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Research Article

Pico Tesla TMS in Parkinson's Disease

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Abstract

Purpose: Magnetoencephalographic (MEG) recordings of Parkinson's disease patients were obtained in order to look for possible effects of external pico-Tesla transcranial magnetic stimulation (pT-TMS).

Methods: Biomagnetic measurements were performed using a whole-head 122-channel MEG device. The Parkinson's disease patients were 10 male volunteers ranging from 56 - 67 years of age. The external pT-TMS was applied to the above patients with proper field characteristics (magnetic field amplitude: 1 - 7.5pT, and frequency: the alpha-rhythm of the patient: 8 - 13 Hz).

Results: Using to the above MEG recordings Fast Fourier statistical analysis we found a significant effect 6/10 (60%) of increase of the frequencies in the range of 2 - 7 Hz across the subjects towards frequencies of less or equal to those frequencies of the alpha frequency range (8 - 13 Hz).

Conclusion: The pT-TMS has some possible effects to be considered as a non-invasive secure and efficient modality in managing the Parkinson's disease patients. Therefore, further investigation is needed before firm conclusions can be drawn.

Keywords: *MEG; Parkinson disease; pT-TMS*

Introduction

A number of studies have suggested that pico-Tesla (pT) (1pT = 10 - 12 T) external transcranial magnetic stimulation (pT-TMS) in Parkinson's disease patients has some medical advantage [1-4]. Anninos., *et al.* [1] using MEG recordings in Parkinson's disease (PD) patients observed exhibited abnormal activities by high amplitudes and low frequencies. Application to the above PD patients of pT-TMS with intensity 1 - 7.5pT and frequency the a-rhythm of the patient (8 - 13 Hz) for 2 minutes, in the left-right temporal, frontal-occipital and vertex and recorded the MEG activity again it was observed that the application of the pT-TMS resulted in a rapid attenuation of the MEG activity in the PD patients. Sandyk., *et al*. [5] evaluated the effect of pT-TMS in a PD patient with severe levodopa-induced dyskinesias. The application of pT-TMS with a frequency of 2 Hz and intensity of 7.5 pT for 6 minute period, resulted in a rapid and dramatic attenuation of PD disability and in an almost complete resolution of the dyskinesias. Furthermore, this effect persisted for about 72 hours and then the patient regressed to his pretreatment state. Rothwell, [6] assessed the safety of repeated short train (4 stimuli) of rapid rate-TMS (rrTMS) over the left motor cortex in normal subjects by monitoring the electroencephalogram (EEG) and assessed aspects of neurological (balance, gait, two-point discrimination, blood pressure, pulse rate) cognitive (attention, memory, executive function) and motor function (speed movement, initiation, execution, manual dexterity) before and after the blocks of rrTMS. Spagnolo., *et al*. [7] suggested that high-frequency repetitive deep TMS might be a safe treatment for PD motor symptoms but additional placebo-controlled, randomized studies are necessary. Moissello., *et al*. [8] suggested that rTMS applied after the acquisition of a motor skill over specific areas might improve retention ability in PD.

Anninos and Tsagas [9], invented an electronic device that increased 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 - 13 Hz) of each individual subject [3]. One possible electrophysiological explanation for the efficiency of pT-TMS has been provided by the proposed "Neural Net Model" [10] that suggests that magnetic stimulation causes a temporally modulated neuronal inhibition in regions exhibiting abnormal activity in the frequency range of 2 - 7 Hz. This hypothesis is in concordance with data presented by other investigators [11,12]. Clinically, this technique was used in our General University Hospital, Laboratory of Medical Physics in the School of Medicine of Democritus University in Greece [1-4,13]. All patients treated in the above references were referred from Neurologists from Greece, England and USA.

The aim of our research is to find out if there is any change in the patients brain consistent with our predictions that the pT helmet electronic device should increase the frequencies of the 2 - 7 Hz band towards frequencies of less or equal to those frequencies of the alpha frequency range (8 - 13 Hz) for each individual PD patient.

Methods

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

All 10 PD patients were male volunteers ranging from 56 - 67 years of age. The research was approved by the Research Committee of the Democritus University of Thrace by a decision with a project number 80347. All PD patients were referred to our Laboratory of Medical Physics in Alexandroupolis, Greece, by practicing neurologists. For all patients informed consent for the methodology and the aim of the study was obtained prior to the procedure. In this study, we set out to show the effect of pT-TMS on PD patients using MEG recording. In our study, we haven't included healthy subjects as controls because this research was already published by Troebinger., *et al.* [14] who have used a double-blind experimental design with our pico-Tesla electronic device in order to look for an effect of pT-TMS on healthy subjects.

