ECRONICON OPEN ACCESS

EC NEUROLOGY
Research Article

MEG Evaluation of the Effects of Pico-Tesla External TMS on Migraine Patients

Photios Anninos[1]*, Adam Adamopoulos[1], Athanasia Kotini[1] and Nicolaos Tsagas[2]

[1]Laboratory of Medical Physics, Department of Medicine, School of Health Sciences, Democritus University of Thrace, University Campus, Alexandroupoli, Greece

[2]Department of Electrical Engineering, Polytechnic School, Democritus University of Thrace, Xanthi, Greece

***Corresponding Author:** Emeritus Professor Photios Anninos, Laboratory of Medical Physics, Department of Medicine, School of Health Sciences, Democritus University of Thrace, University Campus, Alexandroupoli, Greece.

Received: January 25, 2017; **Published:** February 08, 2017

Abstract

Magnetoencephalographic (MEG) recordings of 10 Migraine patients were obtained using a whole-head 122 - channel MEG system in a magnetically shielded room of low magnetic noise. The study consisted of 4 male and 6 female volunteers between 45 - 67 years of age. External pT-TMS was applied on the above patients with proper field characteristics (magnetic field amplitude: 1 - 7.5 pT, frequency: the alpha-rhythm of the patient 8 - 13Hz).

In each patient we have considered of two separate recordings sessions one for the baseline and the other one in which we have tried to see the maximum frequency between the first MEG recordings and the MEG recordings after the application of the real stimulation.

We have found a significant effect of an increase in the 2 - 7Hz frequencies range toward the patients' alpha rhythm followed by an improvement of their MEG. The results were statistically significant at 8 out of 10 patients (80%). The pT-TMS has the potential to be an important non invasive safe and efficacious modality in the management of idiopathic migraine patients.

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

Introduction

The precise cause of cortical excitability changes in migraine pathophysiology still is not clear. However, there is a theory that the blood vessels of the brain become narrower. This contracting of the blood vessels, which accounts for the headache in migraine, can cause a reduced blood supply in such a way that nerves cells die and leave scars [1]. Other studies with evoked potential suggested that the migraine brain seems to be "hyperresponsive" to repetitive stimuli between attacks, and demonstrated a lack of habituation to sensory stimuli. Magnetoencephalography (MEG) showed changes of cortical excitability in accordance with the theory of cortical spreading depression during migraine with aura [2]. Neurophysiological studies have provided an insight into migraine pathogenesis. The results are in part conflicting, which may be due to the methodology, patient selection and timing of study. However, quantitative electroencephalography (EEG) and MEG recordings during migraine attacks provide strong, though indirect, evidence favoring the occurrence of spreading cortical depression during attacks of migraine with, and possibly without, aura. Evoked cortical potential and blink reflex studies demonstrate that lack of habituation during repetitive stimulation is a reproducible CNS dysfunction interictally, in both migraine with and without aura. TMS showed excitability changes of the visual cortex. Additionally, neurophysiological techniques have revealed subclinical abnormalities of cerebellar function and neuromuscular transmission, which may improve phenotyping of migraines for genetic and therapeutic studies [3]. Evoked potential studies showed of lack of habituation to sensory stimuli. In addition, TMS suggests an impairment of

intracortical inihibitory circuits in migraine, mainly in migraine with aura [4-7]. Lipton and Pearlman [8] have applied and studied TMS in the treatment of Migraine patients using the TMS as single pulse or as train of pulses. Their method has shown to be effective as an acute treatment for migraine patients especially with aura. Burke., *et al*. [9] showed that rTMS is a promising new therapy for the prevention of migraine headache but has varied across studies.

Anninos and Tsagas [10] using an electronic device increased the abnormal (2 - 7 Hz) 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 [11-22]. One possible electrophysiological explanation for the efficacy of pico-Tesla (pT) TMS has been provided by the proposed "Neural Net Model" [18] 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 [23-25].

The aim of this study is to identify any change in the abnormal (2 - 7Hz) frequencies in the brain of migraine patients with the use of the pT helmet electronic device within the 2 - 7Hz band towards frequencies of less than equal to those frequencies of the alpha frequency range (8 - 13Hz) for each individual migraine patient.

