

Mechanisms and applications of transcranial magnetic stimulation: an overview

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Abstract

Transcranial magnetic stimulation (TMS), using strong time-varying magnetic fields to stimulate the brain non-invasively, is increasingly used as a mean to safely probe brain function and to alleviate symptoms associated with neurological disorders. TMS has indeed become a precious tool to understand brain function in healthy volunteers, and is actively explored as a novel diagnostic and therapeutic tool for a wide range of neurological disorders. We briefly review here the origins of TMS, its mechanisms of action and its most widely widespread research and clinical uses. We also mention the current limitations that TMS is facing, and how these challenges are motivating novel TMS developments. It appears plausible that TMS will represent, in the near future, a therapeutic option of choice, due to its possibility to non-invasively interfere over extended periods of time with abnormal patterns of brain activity associated to specific neurological disorders.

1. Introduction

Transcranial magnetic stimulation (TMS) is a brain stimulation technique developed in the eighties [1], and is based on the principle of magnetic induction. TMS consists in applying short pulses (in the μs range) of intense, time-varying magnetic fields (MF) in the Tesla range using a handheld coil placed against the scalp, and in which a strong electric current flows. The relationship between the magnetic field generated by the TMS coil and the electric field induced in brain tissue is given by the well-known Maxwell-Faraday's law of induction:

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

The resulting time-varying electric field will in turn impact neuronal membrane polarization depending on the angle between the direction of the induced current and the direction of neuron fibers. The maximal amplitude of a TMS pulse is in a typical range from 1 to 2.5 T, resulting in an induced electric field on the order of several hundreds of volts per meter at the level of cortical tissue, located approximately three centimeters under the skull. Depending on the type of coil used, it is possible to influence the area of brain tissue effectively stimulated by TMS. For example, a common type of coil, termed the "Figure 8 coil" due to its particular shape, results in a significantly more focused stimulus [2].

While a single pulse of TMS is sufficient to induce motor responses, it is necessary to use repeated pulses of TMS to induce clinically relevant, lasting effects. This is termed as repetitive or repeated TMS, labelled as rTMS. rTMS protocols are characterized by their pulse amplitude, total number of pulses delivered, frequency of pulse trains, and frequency of pulses within a pulse train. These parameters are the most important to determine neurophysiological effects, but also the safety of rTMS, which has indeed been the focus of intense research. The overall conclusion is that TMS/rTMS is a safe procedure, pending appropriate precautions are carefully followed [3]. Obviously, this is the large time-varying magnetic field generated by the TMS coil that induces an electric field that has the potential to interact with metallic objects, such as pacemakers or cochlear implants. Therefore, it is critical that subjects or patients do not have any metal implanted in their head or body to avoid any safety hazard (even including earrings or piercings). The most serious possible side effect of TMS is the induction of a seizure, which is however very rare (16 documented cases since 1990 as of 2009, while thousands of patients and volunteers have been enrolled in TMS studies). As explained in details in TMS safety guidelines [3], seizures have occurred due to 1) intake of medications increasing cortical

excitability, increasing seizure probability; 2) alterations in brain anatomy, which could have modified the electrical properties of brain tissue, and 3) TMS pulse amplitude higher than safe limits. The low risk for seizures is highlighted by Rossi et al. [3], stating that “Considering the large number of subjects and patients who have undergone rTMS studies since 1998 [...] and the small number of seizures, we can assert that the risk of rTMS to induce seizures is certainly very low.” A minor issue with TMS is that the noise generated by the coil can be high, which can be easily addressed by using earplugs. Also, when TMS is delivered, it can induce a “twitch” in the scalp, most of the time without any associated pain. Finally, transient lasting effects on working memory have been reported, possibly lasting up to one hour after the TMS session [3].

In this short review, we present the basic mechanisms of rTMS known to date, and briefly review novel developments towards patient-specific rTMS, which appears critical to address current TMS limitations. Finally, we conclude on the possibilities that rTMS offers for the near future.

2. Basic mechanisms and applications of TMS

The methodology and knowledge of TMS have greatly benefited from motor cortex stimulation, since it results in a physiological outcome which can be easily observed and quantified. As an illustration, the amplitude of the TMS/rTMS pulses used is classically defined as a percentage of the so-called *motor threshold (MT)*, defined as the TMS pulse amplitude resulting in at least 5 detectable responses greater than 50 µV on the electromyogram (EMG) out of 10 motor cortex stimulations. The motor threshold is expressed as a percentage of the maximal amplitude that can be generated by the TMS device. As an example, if the MT is measured to be 50% of the maximal TMS device amplitude, and if the stimulation delivered is at 50% MT, the stimulation is at 25% of the maximum device’s output.

