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## Closing Lecture

### The frontier of tDCS in psychiatry and the role of new technologies

#### Les limites de la tDCS en psychiatrie et la place des nouvelles technologies

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Over the past twenty years, neuromodulation techniques have raised a growing number of interest for clinicians and researchers. Numerous studies have been carried out in order to propose these techniques as therapeutic solution in patients with various neuropsychiatric conditions, but optimal stimulation parameters and ideal treatment conditions/situations remain unclear. These techniques aim to deliver a certain quantity of energy to a specific brain target to modify its activity and connectivity. They use various energy sources that can be delivered over several brain regions with various size and depth. For example: Deep Brain Stimulation (DBS) delivers electrical energy deep inside the nervous system over precise areas of the brain, Transcranial Magnetic Stimulation (TMS) uses magnetic energy to deliver currents along the cortical region with a depth of 2 to 3 cm, Electroconvulsive Therapy (ECT) uses electricity over a large area of the brain to induce seizures. While all these techniques are conducted in a hospital environment under medical supervision, some other techniques, which use low intensity electric pulses, such as Transcranial Electrical Stimulation (tES) and transcranial Direct Current Stimulation (tDCS) are portable and may be delivered at home. Owing to its low cost, feasibility and safety, tDCS has gained attention for its clinical purposes, even if the mechanisms of action are not yet fully understood. tDCS is easily setup, the device is usually hand-held, and subjects wear the headgear with scalp electrodes. In the majority of research protocols an intensity set at 1 to 2 mA is delivered during a 20-min session. The number of sessions can vary from one or more session over a period of several weeks. Depending on the clinical indication, other stimulation parameters can also be used. Despite its apparent simplicity, tDCS is a very complex local modulator of brain excitability and plasticity. Arguing for its clinical use, we have reported the safe delivery of over 30 000 sessions of tDCS, [1], Guleyupoglu et al. [2] presented an evolving strategy from historical approaches to contemporary innovations and Woods et al. [3] put forward a technical guide to tDCS. Additionally, tDCS and neuromodulation technologies have also been used in a cognition enhancement approach, as shown by the “Do It Yourself” movement. However, before it can be administered in routine clinical settings, there is a need to update the

understanding of tDCS parameters with precise clinical indications and propose optimization strategies. Moreover, despite more than 400 controlled trial sessions using tDCS in various neurological and psychiatric conditions, much criticism persists. Scientists and clinicians have raised a number of questions that must be addressed before any conclusion on the value of tDCS in clinical practice can be made: 1- there are mixed and contradictory clinical results across studies; 2- there are too many indications with positive results; 3 - tDCS generates an electrical signal whose intensity is too low to trigger neural firing; 4- tDC is not a physiological signal; and there is a lack of a spatial target.

In a first part of this conference, tDCS frontiers were discussed by reviewing frequent criticisms and their limitations. In a second part it was explained how personalized tDCS therapy could be realized in a patient's home.

### **Understanding the frontiers of tDCS through criticism:**

One of the most common criticisms against tDCS is the lack of an accurate target. In this context, it seems primordial to have had better models to predict electrical field distribution.

Understanding targeting begins with experimentally-verified anatomical MRI derived models of current flow. With a classic tDCS montage there is between 50% to 75% of the brain which is stimulated. As illustrated by the treatment for pain or cognition, in which large electrodes are used on regions of interest, other parts of the brain were stimulated. Studies in High-Definition tDCS use small electrodes which are positioned closer to one another. Consequently, their number increases from two, to reach between eight or thirty-two electrodes. An anode, an activating electrode, is placed at the center of the region of interest and is surrounded by several cathodes, the inhibiting electrodes. Software allows to steer currents to the targeted brain regions by selecting an electrode and having a single programmable device. In other words, stimulation becomes more focalized and precise, therefore the target optimization question is solved thanks to HD-tDCS with its small electrodes. Some authors emphasized these questions: Datta et al. with a focal Gyri-precise model of tDCS [4], Minhas et al. with the use of small (HD) electrodes [5], Dmochowski et al. by optimizing multi-electrodes stimulation focality [6] and Huang et al. about measurements and models of electric fields in the human brain [7].

