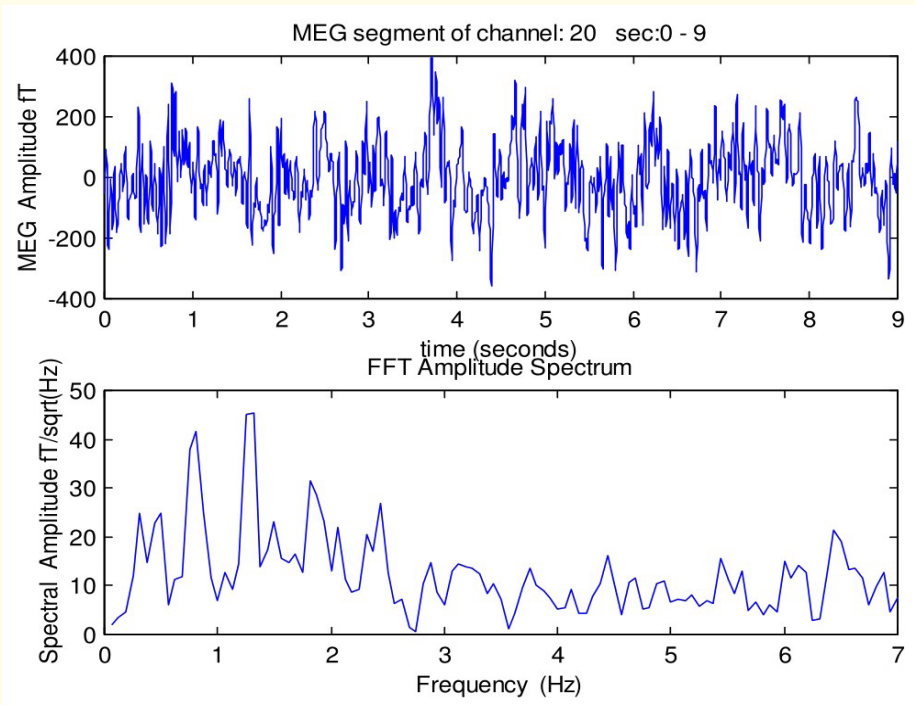

Figure 2: *A) A MEG record of 9 sec obtained from a HI patient B) The application of FFT on the MEG record gives that the primary dominant frequency is 2.4Hz.*

Analysis and Prediction of sham and stimulus runs

As it was 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 it was possible to make a prediction of the likely stage (run2 sham or run3 sham) of pT stimulation in each of the 5 recording MEG HI patients.

The prediction from sham to real stimulation

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

$\Delta f(2) = \text{run } 2 - (\text{run1}+\text{run3})/2$ (1)

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

In these equations run1 is considered as the baseline MEG recording, being the same for both calculations. In order to obtain all the above differences from all brain channels a software program was developed also in our laboratory (using equations 1 and 2) to estimate the (MPFD) of ($\Delta f(2)$ or $\Delta f(3)$) for both calculations. If after all these calculations we have a MPFD from $\Delta f(2)$ in (equation 1) greater for a particular patient then run2 is the real stimulation and run3 the sham stimulation, or if the MPFD is greater from $\Delta f(3)$ in (equation 2) then run3 is the real stimulation and the run2 will be the sham one.

Results

We attempted to determine the order of stimulation (run2 sham or run3 sham) based on the MPFD as shown in table 1. On each of the 5 HI patients our predictions were based (run2 sham or run3 sham) on whichever order gave rise to the largest change in the MPFD from all MEG recorded channels.

Patients Code	Run2	Run3	MPFD
1	Sham	Real	-0.126 < 0.729
2	Real	Sham	0.177 > -0.021
3	Sham	Real	-0.534 < 0.116
4	Sham	Real	No clear
5	Real	Sham	0.032 > -0.059

Table 1: *This table is shown the prediction to determine the order of stimulation (run2 sham or run3 sham) based on the mean MPFD. On each of the 5 Head Injury patients the prediction was based (run2 sham or run3 sham) on whichever order gave rise to the largest change in the mean MPFD from all MEG recorded channels. In patient 4 the MPFD was not clear and after unblinding the prediction was correct in 4/5.*

In table 1 based on the knowledge of the true stimulation sequence, the true effect of pT stimulation is shown. The largest Mean values indicate that our prediction for these HI patients was correct (in 4 cases). Based on the binomial test, the probability for correctly selecting 4 or more events from 5 is highly statistically significant.

The application of pT-TMS literature suggests that the real stimulus runs should have a higher frequency than the sham runs. This was correct in our case after unblinding as it is shown in table 1. Table 2 shows the brain regions and the corresponding channels in each brain region. In table 3 and table 4 in each of the 5 HI patients we can determine the maximum effect of stimulation. In order to determine the maximum effect of stimulation for each of the seven brain regions (Table 2) we have based our results to the maximum on the MPFD for all the 5 HI patients. Thus, in tables 3 and 4 are shown the MPFD in real and sham stimulation in Hz for each of the seven brain regions are shown as stated in table 2 for all the 5 HI patients. Table 5 and 6 represent the statistical analysis for the 5 HI patients. The results were statistically significant at the level of 0.05. We observe that the results of 3 out of 5 patients were statistically significant (60%).