Materials and Methods

Biomagnetic measurements were performed using a whole-head 122-channel SQUID gradiometer device (Neuromag-122, Neuromag Ltd. Helsinki, Finland). 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 4 male and 6 female volunteers between 45-67 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 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 published by Troebinger., *et al*. [26], 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 in healthy subjects.

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 first session (session 1) consisted of a 2-minutes resting of pre-stimulus baseline 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 stimulation and 2 minutes of real 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.

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 5 brain regions (frontal, vertex, right and left temporal and occipital regions) of the subject. 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). Anninos., *et al*. [20] modulated the magnetic field at the individual's mean peak alpha frequency - generated in the subject's occipital lobe [10].

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 each migraine patient and channel after the application of Fast Fourier Transform (FFT) (Figure 1). In Figure 1 we explained the meaning of the primary dominant frequency.

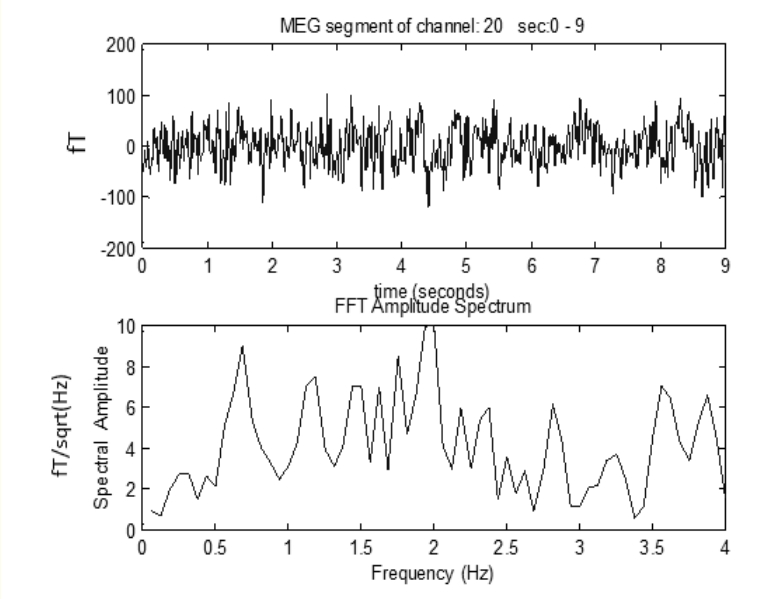

Figure 1: *A) An MEG record of 9 sec obtained from a patient from which in B) after FFT analysis the primary dominant frequency is 2Hz.*

Results

Table 1 shows the brain regions and the corresponding channels in each brain region. Table 2 shows the symptoms in each of the 10 migraine patients before and after the application of the pT-TMS. Table 3 represents the maximum frequency between the first MEG recordings and the MEG recordings after the real stimulation for each of the seven brain regions for the 10 migraine patients. Table 4 represents the statistical analysis for the 10 patients of Table 3. The results were statistically significant at the level of 0.05. We observe that the results of 8 out of 10 patients were statistically significant (80%).

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

Patients	Sex	Symptoms before pT-TMS	Symptoms after pT-TMS
1	F	She has attacks of headaches several a week with aura	She is feeling better
2	M	He has Headaches and feeling nausea and vomiting	He is return to normal
3	M	He has headaches on one side of the head typically at the front	The headaches stopped
4	F	She has moderate or severe headaches and is often described as pulsating	The headaches are moderated
5	F	He has headaches in the morning but may begin at any time of the day or night	The headaches are moderated
6	F	She has headaches and feeling sick(nausea)	The headaches stopped
7	F	She has headaches and not liking bright lights or loud noises, so that she may just want to lie in a dark room	The headaches stopped
8	M	He has migraine headaches attacks with aura	He has less migraine attacks
9	F	She has headaches and feeling sick(nausea)	She is feeling better
10	M	She has moderate or severe headaches and is often described as pulsating	She is feeling more relax

Table 2: *This Table shows the symptoms of 10 migraine patients before and after pT-TMS as were evaluated by interview by clinicians (F: Female; M: Male)*

