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Case Report

A New Possible Application of Transcranial Magnetic Stimulation: Case Report

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Abstract

Background: Trans Cranial Magnetic stimulation is a novel technique for non-invasive cerebral stimulation that is finding many application for neurologic and psychiatric disorders such as Parkinson disease and depression.

The Physical laws that underlie the TMS permit further applications such as drug delivery.

As a matter of fact according to the Biot Savart and Maxwell Faraday electromagnetic laws it is possible to concentrate magnetic substances like gadolinium in specific areas.

Case Description: A 67 year old woman underwent TMS for drug resistant depression. Casually she underwent to gadolinium enhanced MRI in the same day as she performed TMS. The result was of Gadolinium concentration on the same side of stimulation.

Keywords: *Blood; Brain Barrier; Chemotherapy; CNS Tumors; Depression; Psychiatric Disorders; Repetitive Transcranial Magnetic Stimulation*

Abbreviations

AMPA: α-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid; BECF: Brain Extra-Cellular Fluid; CNS: Central Nervous System; DPFC: Dorsolateral Pre-frontal Cortex; ECT: Electroconvulsive Therapy; ENG: Electronic Nerve Gathering; FDA: Food and Drug Administration; fMRI: Functional Magnetic Resonance Imaging; LTD: Long-term Depression; LTP: Long-term Potentiation; MEG: Magneto-Encephalography; MEP: Motor Evoked Potential; MRI: Magnetic Resonance Imaging; MDA: N-Methyl-D-Aspartate; PET: Positron Emission Tomography; PTSD: Post-traumatic Stress Disorders; rTMS: Repetitive Transcranial Magnetic Stimulation; TMS: Transcranial Magnetic Stimulation

Introduction

Transcranial Magnetic Stimulation (TMS) relies on the possibility of using Faraday's law of electromagnetic induction to stimulate the brain, spinal cord and peripheral nerves by applying magnetic pulses in a non-invasive and painless manner (Barker Jalinous and Freeston 1985).

Repetitive Transcranial Stimulation (rTMS) is mostly used to inhibit or facilitate cortical activity [1-3], with the aim of studying brain functions the relation and changes of different cortical areas in cognitive and emotional behavior. The use of rTMS has been also experimental investigate and applied in different of psychiatric disorders [4].

The targeting of dorsolateral pre-frontal cortex (DFPC) as an alternative and coadjutant in depression treatment therapy, presently being one of the most experimented and recognized role of application of rTMS [5,6].

Experimental variations in different aspects of rTMS like targeting different areas, changes in laterality, technical protocols, and stimulation parameters and set up (FDA approved or not yet) have been showing some interesting results in treatment of anxiety, obsessive compulsive disorders, post-traumatic stress disorders (PTSD) and as an alternative to electroconvulsive therapy (ECT) for patients who do not respond to anti-depressive drugs [7].

Researches are also pointing out the role rTMS in the treatment of substance abuse disorders [5].

Case Report

This case report describes a clinical observation in a 67 year old female that has been diagnosed and treated for depression in the last 10 years. The decreasing therapeutical response to antidepressant drugs in the last year, has lead the psychiatrist in-charge of the patient, to take the decision of using rTMS as a coadjutant treatment for the issue of the patient, and the patient was referred to us.

The rTMS used for the treatment is a Duomag XT 100 system (citare il produttore) with an adapted coil to repetitive r TMS. The coil also has a cooling system for prolonged stimulation.

The treatment stimulation applied the FDA approved protocol with 40 pulses at frequency of 10 HZ for a total of 6000 pulses per session (3000 on the left, 3000 on the right) administered on the left DLFC (Dorso Lateral Frontal Cortex) as well as on the right side target because of the specific drug resistance history of the patient. The treatment was administered for 5 days in 6 weeks cycle treatment.

In the second week of treatment once completed the cycle of 3000 pulses on the left side in the target of DLFC the patient waiting for the right side stimulation reported a sudden intense headache, that faded away in few minutes. After an interval of two hours the patient was happy to complete the above mentioned cycle of stimulation on the right DLPC (3000 pulses), carried out without any further side effect.

