Fundamentals and Future Directions of Transcranial Electric and Magnetic Stimulation

Peter Boráros   Eugen Kvašňák

***Abstract*—The methods of transcranial electric and magnetic stimulation (TS) are used to noninvasively modulate cortical activity. The TS techniques found their use in therapy in the areas of psychiatry, neurology, neurophysiology. The methods of TS emerged based on empirical knowledge about modulation of neuronal activity using external electromagnetic field. Nowadays, structured research is focused on understanding of TS principles leading to novel, more efficient methods and protocols. In present work, we brought overview of TS methods in use and we identified some of the future directions of the research and development.**

I. Introduction

Transcranial electric and magnetic stimulation is a set of techniques used to modulate the cortical neuronal activity utilizing the external source of electric or magnetic field applied on the scalp. The field non-invasively affects cortical tissue to few centimeters beneath the skull, therefore it interferes with cortical gyri and to a limited extent with cortical sulci as well. The field causes depolarisation or hyperpolarisation of the neuronal membranes in affected tissue which is accompanied by changes in neuronal excitability or in case of higher intensities also by formation of action potentials in neurons. This techniques have therapeutic and diagnostic applications in psychiatry, neurology, neurophysiology, etc.

II. Classification and operating principles

Depending on the type of electromagnetic field used for stimulation transcranial stimulation (TS) techniques can be divided to *transcranial magnetic stimulation* (*TMS*) and *transcranial electric stimulation* (*tES*).

A. Transcranial magnetic stimulation (TMS)

In Transcranial Magnetic Stimulation (TMS), a brief (0.2 ms) and powerful (0.2~4.0 T) magnetic pulse is generated by the coil. The coil is excited by the pulsing electric current, that reaches its maximal intensity within 0.1~0.2 ms and then decreases to zero during next 0.5~1 ms. Rapid ramping of the magnetic flux leads to formation of an eddy currents in the conductive sections of the tissue. Eddy currents flow in closed loops in planes perpendicular to the magnetic field.

Due to the principle of induction of the electric field in the tissue, the stimulating magnetic field can be effectively applied only within pulses. The pulse ramp rate and the peak intensity are the main parameters affecting the unit dose of the stimulation [1].

P. Boráros is with Czech Technical University in Prague
E. Kvašňák is with Charles University in Prague

Stimulation using rhythmic trains of magnetic pulses with repetition rate up to 100 Hz is referred as a *repetitive TMS* (*rTMS*). Different repetition rates have distinct effects on brain activity. TMS, in which single pulses are used instead of trains of pulses, is sometimes referred to as a *single-pulse TMS*.

1) Single-pulse TMS: This technique has been developed as a diagnostic method for evaluation of cortico-spinal pathway. During stimulation of the motor cortex with single magnetic pulses of sufficient intensity an acute depolarisation of whole population of neurons occurs. It is followed by excitation of neuronal pathways from brain through the spinal cord to the muscles, resulting in measurable motor evoked potentials (MEP). This technique has been also used for evaluation of changes in excitability of cortical neurons resulting from application of different transcranial stimulation methods.

2) Repetitive TMS: Although single-pulse TMS has been developed as a diagnostic tool, it has been observed that the magnetic pulses have an long term neuromodulation effect. This lead to a development of more powerful TMS generators capable of delivery of multiple pulses within short time – the rTMS. Empirically, rTMS has been further subdivided to *low-* (rates below 1 Hz) and *high-frequency rTMS* (rates above 5 Hz). Experimental evidence has revealed that rTMS with repetition rates below 1 Hz causes cortical inhibition and on the other hand rTMS trains above 5 Hz have opposite effect.

In order to increase efficiency of the high-frequency rTMS a repeated individual pulses have been substituted with groups of pulses, or — the burts. In a variant of rTMS, a theta-burst stimulation (TBS), the bursts of two or more pulses with intra-burst rate up to 50 Hz and inter-burst frequency of approximately 5 Hz are used. Although there is an evidence about increased efficiency, concerns about safety of the method arose. One of the limitations of current technology is that rTMS does not affect the deeper structures of the brain, but it is known that rTMS significantly involved in changing the perception of pain.