Another very common criticism is that tDCS delivers an electric current which is not powerful enough to trigger neuronal firing. As a matter of fact, tDCS indeed delivers only 1-2mA whereas ECT, rTMS and DBS deliver hundreds mA to the brain. Several authors conducted research to understand how it is possible that such a low intensity modulation can work: Jackson et al. investigated the effects of DC stimulation in animal models (in correlation with the original Long Term Potentiation protocols) [8], Radman et al. focused on neuron polarization [9] and Reato et al. focused on the modulation of oscillations [10]. Albeit an intensity of up to a thousand times lower compared to other techniques, concrete results have been established. However, there is evidence of clinical recovery in several pathologies. How could these be explained? In fact, with high intensity stimulation the neural network goes into overdrive and the modulation comes from secondary non-linear changes (even if it is a reduction). Most techniques have this form of supra-stimulation threshold (ECT, TMS, DBS).

With tDCS, at 1 to 10 mA, neurons are not firing and there is no induction of action potential in the stimulated neurons. tDCS is modulating on-going activity rather than generating: it is an interaction with specific activity in a neural network, not a drive. When current flows across an entire brain region, there will be a preferential modulation of more active network (activity dependent, engaging

in a specific task). It is a functional targeting: an activity dependent sensitivity to brain stimulation. Hence, another criticism saying direct current is not physiological signal is not suitable too.

An illustrative experiment on brain rodents slices was performed using Theta Burst Stimulation (TBS) and direct cathodal or anodal Current Stimulation with small electrodes (HD-tDCS). By acting on excitatory postsynaptic potential (EPSP), a measure of synaptic activity, it was possible to modulate connectivity between two populations of neurons. When TBS is applied in a population of neurons in brain rodents slides, an LTP phenomena can be measured in the population of postsynaptic neurons. This phenomenon is not observed following DC stimulation when it was delivered alone. However, when tDCS was applied just after TBS, de novo plasticity was observed depending on activity: that was on-going plasticity. tDCS was able to modify the intensity of LTP phenomena generated by Theta Burst Stimulation. These results were found at the level of two neurons populations and at synapsis level, on the same neuron. Differences exist in this tDCS plasticity generation and depend from modulation parameters. For example, direction of changes by anodal or cathodal electrodes depends on LTP types. On certain types, anodal tDCS clearly depress and cathodal excite but animal models with opposite results exist.

There is another interesting experience to understand how low tDCS intensity might modulate neuronal response and help to have specific target. With multiple theta burst stimulation, plasticity reaches a ceiling for synaptic learning. tDCS is not only interesting to accelerate LTP but can also boosts the ceiling for synaptic learning. Thus combining TDCS with a task and ongoing activity could enhance the rate and ceiling learning specifically of that task. It is a functional targeting, activity dependent: if tDCS is applied with a task, it makes the task more effective (as example creativity in piano). It could be used in clinical trials or combined with therapies.

Therefore the answer to the question “Is tDCS deliver a too low intensity to induce neurons firing?” is “Yes”. However, we have to keep in mind that this low current intensity leads to functional targeting. It can in part explain why people with different experiences, placebo or tasks have mixed clinical results. In connection with these results, the real challenge for tDCS is not feasibility, but optimization to meaningful applications. If some problems are solved by functional targeting, it remains questions about task, session timing, inclusion criteria, intensity and biomarker. Nevertheless, maybe these notions do not fit all and tDCS need to be personalized?