When the day session was over, the patient underwent to a previously scheduled MRI with contrast enhancement because of a previously described cystic malformative brain lesion.

While executing the MRI we observed that the Gadolinium was majorly concentrated on the right side, the side where the stimulation was immediately before performed, with the two hours interval toward the previous left side stimulation.

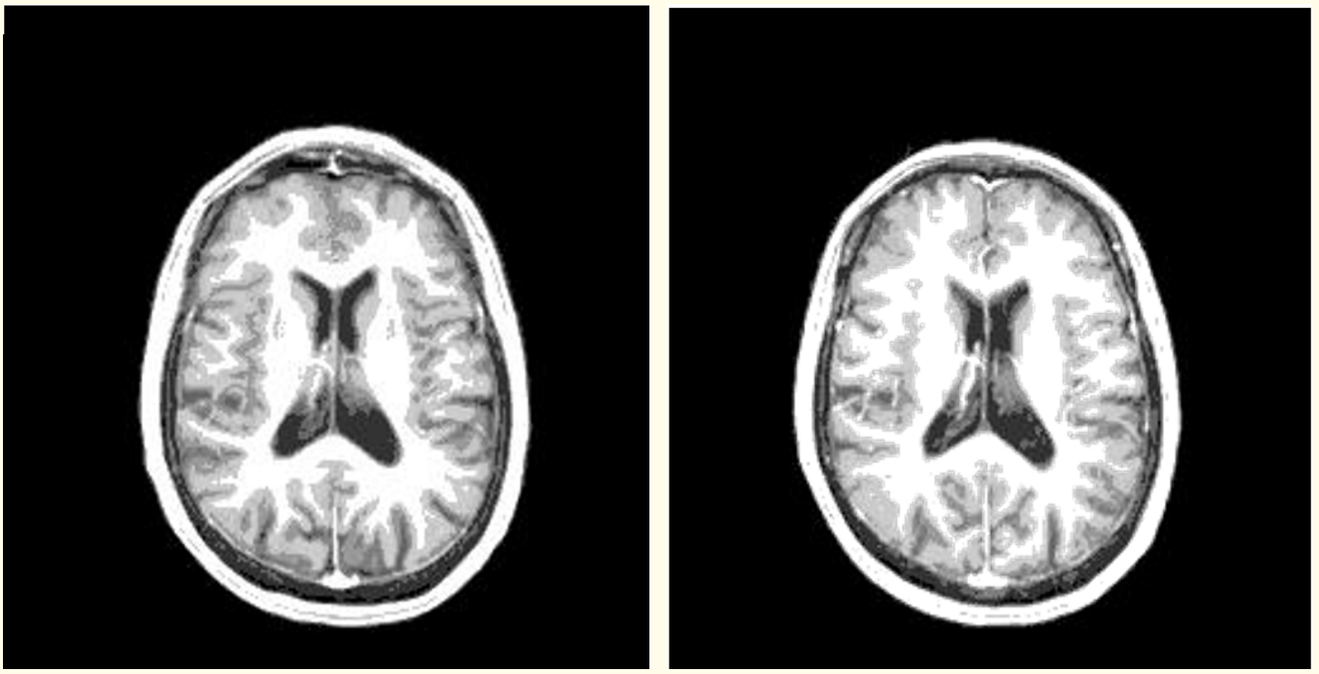

Figure 1: *These Figures show a major contrast enhancement on the right side.*

Physical and Basic principles of TMS

The exact details of how TMS functions are still being explored and not completely clarified.

The cell membrane separates an electrical potential difference between intra-and extracellular space. The average transmembrane potential is about 70 mV. As known the intra cellular space potential is negative.

It has been shown that an applied magnetic field changes the cell membrane potential and activates a depolarization of the membrane that consequently activates the neuronal tissue.

Tailored electric fields for neuronal stimulation can be generated by electromagnetic induction. In transcranial magnetic stimulation a time-varying magnetic field generates a current flow in the neuronal tissue.

Several Tesla are needed in Trans cranial Magnetic Stimulation. These strong magnetic fields are generated brief current pulses of several kiloamperes and delivered to the neural tissue by a specific coil.

