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Opinion

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# Transcranial magnetic stimulation as a promising tailored medicine for neurological disorders: beyond chemical drugs

Volume 3 Issue 4 - 2016

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**Received:** May 04, 2016 | **Published:** May 23, 2016

## Opinion

Despite an ever-growing knowledge of brain function, the cellular and molecular mechanisms that ultimately lead to distinctively human processes such as memory and cognition remain an enigma. Thus, the study of brain is an exciting area of research. Alterations in these pathways seems to play a crucial role in the onset and development of neurodegenerative diseases, both those linked to ageing like Alzheimer and Parkinson diseases, and others such as multiple sclerosis, which presents in young people, limiting quality of life and productive capacity. The management of patients with these conditions impacts negatively on health care systems, especially those public ones in which resources are more limited. Understanding the mechanisms and pathways underlying CNS disorders is critical for the design of therapeutic strategies which not only prevent their evolution but also revert and cure them.

Transcranial magnetic stimulation (TMS) is a novel tool that is helping to reveal how different brain areas and neuronal structures are connected to execute a single coordinating function or process. In addition to its utility for the study of brain networks, TMS is becoming a potent non-invasive instrument, with minimal side effects, for the treatment of neuropsychiatric disorders. The magnetic field generated by TMS is translated into electrical current in the brain when this energy passes through the skull, leading finally to diverse biochemical effects, such as: attenuation of inflammation and oxidative/nitrosative stress, improving cell density by reducing necrotic/apoptotic processes, and promoting neurotrophic/neuro genetic phenomena.[1]

Especially interesting is the effect on brain plasticity induced by some paradigms of TMS.[1] These studies have revealed that TMS modifies the expression of genes and proteins that mediate these phenomena, such as cFos (10Hz repetitive TMS) and zif268 (10Hz intermittent theta-burst stimulation.[2] Moreover, repetitive TMS appears to induce the activity of the cyclic AMP-cyclic AMP response element binding protein pathway in cell cultures.[3] A protein crucial for brain plasticity is brain-derived neurotrophic factor (BDNF), which can also be induced by TMS. In 2012, our group demonstrated that application of 60-Hz extremely low frequency magnetic fields, a paradigm of TMS, alleviated brain injury and prevented loss of neurons in a model of Huntington disease; these effects were accompanied by an increase in neurotrophic factors such as BDNF.[4] Further, low frequency magnetic stimulation participates in regulating structural synaptic plasticity of hippocampal neurons via the activation of BDNF-TrkB signaling pathways.[5] The interrelation of TMS and BDNF has become particularly important as recent studies show that a common single nucleotide polymorphism (BDNF Val66Met) is responsible for altered activity-dependent release and recruitment of BDNF in neurons[6] This special condition appears to be closely linked to the effect of TMS therapy, whereby subjects with said polymorphism exhibit a worse response to TMS in stroke,[7] schizophrenia[8] and drug-resistant depression.[9] Along these lines, patients with C/C genotype of the 5-HT1A serotonergic receptor promoter region (polymorphism, rs6295) show a greater improvement that G/G and C/G genotypes when TMS is applied for a major depressive drug-resistant episode.[10] Likewise, this response was significantly better in LL patients homozygotic for the serotonin transporter (5-HTTLPR) compared to S allele carriers.[9]

There is little doubt that TMS can be an extremely versatile tool. When preparing a session of TMS, it is essential from the beginning to define which effects one desires to achieve. Different stimulation settings concerning frequency and intensity of the pulse, number of trains, pulses/train, and area/angle of stimulation may lead to equivalent or antagonist effects. Besides, the same paradigm of transcranial brain stimulation applied with different settings may result in excitatory or inhibitory stimulations (Table 1), extending the therapeutic potential of TMS. Such is the case for depression in which stimulation with repetitive low-frequency TMS (1Hz) over the right dorsolateral prefrontal cortex (an inhibitory protocol) has been reported to present a quite similar antidepressant effect than repetitive high-frequency TMS (5-20Hz) over the left dorsolateral prefrontal cortex (an excitatory protocol) - emphasizing the complexity of brain networks and TMS therapy.[11] Pre-treatment studies using functional brain tests such as functional magnetic resonance imaging, positron emission tomography, single-photon emission computed tomography, or magnetic resonance spectroscopy could help to select an optimal stimulation protocol and area for each particular patient.[12] The complicated relationships between the configuration of TMS and the stimulated regions could explain, at least in part, the discrepancies found in the literature regarding the effects of TMS. The United State Food and Drug Administration in 2008 approved TMS for the treatment of drug-resistant depression. A large number of studies have pointed out its therapeutic potential for neurological disorders such as Huntington disease, Parkinson disease, Alzheimer disease, multiple sclerosis, epilepsy, pain-related disorders and stroke among others.[13,14]

The above arguments support the idea that some genetic studies and functional brain imaging may be necessary in order to design a tailored therapeutic scheme of TMS for each patient, thereby optimizing clinical outcome. The duration of the sessions and of the effects or tolerance phenomena are other concerns that need further consideration in order to bring about the best use of this novel therapy.

**Table 1** Excitatory or inhibitory effect of several paradigms of transcranial brain stimulation

| | Conventional rTMS | PPS | QPS | PAS | TBS | tDCS |
|---|---|---|---|---|---|---|
| Excitatory effect | >5Hz | Prolonged supra-threshold paired pulses | Short intervals | Synchronous heterosynaptic stimulation | Intermittent TBS | Anodal |
| Inhibitory effect | ≤1Hz | Prolonged sub-threshold paired pulses | Long intervals | Asynchronous heterosynaptic stimulation | Continuous TBS | Cathodal |

PAS, paired associative stimulation; PPS, paired-pulse stimulation; QPS, quadri pulse stimulation; RTMS, repetitive transcranial magnetic stimulation, TBS, theta burst stimulation; TDCS, transcranial direct current stimulation

## Conclusion

To conclude we would like to stress that:

i. TMS is a novel, versatile therapeutic strategy with great possibilities to combat neurodegenerative diseases.

ii. Well-controlled clinical trials as well as experimental studies are still necessary to confirm TMS therapeutic potential and elucidate the mechanisms and pathways involved in its beneficial effects.

iii. The effectiveness of TMS therapy will be linked to how its application is tailored. Genetic studies and functional brain imaging open new paths to optimize the treatment with TMS.

## Acknowledgements

None.

## Conflict of interest

The author declares no conflict of interest.

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**Citation:** Medina-Fernández FJ, Escribano BM, Feijóo M, et al. Transcranial magnetic stimulation as a promising tailored medicine for neurological disorders: beyond chemical drugs. *MOJ Cell Sci Rep*. 2016;3(4):103–104. DOI: 10.15406/mojcsr.2016.03.00062