The SQUID as diagnostic tool to evaluate the effect of transcranial magnetic stimulation in patients with CNS disorders

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Abstract: Magnetoencephalograph (MEG) recordings of patients with CNS disorders were obtained using a whole-head 122-channel magnetometer SQUID and analyzed using Fourier statistical analysis. External transcranial magnetic stimulation in the order of pico Tesla (pTMS) was applied on the above patients with proper characteristics (magnetic field amplitude :1-7.5pT, frequency :the α-rhythm of the patient: 8-13 Hz) which were obtained with MEG recordings prior to pTMS. The MEG recordings after the application of pTMS shown a rapid attenuation of the high abnormal activity followed by an increase of the low frequency components toward the patients α-rhythm.

Key- Words: - SQUID, MEG, Parkinson, Epilepsy, Multiple Sclerosis

1 Introduction

The magnetic activity of the brain is produced by cellular micro-currents,which emerge from ionic movements,due to the dynamical variations of themembrane potentials [1]. Even though transmembrane, intracellular and extracellular neuronal currents each produce surrounding magnetic flux, the neuromagnetic field recordable outside of the head is a selective reflection of intracellular currents flowing in the apical dendrites of pyramidal cells parallel to the skull surface. The magnetic field generated by a single neuron is almost negligible; however, when several thousands of nearby cells are synchronously active, the summated extracranial magnetic field typically achieves a magnitude of only a few hundred femto-Tesla (1fT=10-15) where the strongest neuromagnetic signals like those associated with epileptic spikes are only a few thousands femto-Tesla in magnitude [1-4]. These magnetic signals can be measured with the use of sensors that take advantage of how the strength of a magnetic field changes as a function of the distance from its source. Such magnetic fields emitted from the brain are very weak (of the order of pT; 1pT=10-12T), so very sophisticated devices must be utilized in order to detect and record these fields .These devices are the ones which are based on the Josephson effect of superconductivity [5]. Such sophisticated device is the magnetometer SQUID the name of which comes from the initials of the following words (Superconductive Quantum Interference Device). The SQUID has the ability to detect magnetic fields of the order of 10^{-15} T which is much smaller than the magnetic field of the earth which is $5X10^{-5}$ T or 50μT. The signal measured by each channel of the magnetometer SQUID is a time varying voltage waveform that reflects local changes in the magnetic flux as a function of time. This signal is called magnetoencephalogram (MEG) if we measured the brain emitted magnetic fields and it is very similar to the electroencephalogram (EEG) if we measured the brain emitted electric fields.

The MEG is presently regarded as the most efficient method for recording the brain activity in real time for many reasons. Compared with the EEG, the MEG has unique sensitivity to the CNS disorders and normal functions of the brain. In addition, the MEG offers functional mapping information and measurement of brain activity in real time, unlike CT and MRI and fMRI which only provide structural,

anatomical and metabolic information. With the MEG the brain is seen in 'action' rather than viewed as a still image. Last, and most important is that the MEG has far more superior ability to resolve millisecond temporal activity associated with the processing of information which is the main task of the brain.

Thus, both normal spontaneous rhythms and pathological activities are readily identified in MEG waveforms as we do with the EEG waveforms. Whereas, MEG signals reflect current flow in the apical dentrites of pyramidal cells oriented tangential to the skull surface, EEG signals reflect both tangential and radial activities [6].

The goal of this study was to report the above mentioned potential superiority of the MEG signals obtained in the diagnostic evaluation of CNS patients before and after the application of low intensity external transcranial magnetic stimulation using Fourier statistical analysis in frequency domain.

The transcranial magnetic stimulation (TMS) as currently used, was introduced by Barker et al. [7]. The TMS provided for the first time as a non-invasive, safe and painless method of activating the human motor cortex and assessing the integrity of central motor pathways. Since its introduction, the use of TMS in clinical neurophysiology, neurology, neuroscience and psychiatry has spread widely, mostly in research applications, but increasingly with clinical aims in mind [8,9]. On the other hand Anninos and his associates [3,4,10] applied also with a special electronic device [11] weak external TMS (in the order of pico Tesla) with proper field characteristics (intensity : 1-7.5 pT, frequency : 8-13 Hz) in the frontal, occipital and temporal lobes of the patients with CNS disorders. This electronic device consists of a low voltage generator, which can produce low frequencies, from 2-13 Hz, to a group of 32 coils of 1cm in diameter [11]. The 32 coils are enclosed between two parallel plastic plane surfaces in such a way that the axis of the coils is situated perpendicular to these surfaces.