According to recent studies [2], this method is able to induce changes in the central nervous system at the cellular level including changes at ionic and metabolic level. Therapeutic effects were confirmed in the literature in psychiatric disorders such as depression, acute mania, bipolar disorder, panic attacks, hallucinations, obsessive states, schizophrenia, catatonia or post-traumatic stress disorder [3].

B. Transcranial electric stimulation (tES)

While in TMS the electric current is induced in the conductive parts of the tissue using external and rapidly changing magnetic field, in tES a weak electric current (0.1~2.0 mA) is applied on scalp using electrodes and flows through the tissue. The current flow in not homogenous and has variability among the affected tissue. The most of the current is conducted by surface layers (skin) and only small portion penetrates cortex.

Based on time course of the electric current, tES can be divided to *transcranial direct current stimulation* (*tDCS*), *transcranial alternating current stimulation* (*tACS*), *transcranial random noise stimulation* (*tRNS*) and *transcranial pulsed current stimulation* (*tPCS*) (for reviews see [4, 5]).

Electrode area and placement are important attributes. Area of the electrode must be chosen in accordance to the density and time course of the current to avoid pathological changes in the tissue. In order to decrease current spatial variability, multiple electrodes of same polarity can be placed in circular shape around one electrode of other polarity. This has been used to enhance focality of tDCS and it is denoted as *high-definition tDCS* (*HD-tDCS*) [6].

1) tDCS: In tDCS a direct current with intensity of 0.4~2 mA is applied on scalp via electrode pads for 5~30 minutes. Current causes most of the changes right under the electrodes: under cathode it decreases excitability of cortical neurons and under the anode the effect is opposite. By changing the area of the electrodes a current density can be changed and thus the effect of the stimulation. The effects last for few hours after the stimulation ends as in TMS. In clinical use, tDCS is considered as a noninvasive stimulation that is affordable and easy to use compare to other neuromodulatory techniques. TDCS is a promising method for the treatment of chronic pain [7], as well as for patients with neuropsychiatric diseases and other neurological disorders [8].

2) Novel approaches (tACS, tPCS, tRNS): About novel approaches of transcranial electric stimulation is not known too much. In *transcranial alternating current stimulation* (*tACS*) an oscillatory electric current is delivered to the cortical tissue with oscillation frequency between 0.1~5000 Hz. It is thought that the tACS signal interacts with ongoing cortical oscillations and induce changes [9]. Another method, *transcranial pulse current stimulation* (*tPCS*), is a variation of tACS where the harmonic current is exchanged for the rectangular electric signal. Though the spectra in tPCS is wider, the dominant frequency is still the baseline frequency of the pulses. Recently, interest has emerged in new stimulation method, transcranial random noise stimulation (tRNS) in which a random noise signal is applied with the frequency spectrum normaly distributed over given frequency range. tRNS is usually divided to low- (0.1~100 Hz) and high-frequency tRNS (100~640 Hz) [10].

III. Effects of TS on Neuronal Activity and Adjusting Stimulation Parameters

A. Numerical Simulation of Electromagnetic Field elicited by TS in the Brain

Thanks to growing computational power of computers and developed SW the use of numerical simulations of electromagnetic (*EM*) field have also rosen bringing useful tool to estimate the EM field distribution induced by transcranial stimulation in human brain [11, 12, 13, 14, 15]. Simulations are typically based on finite element method (*FEM*). Simplified model of the human head approximates the head with a sphere exposed to time varying magnetic field [11]. More accurate models use the volumetric imaging of human head [12, 14, 15]. Different labs employ different approximations, e.g. the differences in electrical properties of white/gray matter or cerebrospinal fluid have been neglected [12] or the anisotropy of the tissue has not been taken in account [14]. The modelling and simulation studies report of benefits coming from design improvements of the coil leading to increase of spatial focality and stimulation depth of the magnetic field [13] or from proposal of ring shape assembly of electrodes leading to increase of focality of the electrical stimulation [14, 6, 16].

