РАЗДЕЛ 1

РАЗРАБОТКА НОВЫХ МЕТОДОВ ДИАГНОСТИКИ И ЛЕЧЕНИЯ

PART 1

NEW METHODS OF DIAGNOSTICS AND TREATMENT

Ph. A. Anninos, A.Kotini, A.V. Adamopoulos, A.N.Anastasiadis, N.Tsagas*

THE CONTRIBUTION OF EXTERNAL MAGNETIC STIMULATION IN THE MODULATION OF SEIZURES IN EPILEPTIC PATIENTS

Lab of Medical Physics, Medical School, Democritus Univ. of Thrace
**Lab of Nuclear Physics, Dept of Electrical Engineering and Computer Technology, Democritus Univ. of Thrace*
Alexandroupolis, Greece

Abstract: Objective: The goal of this study was to investigate the influence of external magnetic stimulation (TMS) in epileptic patients using magnetoencephalographic (MEG) measurements and Fourier statistical analytic techniques. Methods: Our study population comprised with 15 men aged 19-56 years (mean: 39.5±11.3) and 15 women aged 15-53 years (mean: 35.7±11.2). For each patient the magnetic activity was recorded from a total of 64 points (32 points for each temporal lobe). External magnetic stimulation (TMS) with proper field characteristics (intensity: 1-7.5 pT, frequency: the α-rhythm of the patient (8-13 Hz)) was applied in the frontal, occipital and temporal lobes for 2 to 6 minutes and the emitted MEG activity was recorded again. Results: The application of TMS resulted in rapid attenuation of the high MEG activity and of the incidence of seizures in epileptic patients. Conclusions: The lower activity and the reduction of seizures after the application of TMS strongly supports the beneficial effects of TMS in epileptic patients.

Keywords: MEG; external magnetic stimulation, epilepsy

Introduction

The cerebral cortex is known to produce weak magnetic fields that can be recorded using the Superconducting Quantum Interference Device (SQUID). Such measurements are known as magnetoencephalogram (MEG). Unlike the electroencephalogram (EEG), the MEG is not subject to interferences from the tissues and fluids lying between the cortex and the scalp. Ionic movements throughout the neuronal cell body creating a current dipole follow changes in membrane potential. The orientation of the current dipole is a critical factor, which affects the measurement of magnetic fields. The MEG produced by such fields is exclusively created by a flow of electric currents tangential to the skull surface and therefore the signal will originate maximally from the cerebral sulci (where the pyramidal cells are more favorably oriented) and only minimally from the gyri surface where their orientation is less favorable [1-4]. As it was pointed out by Elger et al. [5] the single dipole model is not the most appropriate model for the conceptualization of seizure activity since: a) an epileptic focus generates different types of seizure activity; b) the brain area which generates an epileptic discharge varies and different neuronal populations may contribute to a single epileptic event; c) the synchronized potentials of "epileptic" neurons give rise to synchronized projected synaptic activity; d) the interictal activity may be localized only in a limited number of patients with seizure disorders. In order to avoid these difficulties we have proposed [6] an alternative approach for the evaluation of the MEG recorded from patients with CNS disorders. Thus, instead of studying the surface distribution of the MEG in the time domain our method was based on investigating the surface distribution of the MEG in the frequency domain. This was proposed on the basis that the surface distribution of the spectral energy would exhibit patterns for specified locations of CNS disorders [2,5]. The information obtained from each measured point of patients' brain regarded the emitted magnetic field intensity, frequency and coordinates was subsequently stored in a special integrated circuit which was subsequently used to energize an electronic device the principles of which have been previously published [7]. The latter was used to emit back magnetic fields of certain characteristics (intensity: 1-7.5pT, frequency: the α-rhythm of the patient (8-13 Hz)). To achieve this, the coils of the magnetic stimulator were applied for 1-2 min to each point on the patients' scalp. The aim of this study is to investigate any alteration in the brain dynamics of epileptic patients after the application of external magnetic stimulation (TMS) using MEG measurements.