All patients met the UK Parkinson disease Brain Bank Criteria for idiopathic PD [15]. Most patients experienced body bradykinesia, rigidity and tremors and were initially administered with levedopa-carbidopa (sinemet 25/250) (1 tablet, twice daily). All patients were off medication for 24 hours during their participation in the study. They were in the same condition (at rest with eyes closed in order to avoid artifacts and to enhance alpha rhythm) during the MEG measurements. The PD patients were carefully selected, having minimal hand and head or trunk tremors. The recordings were performed with their arms and hand muscles relaxed and tremor developed spontaneously. The head was stabilized within the MEG helmet by plastic patches, so as to reach maximal stabilization. In addition, four indicator coils were attached to the head of each individual PD 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 HPI digitizer. All MEG data tracings were visually inspected carefully off-line for movement artifacts and periods contaminated with movement artifacts were cut off. 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 scanning session (session 2), the protocol was as follows. At all times the pT-TMS electronic device which is connected to the helmet was set to for real stimulation. First, two minutes of pre-stimulus baseline MEG data were recorded (run 1). Next, two minutes of real pT-TMS stimulation were administered with the subject sitting comfortably just outside the scanner room. Following these two minutes of stimulation, a further two minutes of resting state MEG data were acquired (run 2). The helmet of 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 (intensity: 1 - 7.5 pT), in the alpha frequency range (8 - 13 Hz) of each PD 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 alpha frequency - generated in the subject's occipital lobe [16]. 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 PD patient and channel after the application of Fast Fourier Transform (Figure 1). The actual signal length for analysis was 2 minutes and the FFT was applied only to 17 secs of this length. Then we looked for interest (alpha for calibration of the electronic device and (2 - 7 Hz) for the analysis) and as we stated above at the primary dominant frequency of the power spectra of the MEG recordings obtained from each PD patient and channel after the application of the Fast Fourier Transform. In order to explain the primary dominant frequency, we used the Matlab program in order to magnify the spectrum. Thus, in the spectrum we didn't see the whole frequency range which was 2 - 7 Hz but only the range 2 - 5 Hz due to the magnification.

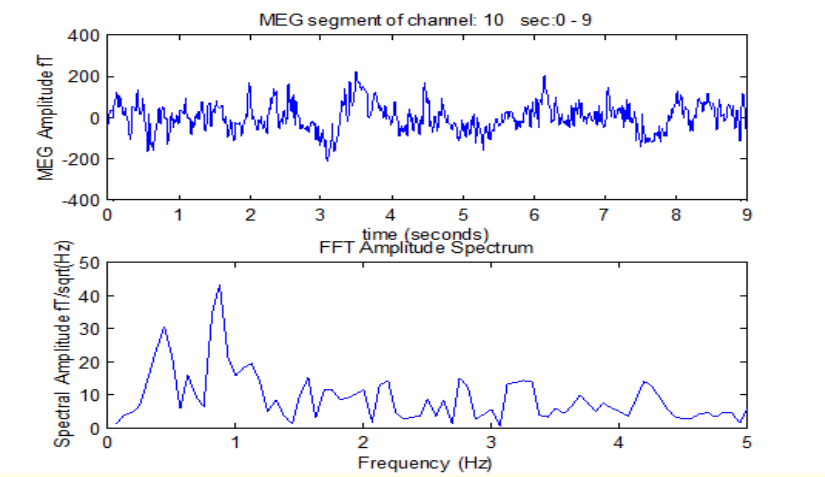

Figure 1: *This is an example for the primary dominant frequency in the 2 - 7 Hz band from A) an MEG record of 9 secs obtained from patient from which B) after Power Fourier Statistical analysis we get that the primary dominant frequency is 2.2 Hz.*

Results

The application of pT-TMS literature suggests that the real stimulus runs should have a higher frequency than the frequencies recorded in the MEG baseline. Table 1 shows the brain regions and the corresponding channels in each brain region. Table 2 shows the symptoms in each of the 10 PD patients before and after the application of the pT-TMS stimulation as were evaluated by interview by clinicians. We assumed that the PD patients before stimulation were characterized by abnormal frequencies in the range of 2 - 7 Hz. By applying pT-TMS to the brain of PD patients the desired effect was to increase the abnormal activity of the 2 - 7 Hz to higher frequencies to those seen in the baseline. MEG recordings.