B. Processing of Neuronal Network Activity and Stimulation Dynamics

TS protocols used in therapy so far neglect the dynamic nature of the neuronal networks in the brain. Typically, TS is applied with static parameters of electric or magnetic field (e.g. the intensity, frequency and timing of the pulses in rTMS are fixed during TS session), spatial configuration (i.e. focus of TS does not change according the tissue response). In order to evaluate stimulation effects or to improve its parameters the brain activity ought to be simultaneously coregistered with the stimulation. Although the main drawback is the interference of stimulating EM field and the acquisition system, some of the problems with interference can be reduced to certain extent by filtering. On the other hand, the artifacts can occur because of contraction of muscles affected by TS [17]. In stimulation by magnetic field the artifacts are generated by the interference of powerful magnetic field with acquisition wires of device recording neuronal activity. In stimulation by electric current the artifacts are generated by the interference caused by galvanic connection of the stimulation and acquisition electrodes with the human body. There are successful attempts to use simultaneous application of TS and coregistration of the brain activity (via e.g. EEG signal, glucose consumption, fMRI, blood flow, etc.) to identify the most effective parameters of stimulation and so that to improve TS efficacy. There are promising results found already for rTMS [18] or for tES in fMRI scanner [19].

IV. Conclusion

Methods of transcranial stimulation (TS) emerged from empirical knowledge that the electric or magnetic field can induce changes in neurons of human brain cortex. The evidence about transient excitation or inhibition of the cortical neurons elicited by TS has been found. In recent years structured and systematic research has provided deeper insight in the effects of TS which facilitates exploration of novel methods and improvements of TS efficacy. Simulations of the electromagnetic field lead to construction of more efficient and more compatible stimulation and acquisition devices. Functional mapping of cortical activity and connectivity of different cortical areas may bring reveal novel applications and locations of TS. Further progress and main challenges in TS research are expected in changing the static stimulation TS protocols into real-time processing of electrophysiological or volumetric data of neuronal network with aim to adjust electrical, temporal and spatial parameters of the stimulation. Thus the research and development of advanced TS techniques and protocols adjusted by outcomes of simultaneous processing of activity of affected neuronal populations (feedback) will be elaborated. This includes the construction of compatible acquisition and stimulation devices, the signal processing and analysis algorithms for artifacts filtering and direct stimulation control.

References

[1] A. V. Peterchev, T. A. Wagner, P. C. Miranda, M. A. Nitsche, W. Paulus, S. H. Lisanby, A. Pascual-Leone, and M. Bikson, "Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices." *Brain stimulation*, vol. 5, no. 4, pp. 435–53, Oct. 2012. [Online]. Available: http://dx.doi.org/10.1016/j.brs.2011.10.001

[2] R. Rokyta and J. Fricova, "Noninvasive Neuromodulation Methods in the Treatment of Chronic Pain," in *Pain and Treatment*, G. B. Racz and C. E. Noe, Eds. InTech, 2014, ch. 5, pp. 175–190. [Online]. Available: http://dx.doi.org/10.5772/57449

[3] R. Rokyta and J. Fricová, "Neurostimulation methods in the treatment of chronic pain," *Physiological research*, vol. 61 Suppl 2, pp. S23–31, 2012. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/23130900

[4] W. Paulus, "Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods." *Neuropsychological rehabilitation*, vol. 21, no. 5, pp. 602–17, Oct. 2011. [Online]. Available: http://dx.doi.org/10.1080/09602011.2011.557292

[5] B. Guleyupoglu, P. Schestatsky, D. Edwards, F. Fregni, and M. Bikson, "Classification of methods in transcranial electrical stimulation (tES) and evolving strategy from historical approaches to contemporary innovations." *Journal of neuroscience methods*, vol. 219, no. 2, pp. 297–311, Oct. 2013. [Online]. Available: http://dx.doi.org/10.1016/j.jneumeth.2013.07.016

[6] E. M. Caparelli-Daquer, T. J. Zimmermann, E. Mooshagian, L. C. Parra, J. K. Rice, A. Datta, M. Bikson, and E. M. Wassermann, "A pilot study on effects of 4x1 high-definition tDCS on motor cortex excitability." in *Engineering in Medicine and Biology Society*, vol. 2012. IEEE, Jan. 2012, pp. 735–8. [Online]. Available: http://dx.doi.org/10.1109/EMBC.2012.6346036