### **Personalized therapy and at patients' homes tDCS**

A better way to optimize treatment seems to have reliable data collection and feedbacks. We describe here most important principles used on patient with personalized and adaptive tDCS sessions. Measurement is made to help clinicians in their decision to modify treatment. Then, another measurement, uses as a feedback, permits to reach therapeutic aim. This is something impossible with pharmacological drugs because pharmacokinetic and pharmacodynamics are fixed. The large tDCS safety permits to easily adapt parameters with a minimal risk (intensity, specific task or target region).

One solution to personalize therapy consists in using the “reciprocity” hypothesis with modern tools. During a task, when a brain region is active, it generates voltages picked up on the scalp that we can catch by EEG. If we stimulate these regions at the adequate timing and intensity, it is reciprocity: an activity guided targeting.

We used an EEG automatically and instantly “inverted” to optimal HD-tDCS montage. Hence subjects performed a task, brain activity is instantly caught by EEG and thanks to an algorithm, HD-tDCS

stimulated the same region that generated the sequence. It is an activity guided targeting who does not require source localization. Dmochowski et al. published about EEG to HD-tDCS reciprocity [11] and Cancelli et al. about method for EEG guided tES without models [12].

In 2016, Castillo-Saavedra et al conducted a phase II trial in patients with fibromyalgia pain using high Definition tDCS [13]. Event-related potentials (ERP) were recorded by EEG during a pain induction and then, brain implicated regions stimulated by HD-tDCS. It is a reciprocity example: pain brain region are activated during a specific "task", EEG activity is caught and then, region of interest are stimulated. It treated fibromyalgia but also modulated brain activity who became closer to a normative response to pain (abnormal in fibromyalgia). At 6 weeks follow up, almost of 50% subjects were responders another large part were dropouts. These results show efficacy for subjects who completed protocol even if proportion of missing data is high. It seems to be link with patient condition (pain, low mobility) preventing move to hospital. In other words, an effective technique exists but it was inaccessible for patients. A solution could be to use tDCS at home. However, before proposing tDCS at home, several points should be debate. First, when neuromodulation is delivered at home, clinicians should have several types of feedback to ensure the safety (e.g., vital signs with Photoplethysmogram, ECG, Respiration, Electrodermal activity) and of the good use of the device (duration of session, intensity delivered, fNIRS or EEG). This can be done by using an app downloaded on the patients' smartphone and connected to clinician website and transferring recorded data. Patients should wear a head-gear sensor with tDCS electrodes and EEG, vital signs recording connected to the app. Yet, these tools will help to update treatment daily and immediately. To measure safety and efficacy of the stimulation, participants should also respond to standardized questionnaires in the app. However, when responding to questions on an app, repetition could be wearisome for patients and this is not useful information for clinicians. Thus adaptive questionnaires with multiple choices could be perform. All these measures are helpful to personalize neuromodulation (for example to report mood, pain or other side effects). Inevitably, no one will have the same neuromodulation parameters. Indeed, asking people different things conduct to different treatment.

According to these raw data feedbacks, the therapy decision is tunable targeted and fast iterative. A task might be added at home to be more specific. A part of the technologies evoked are in development but the means to personalize therapy are all available now. We might imagine than a family member will interact with the neuromodulation software and home tDCS will become a natural option. It could be useful for old patient and child. About personalized home-based tDCS we can found other studies: Charvet et al. for remote supervised tDCS [14], Meiron et al. for pediatric epilepsy [15], Kasschau et al. for multiple sclerosis [16] and Khadka et al for dry tDCS with a novel multilayer hydrogel [17].

### **Conclusion:**

Nowadays, classic tDCS limitations are out-of-date. With HD-tDCS and its multiple electrodes, we have focal and precise stimulation. By modulating ongoing brain activity and by coupling tDCS with a task, we can carry out target function targeting. To optimize applications, one solution is to personalize the modulation technology. Reciprocity is an activity guided targeting which does not require source localization. It is one of the forms of feedback, along with the app and the adaptive questionnaires, used by clinicians to update treatment daily and immediately. In this context, tDCS might become a home technique realized by family members.

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