The conditions seen after the effect of pT-TMS were tested also using the 'Hoehn and Yahr Staging of Parkinson's Disease, Unified Parkinson Disease Rating Scale' (UPDRS). Table 3 is shown the maximum effect of the recording frequencies following the application of pT-TMS for each of the 10 PD patients compared to the maximum frequencies recording of each of the 10 PD patients before the application of the pT-TMS. Table 4 demonstrates the statistical analysis of the results of Table 3 using t tests, being statistically significant in 6 out 10 patients (60%). From the above results the patients reported marked relaxation, complete disappearance of muscular ache, their facial expression returned to normal, tremors disappeared. They also reported feeling less stiff and their gait was improved by about 90%. In addition, they showed minimal akinesia and they were able to rise from the chair and to walk without any assistance. Finally, they were able, for the first time to hold a cup of water or coffee and drink without spilling its contents.

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

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

Patient	Before the pT-TMS	After the pT-TMS
1	I. **Mentation, Behavior and Mood** 2-moderate memory loss **II. Activities of Daily Living** 0- Normal Speech 1-slightly slow handwriting 1-somewhat slow dressing 1-somehow slow Hygiene 1-somewhat slow turning to bed 2-occasional freezing when walking 1-mild difficulty walking 4-tremor marked with most activities III **Motor examination** 2-mild to moderate Rigidity 4-unable to arise from chair without help	I. **Mentation, Behavior and Mood** 0-normal **II. Activities of Daily Living** 0-normal handwriting 0-normal dressing 0-normal Hygiene 0-normal turning to bed 0-normal walking 0-tremor disappeared III **Motor examination** 0-rgidity 1-was mild difficulty to rise from the bed
2	**II. Activities of Daily Living** 2-moderately affected speech III. **Motor examination** 2-moderate difficulty in walking 4-marked tremor	**II. Activities of Daily Living** 0-Normal speech III. **Motor examination** 0-normal walking 0-tremor disappeared
3	I. **Mentation, Behavior and Mood** 2-moderate memory loss **II. Activities of Daily Living** 3-frequent painful sensations 2-moderate tremor 2-moderate difficulty walking III. **Motor examination** 2-slight but definitely abnormal facial expression 2-mild tremor at rest 3-Leg Agility severely impaired	I. **Mentation, Behavior and Mood** 1-mild recovery of memory **II. Activities of Daily Living** 0-normal sensations 1-mild walking recovery 1-mild tremor 1-slight difficulty walking III. **Motor examination** 1-mild expression 1-mild tremor at rest 1-mild lig agility

4	**II. Activities of Daily Living** 2-moderate tremor in the upper limbs and right leg 3-frequent painful sensations in the left shoulder and lower back musles	**II. Activities of Daily Living** 0-normal 0-nomal sensations
5	**II. Activities of Daily Living** 2-moderate tremor bilateral 3-frequent painful sensations on the right foot and uncle	**II. Activities of Daily Living** 0-normal 0-normal sensations
6	**II. Activities of Daily Living** 2-moderate pain sensations in both legs 1-slightly slow or small hand writing III. **Motor examination** 2-mild in amplitude and persistent tremor at rest	**II. Activities of Daily Living** 1-mild hand writing III. **Motor examination** 2-persistent tremor at rest
7	**II. Activities of Daily Living** 1-mildy abnormal walking 1-somewhat slow dressing 1-cutting food 1-somewhat slow to help to shower III. **Motor examination** 2-mild to moderate rigidity and stiff neck	**II. Activities of Daily Living** 0-normal walking 0-normal dressing 0-normal cutting food 0-normal for shower III. **Motor examination** 0-normal
8	**II. Activities of Daily Living** 2-moderate difficulty walking 3-frequent painful sensations in the neck and sweating	**II. Activities of Daily Living** 1- mild walking 1-mild pain
9	**II. Activities of Daily Living** 2-his speech hypophonic 2-moderate difficulty walking III. **Motor examination** 3-moderate resting tremor 4-unable to arise from the chair without assistance	**II. Activities of Daily Living** 0- normal speech 0- normal walking III. **Motor examination** 0- no tremor 0- arise from the chair without assistance
10	III. **Motor examination** 2-slight but definitely abnormal of facial expression **II. Activities of Daily Living** 3-severe tremor bilateral 4-unable to care himself	III. **Motor examination** 1-normal face expression **II. Activities of Daily Living** 1-mild tremor 1-mild caring himself