Trans Cranial Magnetic Stimulation uses the physical principle of electromagnetic induction to generate an electric current across the scalp, the skull and the neural tissue. A plastic-enclosed coil of wire is held next to the skull and when activated, produces a magnetic field oriented orthogonally to the plane of the coil. The magnetic field passes un -impeded through the skin, the skull, inducing an oppositely directed current in the brain. This current flow activates neural cells almost the same way as it would a current applied directly to the brain's cortical surface.

The ways in which the current passes through the neural tissue is difficult to track because of the brain's anatomical irregularity and electric fields and magnetism are not conducted uniformly. The magnetic field is comparable to the strength as a modern MRI up to 3 Tesla. The pulse generally reaches the depth in the brain tissue up to 5 centimeters. There are variants of TMS that reach more than 5 cm of depth.

The law of electromagnetism to which the TMS is referred to is Biot-Savart law. According to the Biot-Savart that a current that passes through a wire generates a magnetic field around the wire, following the formula.

$$\mathbf{B} = \frac{\mu_0}{4\pi} I \int_C \frac{d\mathbf{l} \times \hat{\mathbf{r}}}{r^2}$$

Transcranial Magnetic Stimulation is generated by a quickly discharging current that consequently produces a pulsed magnetic field between 2 and 3 T. By directing the pulsed magnetic field to a targeted area of the brain, it is possible to depolarize or hyperpolarize neurons membrane. The magnetic flux density generated by the pulsed current is explained by the Maxwell-Faraday equation [8-38].

$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t}$$

The generated electric field causes a change in the trans-membrane potential of the neuron, this variation can produce the depolarization or hyperpolarization of the neuron's membrane and so generating an action potential [36,37].

When a TMS coil is applied to the skull of a patient, according to what has been previously described, when the cerebral area stimulated is the site of primary motor cortex, the stimulation will produces muscle activity that can be recorded as a motor evoked potential (MEP) [8,9]. When the coil is applied on the occipital cortex, 'phosphenes are perceived by the patient. In most other areas of the cortex, there is no consciously experienced effect. The stimulation of particular cerebral areas affects the behavior (e.g. slower or fastened reaction time on a cognitive task).

Repetitive TMS produces longer-lasting effects which persist past the initial period of stimulation. The underlying mechanism of these effects is not clear: it is widely believed that this formal effect is due to changes in synaptic efficiency due to long-term potentiation (LTP) and long-term depression (LTD) [10,13]. Both of these mechanisms depend on synaptic receptors AMPA and NMDA.

The localization with TMS of eloquent or functional areas, as the motor one, has also been seen to correlate closely to MEG and also to fMRI data.

fMRI images, recorded during TMS of the motor cortex, have been found to match very closely with PET modifications induced by voluntary movements of the hand muscles activated by TMS.

Conclusions

These observations allow the possibility to propose TMS novel application. As known one of the major aims in neuro-oncology is to reduce side effects of chemo-therapeutical drugs.

A constant problem in neuro-oncology is drug delivery to the cerebral lesion, with single dose reduction but with increase concentration in the lesion possibly only inside it.

The main difficulty to reach such result is the presence of the blood brain barrier:

- The blood-brain barrier (BBB) is a highly selective barrier that separates the blood, from the Central Nervous System (CNS) and from the brain extracellular fluid (BECF)
- The blood-brain barrier histologically is formed by various (endothelial and glial) cells connected by tight junctions with an extremely high electrical resistivity (0.1 Ω·m.). The blood-brain barrier allows the passage of water, some gases and lipid-soluble molecules by passive diffusion, as well as the selective and active transport of essential molecules like glucose and amino acids.

In conclusion, following our serendipity observation on this clinical case, the use of TMS could satisfy both request.

This study demonstrates that activating a magnetic field, by TMS, on the site of the lesion, it is possible to increase the concentration of a paramagnetic substance like gadolinium in the lesion. The coupling of therapeutically agents with a paramagnetic substrate may increase the possibility of better clinical results when applied to the CNS pathology.

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Disclosure of Interest

None.

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