[7] N. E. O'Connell, B. M. Wand, L. Marston, S. Spencer, and L. H. Desouza, "Non-invasive brain stimulation techniques for chronic pain," *Cochrane Database of Systematic Reviews*, vol. 4, 2014. [Online]. Available: http://dx.doi.org/10.1002/14651858.CD008208.pub3

[8] M. F. Kuo, W. Paulus, and M. A. Nitsche, "Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases," *NeuroImage*, vol. 85, pp. 948–60, 2014. [Online]. Available: http://dx.doi.org/10.1016/j.neuroimage.2013.05.117

[9] A. Antal and W. Paulus, "Transcranial alternating current stimulation (tACS)." *Frontiers in human neuroscience*, vol. 7, no. June, p. 317, Jan. 2013. [Online]. Available: http://dx.doi.org/10.3389/fnhum.2013.00317

[10] D. Terney, L. Chaieb, V. Moliadze, A. Antal, and W. Paulus, "Increasing human brain excitability by transcranial high-frequency random noise stimulation." *The Journal of neuroscience : the official journal of the Society for Neuroscience*, vol. 28, no. 52, pp. 14 147–55, Dec. 2008. [Online]. Available: http://dx.doi.org/10.1523/JNEUROSCI.4248-08.2008

[11] T. A. T. Wagner, M. Zahn, A. J. Grodzinsky, and A. Pascual-leone, "Three-Dimensional Head Model Simulation of Transcranial Magnetic Stimulation," *IEEE Transactions on Biomedical Engineering*, vol. 51, no. 9, pp. 1586–1598, Sep. 2004. [Online]. Available: http://dx.doi.org/10.1109/TBME.2004.827925

[12] L. Golestanirad, M. Mattes, J. R. Mosig, and C. Pollo, "Effect of model accuracy on the result of computed current densities in the simulation of transcranial magnetic stimulation," *IEEE Transactions on Magnetics*, vol. 46, pp. 4046–4051, 2010.

[13] S. Tsuyama, Y. Katayama, A. Hyodo, T. Hayami, S. Ueno, and K. Iramina, "Effects of coil parameters on the stimulated area by transcranial magnetic stimulation," in *IEEE Transactions on Magnetics*, vol. 45, 2009, pp. 4845–4848.

[14] A. Datta, V. Bansal, J. Diaz, J. Patel, D. Reato, and M. Bikson, "Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad." *Brain Stimulation*, vol. 2, no. 4, pp. 201–7, 207.e1, Oct. 2009. [Online]. Available: http://dx.doi.org/10.1016/j.brs.2009.03.005

[15] M. Bikson, A. Rahman, A. Datta, F. Fregni, and L. B. Merabet, "High-resolution modeling assisted design of customized and individualized transcranial direct current stimulation protocols." *Neuromodulation*, vol. 15, no. 4, pp. 306–15, Jul. 2012. [Online]. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3418452&tool=pmcentrez&rendertype=abstract

[16] D. Edwards, M. Cortes, A. Datta, P. Minhas, E. M. Wassermann, and M. Bikson, "Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS." *NeuroImage*, vol. 74, no. null, pp. 266–75, Jul. 2013. [Online]. Available: http://dx.doi.org/10.1016/j.neuroimage.2013.01.042

[17] R. J. Ilmoniemi and D. Kičić, "Methodology for combined TMS and EEG." *Brain topography*, vol. 22, no. 4, pp. 233–48, Jan. 2010. [Online]. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2800178&tool=pmcentrez&rendertype=abstract

[18] G. W. Price, J. W. Y. Lee, C.-A. L. Garvey, and N. Gibson, "The use of background EEG activity to determine stimulus timing as a means of improving rTMS efficacy in the treatment of depression: a controlled comparison with standard techniques." *Brain*

Stimulation, vol. 3, no. 3, pp. 140–52, Jul. 2010. [Online]. Available: http://dx.doi.org/10.1016/j.brs.2009.08.004

[19] C. Saiote, Z. Turi, W. Paulus, and A. Antal, "Combining functional magnetic resonance imaging with transcranial electrical stimulation." *Frontiers in human neuroscience*, vol. 7, no. August, p. 435, Jan. 2013. [Online]. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3733022&tool=pmcentrez&rendertype=abstract