# Transcranial brain stimulation: potential and limitations

Stefano Piazza, Maricarmen Sanchez, Aitor Martinez, Rafael Mendoza

10/06/2016

## 1 Historical Background

The era of quantifiable and reproducible transcranial brain stimulation began around 1800 with the invention of the voltaic pile.In its clinical applications, the pile was used fotr the application of transcranial direct current stimulation in patients. However, there were no methods to quantify plastic changes in the brain, and these early as well as many later approaches failed due to the lack of reliable biomarker data on the parameters of stimulation. In the 20th century, more complex current stimulation methods suffered the same fate.

## 2 Evaluation of cortical plasticity

This situation changed with the development of transcranial magnetic stimulation (TMS) in 1985. TMS triggers muscle twitches (motor-evoked potentials in the muscle, MEP), whose electromyographic correlate before and after an intervention such as repetitive TMS (rTMS), allows a simple measurement of induced plastic changes. TMS can induce both activation as well as inhibition. For physical reasons, TMS can generate only tangential but not radial current flow. Due to the convolutions of the human cortex, the efficien- cy of TMS is strongly dependent on the geometry, with radially impinging current having the greatest efficiency and tangential current the least. Current flowing in the parietal to frontal direction has the lowest MEP threshold.

Stimulation effects are used in clinical routine to quantify central motor conduction times of the corticospinal tracts or for inducing cortical plasticity. For example, using double-train stimulation MEP is possible to detect intracortical inhibition and facilitation and to differentiate possible spinal plasticity changes. TMS can thus be used for measuring and repetitively (rTMS) for modulating cortical plasticity.

## 3 Repetitive transcranial magnetic stimulation

High frequency rTMS is based on the fact that slow repetition frequencies of about 1 Hz cause inhibition, while frequencies above 5 Hz induce activation that persists after the end of stimulation if an adequate number of stimuli are applied. The standard protocols prescribe a sequence duration of 15?30 min with 900?1500 stimuli, which induce a subsequent inhibition of the motor cortex that lasts for about 30 min.

Paired associative stimulation (PAS) is a method that will still be of particular importance in the future. Basically, every external or internal activation of the brain can be combined with transcranial stimulation. The best-studied combination is activation of the somatosensory cortex by peripheral electrical stimulation with TMS of the contralateral motor cortex. Repetitive TMS at 10-s intervals alone does not induce plasticity effects; However, if TMS of the motor cortex is paired with electrical stimulation of the contralateral median nerve, a stimulation delay of 10 ms between electrical stimulation and TMS causes inhibition, while a 25 ms delay induces facilitation of the motor cortex. Distinct from simple TMS or tDCS protocols, it can be assumed that TMS specifically influences synapses that had been facilitated by the preceding stimulation of the median nerve.

## 4 Transcranial direct current stimulation

Transcraneal direct current stimulation (tDCS), known as the most simple form of stimulation, is performed with currents of approximately 1 mA and potentials of about 10 V. It modulates the spontaneous rate of cortical neurons by membrane hyperpolarization or depolarization. With this stimulation, as in TMS, there are virtually no limits to the physical possibilities with variations of intensity, duration, repetition intervals, stimulation frequency, pulse shape or electrode position.

The assumption is that current components flowing in a direction radial to the cortical surface act through somatic hyper or depolarization, while tangential current components tend to inhibit or facilitate incoming afferents by hyper or depolarizing nerve endings, but with a reversed effect on cortical polarity dependence. The position of the return electrode determines the direction of current flow, although the stimulation electrode is usually positioned above the targeted cortical area. Modern algorithms make it possible to calculate the optimal positions for stimulating targeted areas.

# 5 Transcranial alternating current stimulation

The currents and potentials of transcranial alternating current stimulation (tACS) are in the range of 1–5 mA and 10–20 V, depending on the frequency. EEG potentils are in the microvolt range. As a result, EEG registration during tACS is a challenge.

However, longer periods of tACS can induce plastic after-effects. For instance, theta frequency (4–8 Hz) tACS between frontal and parietal electrodes alter reaction times in a letter discrimination task. The reaction times are shortened when the frontal and parietal theta stimulation with a central reference electrode is performed in phase, but they are lengthened when anti-phase stimulation is employed. This contributes to the understanding of the temporary electrical linkage between cortical areas in humans.

# 6 Specificity

Due to brain volume, transcranial stimulation procedures excite large cell assemblages and will never be able to selectively excite individual cells.