P	RT BS	RT AS	LT BS	LT AS	RP BS	RP AS	LP BS	LP AS	F BS	F AS	V BS	V AS	O BS	O AS
1	2.94	6.88	6.38	6.88	3.88	6.94	5.63	6.94	6.38	6.94	5.63	6.94	6.81	5.75
2	4.81	6.69	5.19	6.94	6.00	6.81	5.13	6.88	4.94	6.69	6.69	6.88	6.69	6.50
3	5.38	7.00	7.00	6.94	6.31	7.00	6.44	6.94	6.06	6.31	6.44	6.94	6.31	6.81
4	6.31	6.25	6.13	6.94	5.50	6.20	6.13	5.69	6.69	4.56	6.13	6.25	6.31	6.88
5	6.88	6.88	6.88	6.56	6.88	6.88	6.88	6.25	5.50	6.56	6.88	6.25	6.00	3.94
6	5.25	6.70	5.88	6.94	5.25	6.81	5.56	6.88	5.63	6.69	5.56	6.88	6.13	6.50
7	6.00	7.00	6.00	7.00	4.8	7.00	6.9	6.9	6.00	7.00	6.9	7.00	7.00	6.5
8	5.6	7.00	4.9	6.9	7	4.7	4.6	8.00	4.6	6.00	4.6	8.00	4.9	7.7
9	4.5	7	3.8	3.6	6.2	6.6	3.6	8	5.7	5.4	4.5	8	4.6	7
10	6.69	7.00	6.50	7.00	6.69	7.00	6.50	7.81	7.75	7.44	7.13	7.75	6.50	7.88

Table 3: *This Table is shown the maximum frequency (between the first MEG recording (Run1) and the MEG recording after the real stimulation (Run2) for each of the 10 migraines patients. In this Table the first column P is for the patient number, in the other columns the RT is for the right temporal brain region, the LT for the left temporal 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 for the Occipital brain region.(BS and AS are for before and after stimulation).*

Patients	BS (Mean ± SD)	AS (Mean ± SD)	t-test (P values)
1	5.38 ± 2.06	6.75 ± 0.19	0.0324
2	5.64 ± 0.66	6.77 ± 0.02	0.0035
3	6.27 ± 0.24	6.84 ± 0.06	0.0171
4	6.17 ± 0.13	6.11 ± 0.65	0.8569
5	5.5 ± 3.19	6.69 ± 016	0.0963
6	5.60 ± 0.10	6.77 ± 0.02	0.0001
7	6.23 ± 0.62	6.91 ± 0.035	0.0405
8	5.17 ± 0.78	6.90 ± 1.45	0.0104
9	4.7 ± 0.89	6.51 ± 2.44	0.0220
10	6.82 ± 0.22	7.41 ± 0.17	0.0273

Table 4: *Statistical analysis for the 10 migraine patients in Table 3. The results are statistical significant at the level of 0.05 (marked bold).*

Discussion

Research into migraine pathophysiology has been hampered by the episodic nature and unpredictable onset of migraine attacks. 133Xe blood flow techniques, transcranial Doppler, and SPECT have all been employed to investigate hemodynamic changes during migraine aura. PET has been useful in the study of migraine without aura, with findings of increased blood flow related to pain in cortical areas and in the medial brainstem. Currently, three functional MRI imaging techniques are also being used in migraine research. Studies using perfusion-weighted imaging have shown alterations in relative cerebral blood flow (CBF), relative cerebral blood volume, and mean transit time during migraine with visual aura. MEG studies support the presence of a spreading depression-like phenomenon in migraine with aura [27].