The TMS can be applied as single pulses of stimulation, pairs of stimuli separated by variable intervals to the same of different brain areas, or as trains of repetitive stimuli at various frequencies.

Single stimuli can depolarize neurons and evoke measurable effects. Repetitive TMS can modify excitability of the cerebral cortex at the stimulated site and also at remote areas along functional anatomical connections [12]. With this new medical tool we ought to ask ourselves what it can offer that established methods do not for diagnostic, prognostic and therapeutic parts of clinical neurology. A new neurological tool might have several benefits: establishment of a differential diagnosis earlier or with greater certainty for a given clinical presentation than existing methods; better prediction of the likely course of the disease; further support for sustained and intensive interventions; help in identification of the most suitable treatment strategy; or improvement of clinical outcome as a therapy itself.

The main clinical application of TMS concerns testing of the functional integrity of the corticospinal tract in patients with disorders affecting the CNS. Use of standard TMS in these neurological disorders provides information on detection of subclinical upper motoneuron involvement, localization of anatomical site of lesions, longitudinal monitoring of motor abnormalities during course of diseases, and valuable aid to differential diagnosis. Repetitive stimulation of the brain opens a new field of investigations of cognitive function and mood and therapeutic possibilities. There are interesting results in the short-term treatment of refractory depression by daily sessions of repetitive TMS. By changing the frequency of stimulation, it may be possible to modulate cortical excitability for therapeutic benefit. Thus, the ability of TMS to measure and modify cortical activity offers possibilities to apply this methodology to clinical neurology, neurorehabilitation and psychiatry [13].

2. TMS in clinical Neurology

The TMS has been tested to study different forms of epilepsies from generalized to focal epilepsies. The most common abnormality in all types of epilepsies that we have studied was an increased excitability with a reduction of intracortical inhibitory mechanisms. In order to test the effect of the application of TMS to all these types of epilepsies MEG measurements were performed using the whole-head 122-channel SQUID gradiometer device operated at low liquid helium temperatures ($4K^0$). Recordings were taken in an electromagnetically shielded room in order to avoid extraneous electromagnetic noise. The MEG recordings were obtained with sampling frequency of 256Hz and filtered with cut-off frequencies between 0.3 to 40

Hz. The time taken for each recording was 2min in order to ensure alertness for each subject.

A software program was developed in our lab in order to detect the primary dominant frequency of the power spectra of the MEG obtained from each channel after the application of Fast Fourier Transform for each epileptic patient. Then, it was constructed a two dimension map for the spatial distribution of the above mentioned primary dominant frequencies over the scalp. Different colors in the map represent different dominant frequencies (red=2Hz, pink=3Hz, yellow=4Hz, green=5Hz, blue≥6Hz). Figures 1 and 2 respectively demonstrate the maps of the spatial distribution of the 1st dominant frequency over the scalp for a particular epileptic patient randomly selected from a large pool of epileptic patients and a normal volunteer before the application of external pTMS. As it is observed prominent low frequencies can be seen in the map for the epileptic patient, whereas in the control volunteer map show that the frequency range was ≥6 Hz in the majority of channels indicating the appearance of a-rhythm which is the control rhythm for normal subjects. Thus, the spatial distribution of the power frequency amplitude in the maps of all examined epileptic patients tend to be located over a wide area in the low frequency domain, whereas in normal subjects the spatial distribution of the power frequency amplitude is clustered in the map showing domains with higher frequency.

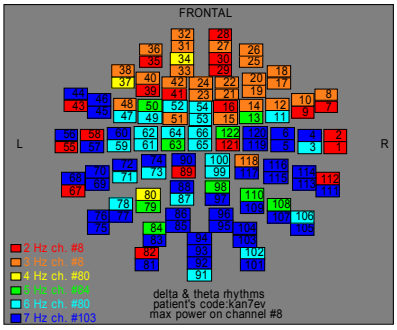

Figure 1. This figure gives the spatial distribution of the first dominant power frequency amplitude for one epileptic patient in which it is seen prominent low frequencies in most of the brain areas.

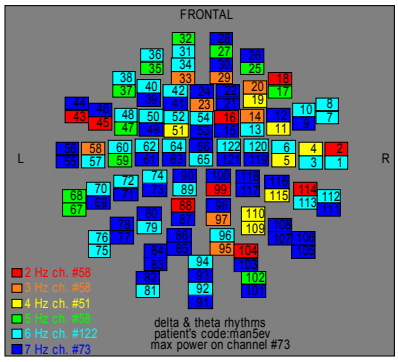

Figure 2. This figure shows the spatial distribution of the power spectra for the first dominant frequency amplitude from a normal subject. In this map it is observed in all brain regions prominent frequencies ≥6Hz.