The stimulation effects can be modified considerably by varying the physical parameter frequency with tACS or pulse duration with TMS and by co-application of neuropharmacologically active substances. For instance, Dopamine suppersses synapse non-specific plasticity and facilitating synapse specific activity.

# 7 Clinical applications

For many years Transcraneal Electric Stimulation procedures have been used as a parallel treatment method. Insurance companies now pay for the treatment of depression using rTMS. The research took the way of primarily due to abandon other methods that were mucho more invasive like electroconvulsive therapy. The were other works with small differences but with negative results. In contrast a successful co-aplication of tDCS with SSRI had very good results in the treatment of deprssion. In healty subjects it has bee demostrated that the prior administration of an SSRI inverts the cathodal inhibition to facilitate and also markedly prolongs the after-effects of anodal tDCS. Studies currently working deal with the problem of wheter simultaneous stimuly of the infarted area (anode) and inhibition of the contralateral motor cortex (cathode) with reduction of transcallosal inhibition give better rehabilitation results than unilateral stimulation alone.

# 8 Limitations of transcranial electrical stimulation

Glioblastoma patiens' brain is stimulated around the clock asuming that the dividing tumor cells react particulary during mitosis and will be selectively destroyed. It is a fact thet current limitations of transcraneal electrical stimulation will expand with the continious growing knowledge of the underlying physiological processes. Clasical after-effects such as inhibition of the motor cortex after 1Hz rTMS can be inverted when a second conditioning stimulation such as tDCS is applied first. The relationships between stimulation duration and intensity and biological effects are not linear. By doubling the period of an anodal tDCS from 13 to 26 min it has got a non-linear inversion of the after-effect to inhibition.

# 9 Alternatives to transcranial electrical stimulation

Atempts to reach deep brain areas using more sophisticated models are limitated by the biophysical constrains of a high conductivity of cerebrospinal fluid and poor conductivity of gray and white matter. In contrast, ultrasound can be focused much better on a certain area. Using large number of ultrasound transducers and thermo sensitive MRI sequences, it is possible to locate the center of the planned heat application with milimiter precision, after that it is possible to coagulate using higher intensities. With albeit invasive method, that is reversible non invasive deep brain stimulation, yet stereotaxis is emerging, but this last one is still destructive.

# 10 Safety

The principal safety problem due to stimulation of the brain it is seizure induction, another side effects are reported like light pain or unpleasant skin sensations due to stimulation, and there are more related with tDCS than with tACS. Looking to the histological perspective has been seen changes in rat models after current intensities about 400-fold higher than in humans trials.

For this reason, in order to avoid the actual and more relevant issue related to rTMS (seizure induction) it is needed to take into consideration the safety intensity and frequency limits exposed by Rossi et al. 2009 (Rossi S, Hallett M, Rossini PM, Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120:2008–2039) Apart of that there are no seizures induced by electrical stimulation interventions,

In the same way there is no comparable the charges given in ETC (Electroconvulsive therapy) for clinical seizure induction with tACS in plasticity research studies.
In relation to the waveform, sinus wave stimulation is not enought in the case of ECT, and the differences are smaller for rTMS, since the TMS protocols used to induce seizures are four timer higher maximal stimulation intensity.

# 11 Neuroenhancement

Today there is an actual discussion in research teams around the world about this issue. Neuroenhancement like cognitive enhancement are under research focus because of trying to know the effects on brain functions before and after NIBS either on healthy subjects and patients. In this vein with tDCS it is possible to shorten reaction times in implicit motor learning also aritmetic tasks can be improved, this technique doesn't do the same effects on signal recognition in noisy environments
Moreover there are some findings on motion recognition, improving in that way the visual performance by appliying cathodal tDCS, and between other things this effect can be attributed to a better signal-to-noise ratio in this device.
Appart of that improvements only a little percentaje of researchers have done self-experimentation maybe due to insufficient published effects, for the methodology issues on research it, or for stimulation algorithms have not been suffiently optimized yet, or due to missunderstand of dependent inhibition-facilitation effects on homeostatic situation. tDCS cognitive enhancement could be important for military applications specially in visual performance improvements.

# 12 Outlook

Many successful transcraneal stimulation protocols have been developed. Many other still in continuos development based on hypotesis and a basis of basic neurophysiological research. It looks very dificult to achieve any meaningful effect on brain functions using pulsed (TMS), uniform (tDCS), oscillating (tACS) or random (tRNS) types of stimulation. Probably in the future the developments will procced using stimulation of hypoactive areas or motor cortex in hemiparesis and activity-enhancing stimulation of the motor cortex for chronic pain. The complex the dissease the complex the paradigm, which will usually mean paired associative stimulation.