Methods and Results

The epileptic patients were referred to our Laboratory by practicing Neurologists. The examined group consisted of 15 men aged 19-56 years (mean = 39.5, SD=11.3) and 15 women aged 15-53 years (mean = 35.7, SD=11.2). All patients have been diagnosed independently to suffer from idiopathic epilepsy and had normal routine serum biochemical studies, as well as, normal CT or MRI scans. Due to the limited resolution and low sensitivity of the EEG methods, a number of them appeared to have normal EEG, although the patients experienced seizures. The Hospital Ethics Committee approved the whole examination procedure and informed consent for the methodology of the study was obtained from all patients. Biomagnetic measurements were performed using a second order gradiometer SQUID (model 601 of the Biomagnetic Technologies Inc.), which was located in an electrically shielded room of low magnetic noise. The MEG recordings were performed after positioning the SQUID sensor 3 mm above the scalp of each patient using a reference system. This system is based on the International 10-20 Electrode Placement System and uses any one of the standard EEG recording positions as its origin (in this study we used the P3, P4, T3, T4, F3, and F4 recording positions) [2,7]. Around the origin (T3 or T4 for temporal lobes) a rectangular 32-point matrix was used (4 rows x 8 columns, equidistantly spaced in a 4.5 cm x 10.5 cm rectangle) for positioning of the SQUID [2,7]. The MEG was recorded from each temporal lobe at each of the 32 matrix points of the scalp for 32 sec and was digitized with a sampling frequency of 256 Hz. The MEG signal was band-pass filtered with cut-off frequencies of 0.1 and 60 Hz. External magnetic stimulation (TMS) was applied in the frontal, occipital and temporal lobes using an electronic device [6, 7, 8] and the emitted magnetic activity were recorded again. The electronic device consists of a low voltage generator, which can produce low frequencies from 2-13 Hz to a group of coils of 1 cm diameter. The 32 coils are enclosed between two parallel plane surfaces in such a way that the axis of the coils is situated perpendicular to these surfaces. They are situated on the 32-point matrix, which is defined previously. The applied TMS carried similar field characteristics (intensity: 1-7.5 pT and frequency the α-rhythm of the patient (8-13 Hz)) with the ones emitted from the patient's brain prior of the application of TMS. The time between the 1st MEG and post-stimulation MEG is about an hour. None of the patients experienced side effects during or after the procedure. The above-discussed method for measuring the

Table 1.

The clinical data of the 30 patients and their response to TMS
(N:normal, A:abnormal, P:partial normal)

SUBJECTS	AGE	AGE START	MEG DIAG BMF	MEG DIAG AMF	EEG DIAG BMF	EEG DIAG AMF	TYPE OF EPILEPSY	PLACEBO
WOMEN	19	5	A	P	P	N	GENERALIZED	NO EFFECT
	15	3	A	P	P	P	GRAND and PETIT MAL	NO EFFECT
	39	12	A	P	A	P	GENERALIZED	NO EFFECT
	49	28	P	N	N	N	GRAND MAL	NO EFFECT
	31	5	A	N	P	N	GRAND MAL	NO EFFECT
	30	4	A	P	A	P	GRAND MAL	NO EFFECT
	53	15	A	N	A	N	GRAND MAL	NO EFFECT
	48	2	A	N	A	N	GRAND MAL	NO EFFECT
	34	8	A	P	A	P	GRAND MAL	NO EFFECT
	29	15	A	N	P	N	GRAND MAL	NO EFFECT
	41	12	A	P	A	P	GRAND MAL	NO EFFECT
	33	16	A	N	P	N	GRAND MAL	NO EFFECT
	48	11	A	N	A	N	PETIT MAL	NO EFFECT
	26	5	A	P	P	N	GENERALIZED	NO EFFECT
	43	7	A	N	A	P	GENERALIZED	NO EFFECT
MEN	40	15	A	N	A	P	GENERALIZED	NO EFFECT
	37	7	A	N	P	N	GENERALIZED	NO EFFECT
	34	15	A	N	A	P	GENERALIZED	NO EFFECT
	49	36	P	N	P	N	GRAND and PETIT MAL	NO EFFECT
	45	5	A	P	A	P	GRAND and PETIT MAL	NO EFFECT
	35	8	A	N	A	N	GRAND MAL	NO EFFECT
	33	14	P	N	P	N	GRAND MAL	NO EFFECT
	19	3	P	N	N	N	GRAND MAL	NO EFFECT
	56	10	P	N	P	N	GRAND MAL	NO EFFECT
	49	20	A	N	P	N	GRAND MAL	NO EFFECT
	51	22	A	P	A	P	GENERALIZED	NO EFFECT
	21	12	P	N	N	N	GENERALIZED	NO EFFECT
	55	20	A	N	P	N	GENERALIZED	NO EFFECT
	35	3	A	P	P	N	GENERALIZED	NO EFFECT
	33	5	P	N	P	N	GENERALIZED	NO EFFECT