There are interesting results in the short-term treatment by daily sessions by applying TMS(magnetic intensity:1-7.5pT; frequency: the a-rhythm of the patient:8-13Hz) in all epileptic patients including the randomly selected one stated above. This was done by placing the coils of the device [11] on the patient's scalp for a total of 6 minutes (2 minutes over each of the following areas: left and right temporal regions, frontal and occipital regions, and over the vertex). The time between the first MEG and the MEG obtained after the application of the TMS was about one hour. By applying the same shoftware program, as it was stated above, we can detect the primary dominant frequency of the power spectra of the MEG records obtained from each channel after the application of TMS for the selected epileptic patient. Then, it was constructed a similar map for the spatial distribution of the primary dominant frequencies over the scalp.

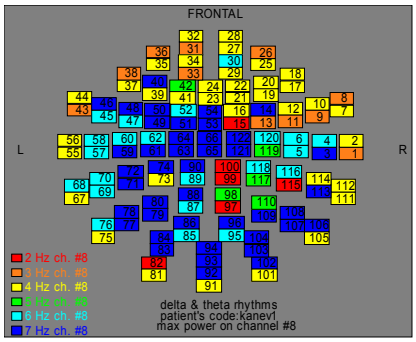

Figure 3. This figure shows the spatial distribution of the power spectra for the first dominant frequency amplitude from the MEG records after TMS for the epileptic patient of Fig.1.

Similar studies we have performed also with Parkinson's disease patients before and after the application of external transcranial magnetic stimulation. All the Parkinson patients had diagnosed independently to suffer from idiopathic Parkinson disease (PD) and none of the patients had a history of other neurological disease other than PD. Biomagnetic MEG measurements were performed, as before using the whole-head biomagnetomer 122 channel SQUID in a magnetically shielding room of low magnetic noise.
During the MEG recordings the subjects, as before, were sitting in a chair with their heads covered by a helmet shaped dewar. Four indicators coils attached to the patient head determined the exact position of the head with respect to the MEG sensors.
The exact positions of the coils were determined using a three dimensional digitizer. In Figure 4 it is shown the spatial distribution of the power spectra for the first dominant frequency amplitude obtained from the MEG records from a particular PD patient selected randomly from the pool of all examined Parkinson patients prior to the application of external magnetic stimulation.

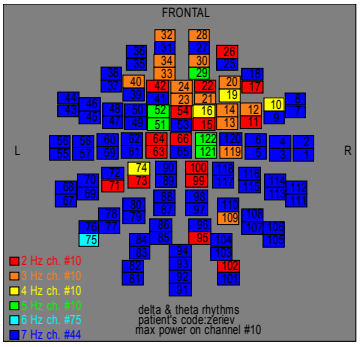

Figure 4. The spatial distribution of the power spectra for the first dominant amplitude frequency obtained from the MEG records of a Parkinson patient before TMS.

As it can be seen from Fig.4 the spatial distribution of the power spectra for the first dominant frequency is characterized by low frequencies. On the other hand the application of external magnetic stimulation on the Parkinson patient of Fig.4, as it is seen in Figure 5 shows that the power spectra distribution of the first frequency amplitude is cluster in domains showing higher frequency as it should be for normal subjects.

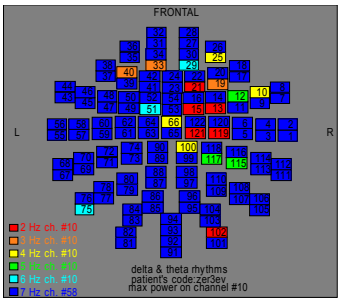

Figure 5. This figure is showing the distribution of the power spectra for the first dominant frequency amplitude of the MEG records obtained from the Parkinson patient of fig.4 after the application of TMS.

To confirm that the responses to TMS were reproducible, as it is shown in Fig.3 and fig.5, the patients were instructed to apply TMS with the same characteristics, with those used in our laboratory, nightly at home. Since this resulted in the same reaction to the one obtained in our laboratory and since this effect was sustained for a period more than a year, we preliminarily concluded that the application of the TMS is a non-invasive, safe and efficacious modality in managing patients with CNS disorders.

3. Results

The results reported in this section are representative for the group of epileptic and Parkinson patients that were diagnosed for the last five years using the whole-head 122 channel SQUID. The first case presented here refers to 30-years old patient suffering from idiopathic epilepsy since the age of 11. When he was first visited our Laboratory (in September 2001), he was manifesting five to 10 seizures per day with loss of consciousness and without falling down. The use of MEG recordings with the 122 channel SQUID diagnosed as having generalized epilepsy as it is seen in the map of Figure 1. This figure is showing the spatial distribution of the power spectra for the first dominant frequency amplitude of the

MEG recordings obtained from the scalp of the patient prior to the external magnetic stimulation.