Brain Regions	Channels
Right Temporal	1-14, 111-120
Left Temporal	43-50, 55-62, 67-74
Right Parietal	5-6, 11-16, 97-100, 109, 110, 115-122
Left Parietal	47-52, 59-64, 71-74, 79, 80, 87-90
Frontal	17-42
Occipital	75-86, 91-96, 101-110
Vertex	13-16, 49-54, 61-66, 73, 74, 89, 90, 99, 100, 117-122

Table 2: *This table shows the brain regions and the corresponding channels in each brain region.*

P	RT Run3 (Real)	RT Run2 (Sham)	LT Run3 (Real)	LT Run2 (Sham)	LP Run3 (Real)	LP Run2 (Sham)	RP Run3 (Real)	RP Run2 (Sham)	F Run3 (Real)	F Run2 (Sham)	V Run3 (Real)	V Run2 (Sham)	O Run3 (Real)	O Run2 (Sham)
1	4.56	4.56	4.81	5.19	4.81	5.00	5.00	4.25	5.00	3.19	4.81	3.13	5.00	2.69
3	4.53	1.22	4.56	1.72	4.66	1.72	4.53	1.22	4.63	2.34	4.56	1.50	4.56	0.66
4	5.38	0.25	4.00	1.75	4.00	0.63	5.38	0.63	0.75	0.50	5.38	0.63	5.00	1.88

Table 3: *This table is shown the effect of the maximum MPFD in real and sham stimulations for each of the 1, 3 and 4 Head Injury patients according to the order of stimulation (ru2 sham or run3 sham) in table 1. (In this table in the first column P is for the patient number, in the other columns the RT is the Right temporal brain region, the LT is for the Left temporal brain region, the RP is for the Right parietal region, the LP is for the Left parietal region, the F is for the Frontal region, the V is for the Vertex region and the O is for the occipital brain region).*

P	RT Run2 (Sham)	RT Run3 (Real)	LT Run2 (Sham)	LT Run3 (Real)	LP Run2 (Sham)	LP Run3 (Real)	RP Run2 (Sham)	RP Run3 (Real)	F Run2 (Sham)	F Run3 (Real)	V Run2 (Sham)	V Run3 (Real)	O Run2 (Sham)	O Run3 (Real)
2	0.88	1.06	1.19	1.19	2.19	1.13	0.88	0.63	3.50	1.19	2.19	2.13	3.25	2.00
5	4.56	2.63	4.69	2.94	3.44	2.94	4.56	2.63	1.06	2.31	3.38	4.75	4.63	3.50

Table 4*: This table is shown the effect of the maximum MPFD in sham and real stimulations for each of the 2 and 5 Head Injury patients according to the order of stimulation (ru2 sham or run3 sham) in table 1. (In this table in the first column P is for the patient number, in the other columns the RT is the Right temporal brain region, the LT is for the Left temporal brain region, The RP is for the Right parietal region, the LP is for the Left parietal region, the F is for the Frontal region, the V is for the Vertex region and the O is for the occipital brain region).*

Patients	Run3(Real) Mean ± SD	Run2(Sham) Mean ± SD	t-test P values
1	4.8557 ± 0.1613	4.0014 ± 0.9934	0.0443
3	4.5900 ± 0.0583	1.4786 ± 0.5343	0.0001
4	4.2700 ± 1.6716	0.8957 ± 0.6434	0.0003

Table 5: *This table shows the statistical analysis of the patients 1,3 and 4 of table 3. The results are statistical significant at the level of 0.05 (marked bold).*

Patients	Run2 (Real) Mean ± SD	Run3(Sham) Mean ± SD	t-test P values
2	2.0094 ± 1.0855	1.3311 ± 0.5370	0.1642
5	3.7604 ± 1.3179	3.1004 ± 0.8159	0.2820

Table 6: *This table shows the statistical analysis of the patients 2 and 5 of table 4. The results are not statistical significant at the level of 0.05 (marked bold).*

Discussion

In this study was set out to reproduce the effects of the increased abnormal dominant frequencies of 2 - 7Hz band due to the effect of the pT-TMS in patients with Head Injuries which are a common feature of many of the diseases that affect the brain. A head Injury is any sort of injury to brain, skull, or scalp. This can range from a mild bump or bruise to a traumatic brain injury. Common Head Injuries include concussions, skull fractures and scalp wounds. In our patients the brain injury were mostly bump or bruise traumatic brain injury with headache and loss of coordination.

The consequences and treatments vary greatly, depending on what caused by the head injury and how severe it is [15,16]. Our experimental design was double-blind and our predictions were based of 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 4 out 5 patients. The prediction was in line with what one would expect by chance.

In addition, after unblinding we have found a preliminary effect of an increase in their frequencies of the 2 - 7 Hz across the HI patients and a substantial improvement and normalization of their MEG as it is shown in tables 5, 6 in which we can see that in 3 out of 5 patients the results are statistical significant at the level 0.05 (60%). The mechanisms by which the application of the pT-TMS increase the abnormal frequencies observed in the HI patients are unknown. However, one possible explanation is that these applied magnetic fields have shown to influence the activity of the pineal gland which regulates the endogenous opioid functions [17] and the dopaminergic modulator [18]. Although our positive results are very preliminary with small number of patients, it is encourage to do more studies using this method of pT-TMS in order to evaluate its beneficial contribution for managing the symptoms of HI patients.

Conclusion

Therefore, it is possible to conclude that the treatment of the HI patients with pT-TMS has some potential effect to be an important non-invasive, safe and efficacious modality. However, further investigations are necessary with more subjects using this method of pT-TMS in order to evaluate its possible beneficial contribution for managing the symptoms of HI patients.

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Volume 10 Issue 7 July 2018