There are only a few MEG studies regarding the effect of TMS in migraine patients. Nitsche., *et al*. [28] tested the role of dopamine in human cortical neuroplasticity. Changes of excitability were induced by transcranial direct current stimulation (tDCS). The results of this study render the application of tDCS practicable in diseases displaying enhanced cortical excitability, e.g. migraine and epilepsy. Aurora., *et al*. [5] examined TMS indices of cortical excitability in patients with episodic migraine (EM) and probable chronic migraine (PCM), and matched controls. TMS-based methods would be important for future research examining the evolution of chronic migraine from episodic migraine over time. Aurora., *et al*. [4] reported a preliminary study confirming hyperexicitability of the occipital cortex in migraine with aura (MwA) using TMS. Aurora., *et al*. [6] studied the cortical stimulation silent period (CSSP) elicited by TMS, which is in part a measure of central inhibition of motor pathways in migraine with aura (MwA) patients and normal controls. There was an inverse correlation between the duration of CSSP and an increased frequency of headache. The shortened CSSP that they measured in MwA patients compared to normal with low intensity magnetic stimulation suggests reduced central inhibition resulting in increased excitability of cortical neurons in migraine subjects. The association of CSSP reduction with increased frequency of migraine is further suggestive that brain excitability is the basis of susceptibility to migraine attacks. Aurora., *et al*. [7] compared the threshold for eliciting phosphenes by TMS and the ability to visually trigger headache in a select group of individuals with migraine with and without aura to normal controls. There is a difference in threshold for excitability of the occipital cortex in migraineurs and controls. The hyperexcitable visual cortex in migraine is predisposed to visually triggered headache.

In this study we set out to replicate the effects of the increased abnormal dominant frequencies of 2 - 7 Hz band due to the effect of the pT stimulation [11-22,26] in a group of 10 migraine patients. We tried to do our MEG measurements so as to have the highest possible precision as stated before.

In this study we haven't included healthy control subjects because as we have stated before, Troebinger., *et al*. [26] used a double-blind experimental design to look for an effect of our pT-TMS electronic device [10] in healthy subjects using MEG to measure resting state brain activity. After unblinding, we found no significant effect of an increase in the frequency range (2 - 7Hz) across the subject group. This was due to the fact that from the 14 healthy subjects that were involved in the above study only 8 were characterized with abnormal frequencies (2 - 7 Hz) and had the effect of pT-TMS.

In our studies we thought it would be interesting to look for more substantial effects in different brain regions of the migraine patients, as explained in Table 3.

Examination of the migraine patients in the following day with the MEG shows that their spectrum was almost like normal with most of the high abnormal frequencies in the 2 - 7Hz frequency band being absent. All the migraine patients were evaluated clinically and with the MEG once again after one week after the first application of the pT-TMS in our laboratory. Most of the patients reported that they progressively deteriorated to their pretreatment status. To ascertain if the responses elicited in our lab were reproducible, the patients were advised to apply nightly at (23.00 pm) the pT-TMS treatment at home with the electronic device mentioned before in the methods. After this all the migraine patients were evaluated again and they all reported to have benefited from this treatment. The mechanisms by which the application of the pT-TMS attenuated the migraine patient's syndrome are unknown. However one possible explanation is that these magnetic fields have been shown to influence the activity of the pineal gland (PG) which regulates the endogenous opioid functions [29] and the dopaminergic modulator [30], GABA [27,31]. Moreover on the cellular level, magnetic fields have been shown to influence the properties and stability of biological membranes as well as their transport characteristics including the intra and extracellular distributions and flux of calcium ions [25].

Conclusion

Therefore, it is possible to conclude that this method of the pT-TMS has some potential to be an important non invasive, safe and efficacious modality in the management of idiopathic migraine patients. 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 idiopathic migraine patients.

Acknowledgement

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 have declared that no conflicts of interest exist.

Bibliography

1. Mogens D and Lennart G. «Epilepsy», prejudice and fact/Mogens Dam and Lennart Gram) translated into English by Priscilla Mouritzen, 1st ed. Munksgaard, Copenhagen (1985).

2. Demarquay G., *et al*. "Neurophysiological evaluation of cortical excitability in migraine, a review of the literature". *Revue Neurologique Paris* 169.5 (2013): 427-435.

3. Schoenen J. "Neurophysiological features of the migrainous brain". *Neurological Sciences* 27.2 (2006): S77-S81.

4. Aurora SK., *et al*. "The threshold for phosphenes is lower in migraine". *Cephalalgia* 23.4 (2003): 258-263.

5. Aurora SK., *et al*. "Cortical inhibition is reduced in chronic and episodic migraine and demonstrates a spectrum of illness". *Headache* 45.5 (2005): 546-552.

6. Aurora SK., *et al*. "The cortical silent period is shortened in migraine with aura". *Cephalalgia* 19.8 (1999) :708-12.

7. Aurora SK., *et al*. "The occipital cortex is hyperexcitable in migraine, experimental evidence". *Headache* 39.7 (1999): 469-476.