After the application of external magnetic stimulation to the above epileptic patient, using the electronic device [11] with the specific characteristics in the field intensity and frequency, as were stated in the introduction, we can obtain again a new MEG record.

Figure 3 illustrates the effect of the spatial distribution for the power spectra of the first dominant frequency amplitude for this randomly selected epileptic patient from the pool of epileptics patients examined in our laboratory. As it is seen the new map is characterized by a cluster of higher frequencies similar to the map of normal subjects. In addition, we have seen that this procedure was associated with the attenuation in the frequency and severity of patients seizures.

The second case is for a Parkinson patient selected also randomly from the group of Parkinson patients diagnosed in our laboratory. All these patients have diagnosed to suffer from idiopathic tremor, rigidity, and dyskinesia on the basis of clinical observations and routine EEG recordings. The use of MEG recordings again with the whole-head 122 channel SQUID we obtained the map of Figure 4. This map is showing the spatial distribution of the power spectra for the first dominant frequency amplitude of the MEG recordings obtained from the Parkinson patient scalp prior to the external magnetic stimulation. This Parkinson patient was selected randomly from the whole group of Parkinson patients diagnosed with the 122 channel SQUID in our laboratory.

In this map we noticed that there are certain areas where the first dominant frequency amplitude, obtained from the power spectra of the MEG recordings from the scalp of the above mentioned Parkinson patient, are showing domains of low frequency . After the application of external magnetic stimulation to the above selected Parkinson patient we can record again a new MEG as before.

Figure 5 illustrates again the effect of the spatial distribution for the power spectra of the first dominant frequency amplitude which is characterized by similar cluster of higher frequencies similar to the map seen in normal subjects. Furthemore, it was noticed that with this procedure the Parkinson patients resulted in rapid attenuation of Parkinson symptoms.

4. Discussion

The brain is a complex dynamical system, so multichannel measurements are necessary to gain a detailed understanding of its behavior. Such multichannel measurements include optical brain images, multielectrode recordings, functional magnetic resonance imaging, MEG, etc[14-16].

In the MEG recordings, weak magnetic fields of the order of tens of fT/√Hz generated by electric currents in the brain are measured using the SQUID's detectors placed on the skull of the patients. The MEG is a noninvasive imaging technique, applicable to the human brain with temporal resolution approximately ~1ms [17]. Several authors have demonstrated the importance of the MEG in the investigation of normal and pathological brain conditions during the last decade [18-22]. The major advantage of MEG over EEG is that MEG has higher localization accuracy. This is due to the fact that different structures of the head (brain, cerebrospinal fluid, skull and scalp) influence the magnetic fields less than they influence the volume current flow that causes the EEG. Additionally, the MEG is reference free, so that the localization of the sources with a given precision is easier for the MEG than it is for EEG [23].

Frequency analysis is being increasingly applied in the investigation of CNS disorders before and after the application of low external magnetic fields with several advantages over the time domain technique [24]. Low frequency activities have been observed in our maps and occurred as thalamocortical synchronization transiently during wakefulness, under specific conditions of mental and emotional activity. Comparing all the maps which were obtained from the spatial distribution of the power MEG spectra for the first dominant frequency amplitude from all subjects, it can be seen that there is an increase number in the low first dominant frequency power amplitude for all subjects before the application of TMS, whereas the opposite is true for all subjects after the application of TMS.

Therefore, due to this beneficiary effect, the application of such external magnetic fields has been used recently by more and more scientists using transcranial and intracranial methodologies and have become convinced that it is proven to be a valuable tool for managing CNS disorders [25-27].

5. Conclusion

Although the beneficial effects of the application of TMS on the clinical picture in all CNS patients are well observed, the mechanisms underlying the efficacy of TMS remains an open question. One possible explanation of our findings is provided indirect support of our hypothesis that the beneficiary properties of the TMS are mediated via the pineal gland which is a magnetosensitive organ of our brain [3]. Taking this into account, the activity of this gland may be one of the crucial factors which determine and control the neural activity of all these patients suffering from CNS disorders. However, the question is difficult to be answered given the complexity of cellular, systemic and neuroendocrine effects of the TMS on biological systems and their potential impact on neurotransmitter functions. Despite all these facts, this method of magnetic stimulation may be considered as a very important noninvasive modality in the management of idiopathic CNS disorders.

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