brain dysfunctions in epileptic patients before and after the use of TMS has been tested in over 300 patients [6,7]. In the present study we present only 30 patients randomly chosen giving their clinical response (Table 1).

Discussion

The possible mechanisms by which magnetic fields have attenuated the patients' symptoms are still controversial. However, one possible electrophysiological explanation for the efficacy of magnetic stimulation has been provided by the proposed "neural net model" [9], which suggests that magnetic stimulation causes a temporary neuronal inhibition in regions exhibiting paroxysmal discharges. The hypothesis is in accordance with data presented by other investigators. However, it is known that magnetic fields alter the activity of the pineal gland, which has been shown to regulate dopaminergic, and endogenous opioid functions [10]. On a cellular level, the effects of magnetic fields on seizure activity maybe 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 [11]. Another explanation for the management of epileptic activity using TMS is based on Morrell's hypothesis that every stimulus entering the brain is maintained for a certain period of time representing the short-term memory of the particular stimulus experience [12]. 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 is possible to make the brains of epileptic patients to respond from their abnormal activities to normal ones using TMS of proper frequencies and intensities. In terms of the pathophysiology of epilepsy, the distortion of the high rhythmicity or abnormal synchronization and coherence of neural activity, which characterized brain activity of epileptic patients is an indication that we are modulating seizure activity in such a way that the characteristics of the time series are approaching the behavior of normal subjects.

References

1. Anninos, P.A. Electromagnetic fields generated from neuronal activity TIT. J Life Sci 1973, 3 : 15-18
2. Anninos, P.A., Anogianakis, G., Lehnertz, K., Pantev C. and Hoke, M. Biomagnetic measurements using SQUID. Int. J. Neurosci. , 1987 , 37: 149-168
3. Rose, D.F., Smith P.D. and Sato, S. Magnetoencephalography and epilepsy research, Science 1987, 238 : 329-335
4. Sutherling,W.W., Crandall, P.H., Cahan, L.D. and Barth, D.S. The magnetic field of epileptic spikes agrees with intracranial localizations in complex partial epilepsy. Neurology , 1988,38: 778-786
5. Elger, C.E., Hoke, M., Lehnertz K. et al., Mapping of MEG amplitude spectra Its significance for the diagnosis of focal epilepsy. In: K. Maurer (Ed). Topographic brain mapping of EEG and evoked potentials, Berlin Springer - Verlag, 1989. pp. 565-570
6. Anninos, P.A., Tsagas, N., Jacobson J.I. and Kotini, A. The biological effects of magnetic stimulation in epileptic patients. Panminerva Med., 1999, 41 : 207-215
7. Anninos, P.A. , Tsagas, N. , Sandyk R. , and Derpapas, K. Magnetic stimulation in the treatment of partial seizures. Int J Neurosci, 1991, 60 : 141-171
8. Anninos P.A. and Tsagas, N. Electronic apparatus for treating epileptic individuals, US patent number 5,453,072, Sept 26,1995.
9. Anninos, P.A., Tsagas N. and Adamopoulos, A. A brain model theory for epilepsy and the mechanism of treatment with experimental verification using SQUID measurements. In Cotterill RM, editor. Models of brain function. New York Cambridge University Press, 1989 405-21
10. Lissoni, P., Esposti, D., Esposti, G. et al. A clinical study on the relationship between the pineal gland and the opioid system. J. Neural Trans., 1986, 65 : 63-73
11. Ossenkopp K.P. and Cain, D.P. Inhibitory effects of acute exposure to low intensity 60 Hz magnetic fields on electrically kindled seizures in rats. Brain Res. 1988, 442 : 255-260

Prof. Photios A. Anninos
e-mail: anninos@axd.forthnet.gr; akotin@axd.forthnet.gr