8. Lipton RB and Pearlman SH. "Transcranial magnetic simulation in the treatment of migraine". *Neurotherapeutics* 7.2 (2010): 204-212.

9. Burke MJ., *et al*. "Repetitive TMS for migraine prevention, evaluating rationale for location and frequency of stimulation". *Brain Stimulation, Basic, Translational, and Clinical Research in Neuromodulation* 8.2 (2015) : 334-335.

10. Anninos PA and Tsagas N . "Electronic apparatus for treating epileptic individuals US patent 5453072" (1995).

11. Anninos P., *et al*. "MEG evaluation of Parkinson's diseased patients after external magnetic stimulation". *Acta Neurologica Belgica* 107.1 (2007): 5-10.

12. Anninos P., *et al*. "Transcranial magnetic stimulation. A case report and review of the literature". *Acta Neurologica Belgica* 106.1 (2006): 26-30.

13. Anninos P., *et al*. "Magnetic stimulation can modulate seizures in epileptic patients". *Brain Topography* 16.1 (2003): 57-64.

14. Anninos P., *et al*. "Meg recordings of patients with CNS disorders before and after external magnetic stimulation". *Journal of Integrative Neuroscience* 7.1 (2008): 17-27.

15. Anninos P., *et al*. "Evaluation of an intracranial arachnoid cyst with MEG after magnetic stimulation". *Journal of Integrative Neuroscience* 6.2 (2007): 227-232.

16. Anninos PA., *et al*. "Nonlinear analysis of brain activity in magnetic influenced Parkinson patients". *Brain Topography* 13.2 (2000): 135-144.

17. Anninos PA., *et al*. "Dynamics of neural structures". *Journal of Theoretical Biology* 26.1 (1970): 121-148.

18. Anninos PA., *et al*. "A brain model theory for epilepsy and the mechanism for treatment with experimental verification using SQUID measurements". In Cotterill RM, (ed). Models of brain function. New York: Cambridge University Press (1989): 405-421.

19. Anninos PA., *et al*. "The biological effects of magnetic stimulation in epileptic patients". *Panminerva Medica* 41.3 (1999): 207-215.

20. Anninos PA., *et al*. "Magnetic stimulation in the treatment of partial seizures". *International Journal of Neuroscience* 60.3-4 (1991) : 141-171.

21. Kotini A and Anninos P. "Alpha, delta, and theta rhythms in a neural net model. Comparison with MEG data". *Journal of Theoretical Biology* 388 (2015): 11-14.

22. Anninos P., *et al* . "MEG as a Medical Diagnostic Tool in the Greek Population". *Acta Medica (Hradec Kralove)* 58.3 (2015): 71-78.

23. John ER. "Mechanisms of memory in representational systems". *Academic Press, New York* (1967).

24. Kaczmarek LK and Adey WR. "Weak electric gradients change ionic and transmitter fluxes in cortex". *Brain Research* 66 (1974): 537-540

25. Ossenkopp KP and Cain DP. "Inhibitory effects of acute exposure to low intensity 60Hz magnetic fields on electrically kindled seizures in rats". *Brain Research* 442 (1988):255-260

26. Troebinger L., *et al*. "Neuromagnetic effects of pico-Tesla stimulation". *Physiological Measurement* 36.9 (2015): 1901-1912.

27. Cutrer FM., *et al*. "Functional neuroimaging, enhanced understanding of migraine pathophysiology". *Neurology* 559.2 (2000): S36-S45.

28. Nitsche MA., *et al*. "Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex". *European Journal of Neuroscience* 23.6 (2006): 1651-1657.

29. Lissoni P., *et al*. "A clinical study on the relationship between the pineal gland and the opioid system". *Journal of Neural Transmission* 65.1 (1986): 63-73.

30. Brandbury AJ., *et al*. "Melatonin action in the mid-brain can regulate dopamine function both behaviourally and biochemically". In, Brown GM, Wainwright SD, (eds). The Pineal gland, endocrine aspects. Oxford : Pergamon Press (1985): 327-332.

31. Antón-Tay F. "Melatonin, effects on brain function". *Advances in Biochemical Psychopharmacology* 11 (1974): 315-324.

Volume 4 Issue 5 February 2017