Table 2: *This table shows the Unified Parkinson's Disease Rating Scale for the PD patients before and after the pT-TMS as were evaluated by interview by clinicians.*

P	RT pT-TMS	RT BL	LT pT-TMS	LT BL	RP pT-TMS	RP BL	LP pT-TMS	LP BL	F pT-TMS	F BL	V PT-TMS	V BL	O PT-TMS	O BL
1	4.53	2.38	3.88	2.84	4.53	3.53	4.94	2.84	4.78	1.16	4.53	3.53	5.44	2.88
2	2.00	1.94	5.00	1.72	2.00	1.94	5.00	1.72	1.5	1.81	5.00	1.94	5.00	1.34
3	3.94	3.72	4.53	1.72	3.97	3.44	4.53	0.91	4.38	5.03	4.53	3.44	3.03	5.09
4	3.81	4.81	2.75	3.94	3.81	3.06	2.38	4.44	2.38	3.44	3.88	4.44	2.38	5.00
5	5.1	3.44	4.25	4.59	4.75	3.44	3.94	3.81	5.63	4.34	4.38	3.81	3.75	4.06
6	3.00	4.50	4.75	2.91	3.81	4.50	4.75	2.72	3.94	4.69	4.63	4.53	5.44	5.25
7	3.60	2.00	4.97	2.47	3.60	3.50	5.10	2.47	4.06	0.06	3.60	3.50	5.10	1.50
8	4.41	3.44	4.84	5.34	4.41	4.21	4.84	5.34	4.63	3.78	4.84	3.81	4.72	4.72
9	4.31	0.56	2.20	0.06	4.31	3.16	2.94	1.72	3.66	0.38	2.94	3.16	3.10	1.31
10	4.25	4.13	2.53	4.19	4.25	3.13	3.75	5.84	1.47	1.03	4.25	3.13	3.75	5.84

Table 3: *This table is shown the maximum frequencies for baseline(BL) and pT-TMS MEG recordings in each brain channel for each of the 10 Parkinson patients. The symbols are (P: Patient Number; RT: Right Temporal; LT: Left Temporal; RP: Right Parietal; LP: Left Parietal; F: Frontal; V: Vertex; O: Occipital).*

Patients	BL (Mean ± SD)	pT (Mean ± SD)	t-test (P values)
1	2.74 ± 0.81	4.66 ± 0.48	**0.0002**
2	1.74 ± 0.22	3.64 ± 1.70	**0.0126**
3	4.32 ± 0.74	3.27 ± 1.54	0.1283
4	3.056 ± 0.74	4.16 ± 0.71	**0.0147**
5	3.89 ± 0.42	4.57 ± 0.65	**0.0380**
6	4.14 ± 0.95	4.28 ± 0.88	0.7826
7	2.21 ± 1.24	4.26 ± 0.69	**0.0025**
8	4.74 ± 0.27	4.24 ± 0.68	0.098
9	3.36 ± 0.78	1.49 ± 1.29	**0.0066**
10	3.87 ± 1.69	3.36 ± 1.07	0.5083

Table 4: *Statistical analysis for the 10 Parkinson patients of Table 2. The results are statistical significant at the level of p=0.05 (marked bold).*

Thus, according to the purpose of our study, we identified the changes in the brain state in accordance with our predictions that the pT-TMS should increase the frequencies in 2 - 7Hz band towards frequencies ≤ 8 - 13Hz for each PD patient.

Discussion

In our research, we set out to replicate the effects of the increased abnormal dominant frequencies of the 2-7Hz band due to the effect of pT-TMS [1-4] in a group of 10 PD patients. We tried to do our MEG measurements so as to have the highest possible precision as we have stated before.

We then went on to look for more substantial effects in different brain regions of the PD patients. The mechanisms by which the application of the pT-TMS attenuated the PD patient's symptoms are unknown. However, one possible explanation is that these magnetic fields have been shown to influence the activity of the pineal gland (PG) which regulate the dopaminergic [17], GABA [18] and the endogenous opioid functions [19]. 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.

Conclusion

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

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