Characterizing neuronal response following rTMS is complex and is the focus of intense research. There is strong evidence that TMS induces a depolarization of neuron fibers, especially at sites where fibers are bent [4]. Activation of neuronal pathways using recordings of the pyramidal tract in monkeys has shown that motor cortex stimulation at MT induces specific wave patterns. The first recorded response is termed D-waves (D standing for “direct” waves), and is likely caused by the direct activation of corticospinal neurons. Shortly after D-waves, I-waves (I for “indirect”) can be detected, and are likely the result of transsynaptic (i.e., through pathways involving several synapses) activation of pyramidal neurons [4]. Such response patterns constitute an interesting possibility to probe the function and dysfunction of brain tissue using TMS, or the effect of specific drugs. In addition, let us note that there is a frequency-dependence of TMS effects, with a tendency towards inhibitory effects at low frequency (< 5 Hz in the area of TMS) and excitatory at high frequency [4]. The interest of inhibitory rTMS protocols lies into the possibility to stimulate the hemisphere contralateral to a brain lesion (e.g., after stroke), to indirectly increase neuronal activity in the lesioned hemisphere [5]. Another interesting aspect of TMS is its capacity to induce effects outlasting the duration of stimulation (i.e., changes in brain activity and/or behaviour do not necessarily return to baseline immediately after stimulation), suggesting effects on brain synaptic plasticity [6]. This can be assessed by estimating cortical excitability, which is an estimate of how strong a stimulus needs to be to elicit a response in brain tissue; by measuring the amplitude of D-waves and I-waves, before and after a rTMS protocol. Increased/decreased cortical excitability results likely from long-term synaptic potentiation/depression processes. Cortical excitability is not only an indicator of the effects of TMS on brain activity, but it is also well known that cortical excitability is affected in numerous neurological disorders, such as in epilepsy where cortical excitability is pathologically high.

TMS can be used, for instance, to map the motor cortex by triggering movements on a subject (hand, leg, specific fingers [7]). In addition to the contribution of rTMS to studying basic mechanisms of brain function, rTMS is also used routinely in the clinic as a therapeutic option. rTMS has demonstrated solid therapeutic effects in drug-refractory depression and pain [8,9], and is being explored for the symptomatic treatment of several other neurological disorders such as tinnitus, Parkinson’s disease, Alzheimer’s disease or post-stroke recovery. However, there is a lack of convergence in the literature regarding the clinical benefits reported in these different diseases. Possible factors to explain these discrepancies might include the diversity of stimulation protocols used, such as number of TMS pulses delivered, amplitude of the TMS pulse, orientation of the coil, or brain region targeted. Another factor which is more challenging to take into account consists in the modifications in brain tissue geometry present in numerous neurological disorders, which in turn can impact the electrical conductivity of brain tissue. Therefore, neurological disorders characterized by the destruction of brain regions, such as stroke, are more challenging to address since they would require a patient-specific rTMS protocol in order to take into account these specificities.

3. Patient-specific TMS and beyond

As mentioned previously, one challenge in using TMS for therapy is that a large number of factors determine the effect of TMS on cortical activity, possibly explaining discrepancies in the litterature between TMS studies investigating its potential for neurological disorders management. First, the time-varying electric field induced in brain tissue is shaped by coil geometry (regular coil vs. figure eight coil for example), the parameters used for TMS (frequency of repetition, amplitude), but also brain geometry and local electrical conductivity (grey matter vs. white matter). Therefore, there is a strong need for patient-specific rTMS protocols to reduce experimental variability and improve treatment consistency. In order to fill this gap, different neuronavigation systems have been developed, including the possibility to import the brain MRI of a specific subject/patient to generate a computerized 3D-model of the brain. Reference points (e.g., nasion) can then be given to the system using passive sensors tracked using a dedicated camera for calibration, while coils are equipped as well with tracking systems. The neuronavigation system can then be used to visualize in real-time the position of the coil with respect to the head, but also the estimated induced electric field distribution at the cortical level (see Figure 1). Sites of stimulation can also be recorded, and the accuracy of targeting between different pulses can be estimated. Therefore, neuronavigation systems are a precious addition to rTMS since they compensate part of the variability in targeting, but also take into account the brain geometry for a specific patient. It has been shown that rTMS neuronavigation systems significantly improves the consistency of rTMS effects [10].

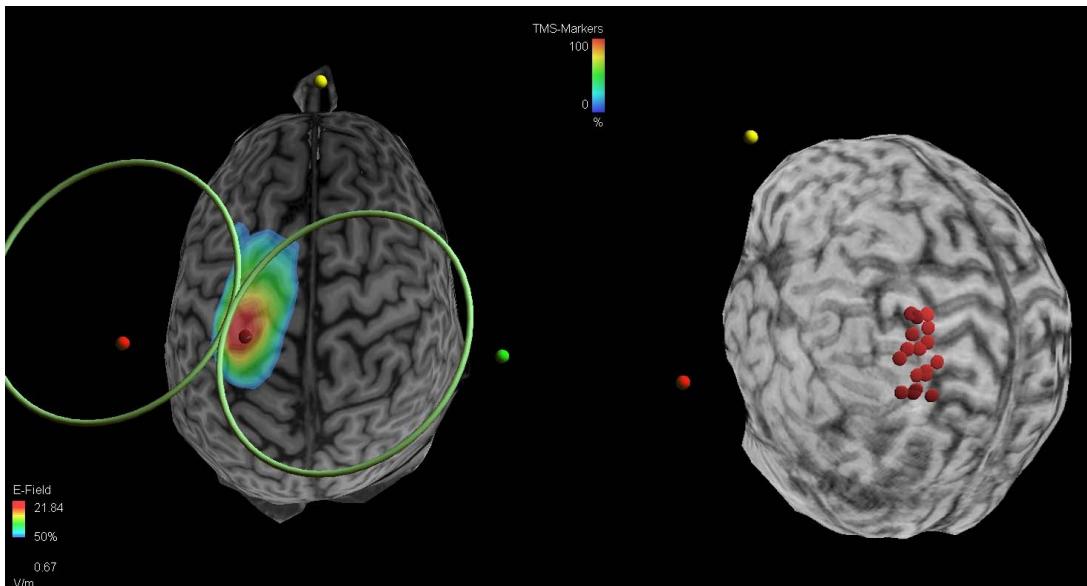


Figure 1. Example of image-guided rTMS using a commercial neuronavigation system (Visor 2, ANT-Neuro, The Netherlands). *Left panel:* real-time visualization of the Figure 8 coil (Magstim, UK) and corresponding estimated electric field at the cortical level, on the MRI image of the subject. *Right panel:* Localization of the different stimulation sites after a rTMS session.

However, one significant current limitation of rTMS is that rTMS functions in “open-loop”, i.e. rTMS pulses are delivered according to pre-programmed stimulation parameters, without taking into account ongoing brain activity. Since the impact of stimuli on neuronal oscillations is strongly non-linear and phase-dependent [11], the possibility to know and adjust the relative phase between TMS pulses and targeted neuronal oscillations is likely of importance. Therefore, one interesting avenue of research would consist in determining the phase response curve (PRC) of cortical oscillations in response to TMS pulses, thereby enabling the design of a completely new, on-demand TMS system delivering, as needed, TMS pulses with the appropriate timing to interfere with abnormal neuronal activity. One possible solution could consist in the use of EEG, which could be online-corrected to compensate for rTMS-induced artefacts, or motion sensors (e.g., accelerometers) placed on the body in the case of movement disorders. Overall, rTMS could be greatly improved by moving forward from open-loop to a closed-loop paradigm. Such closed-loop stimulation associated with neuronavigation systems would provide a patient-specific, non-invasive brain stimulation technique which would be widely usable with more consistent clinical benefits. This solution would enable rTMS flexibility and

adaptability regarding patient's brain anatomy and ongoing brain activity, decreasing variability between and within subjects and patients.

Another possibility of improvement for TMS could be to optimize coil design in order to stimulate deeper structures, e.g. the subthalamic nucleus targeted by deep brain stimulation (DBS) in Parkinson's disease. DBS is an effective but invasive therapy, with clinical benefits stopping seconds after stimulation offset. rTMS protocols delivered on a regular basis and effectively targeting the STN could provide, if technically achievable, clinical benefits outlasting the period of stimulation. Coil design could also be optimized to stimulate smaller areas of cortical tissue, reducing undesirable stimulation of neighbouring brain areas and focusing the stimulation on the area of interest. Finally, the field of TMS will greatly benefit from the emerging integration of TMS within multi-modalities imaging platforms in order to provide further insights on characterizing the effects of TMS on the electrical activity and metabolism of brain tissue.

4. Conclusion

TMS has become a safe, widely used tool based on time-varying MF, with applications both in basic research and therapy. The tremendous amount of experimental data obtained using TMS has provided novel insights on the mechanisms underlying the excitability of cortical circuits and synaptic plasticity processes, which can be used for the quantitative assessment of abnormal cortical changes in neurological disorders. Overcoming current technical challenges of TMS will undoubtedly increase its therapeutic value and should lead to more consistent experimental results between studies.

5. Acknowledgments

The authors would like to thank the Saint Joseph Health Care Foundation and Armatec Survivability for funding this TMS neurostimulation and neuronavigation platform at Lawson Health Research Institute, and Dr. Frank Prato for carrying and defending this new plateform project in many different occasions.

6. References

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