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Using of transcranial direct-current stimulation during motor task for a better outcome

Pierre Besson

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THÈSE POUR OBTENIR LE GRADE DE DOCTEUR DE L'UNIVERSITÉ DE MONTPELLIER

En Sciences et Techniques des Activités Physiques et Sportives

École doctorale des Sciences du Mouvement Humain (ED 463)

Unité de recherche EuroMov (EA 2991)

Using transcranial Direct-Current Stimulation during motor task for a better outcome

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Le 30 novembre 2017

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UNIVERSITÉ
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"I am a great believer in luck.

**The harder I work,
the more of it I seem to have."**

Coleman Cox

Listen to this, 1922

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2. **Besson, P.**, Perrey, S., Teo, W. P., & Muthalib, M. (2016). *Commentary: Cumulative effects of anodal and priming cathodal tDCS on pegboard test performance and motor cortical excitability*. **Frontiers in Human Neuroscience**, 10, 70. <http://doi.org/10.3389/fnhum.2016.00070>
3. Sood, M., **Besson, P.**, Muthalib, M., Jindal, U., Perrey, S., Dutta, A., & Hayashibe, M. (2016). *NIRS-EEG joint imaging during transcranial direct current stimulation: online parameter estimation with an autoregressive model*. **Journal of Neuroscience Methods**, 274, 71-80. <http://doi.org/10.1016/j.jneumeth.2016.09.008>
4. **Besson, P.**, Vergotte, G., Muthalib, M., & Perrey, S. (2017). *Abstract: Test-retest reliability of transcranial direct current stimulation-induced modulation of resting-state sensorimotor cortex oxygenation time course*. **Brain Stimulation**, 10(2), 400. <http://doi.org/10.1016/j.brs.2017.01.186>
5. Muthalib, M., **Besson, P.**, Rothwell, J., & Perrey, S. (2017). *Focal Hemodynamic Responses in the Stimulated Hemisphere During High-Definition Transcranial Direct Current Stimulation*. **Neuromodulation: Technology at the Neural Interface**, Ahead of print <http://doi.org/10.1111/ner.12632>

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National

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Other related Publications

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List of abbreviations

AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AP: action potential

atDCS: anodal transcranial direct-current stimulation

BA: Brodmann area

BG: basal ganglia

BCM: Bienenstock-Cooper-Munro

BDNF: brain-derived neurotrophic factor

BOLD: blood oxygen level dependent

C: cerebellum

cAMP: cyclic adenosine monophosphate

CBF: cerebral blood flow

CBV: cerebral blood volume

CMRO₂: cerebral metabolic rate of oxygen

CNS: central nervous system

ctDCS: cathodal transcranial direct-current stimulation

dPM: dorsal premotor cortex

DPF: differential pathlength factor

ECT: electroconvulsive therapy

EEG: electroencephalography

E / I: excitation / inhibition ratio

EPSP: excitatory postsynaptic potentials

fMRI: functional magnetic resonance imaging

fNIRS: functional near infrared spectroscopy

GABA: γ -aminobutyric acid

GPT: grooved pegboard test

Hb: hemoglobin

Hbdiff: hemoglobin difference (i.e., O₂Hb-HHb)

HHb: deoxyhemoglobin

ICF: intracortical facilitation

IPSP: inhibitory postsynaptic potentials

LTD: long-term depression

L-LTD: late-LTD

LTP: long-term potentiation

L-LTP: late-LTP

HD-tDCS: high definition transcranial direct current stimulation

M1: primary motor cortex

MBLL: modified Beer-Lambert law

MEG: magnetoencephalography

MEP: motor evoked potential

NIBS: non invasive brain stimulation

NMDA: *N*-methyl-D-aspartate

NVC: neuro vascular coupling

O₂Hb: oxyhemoglobin

PET: positron-emitting tomography

PFC: prefrontal cortex

PSP: postsynaptic potential

ROI: region of interest

rTMS: repetitive transcranial magnetic stimulation

S1: primary somatosensory cortex

SEP: somatosensory evoked potential

SFO: simple finger opposition

SICI: short interval intracortical inhibition

SMA: supplementary motor area

SMC/SM1: sensory motor cortex

SPECT: single photon emission computed tomography

STD: short-term depression

STDP: spike-timing dependent plasticity

STP: short-term potentiation

tACS: transcranial alternating current stimulation

tDCS: transcranial direct current stimulation

tES: transcranial electrical stimulation

TMS: transcranial magnetic stimulation

Trk: tropomyosin-receptor kinase

tRNS: transcranial random noise stimulation

V1: primary visual cortex

Résumé

De tout temps, les humains ont cherché différents moyens pour améliorer leur quotidien. Avec les avancées technologiques actuelles, cette quête s'en trouve facilitée, notamment dans la volonté d'accroître leurs capacités cognitives et/ou motrices. La neuro imagerie permet dorénavant de renseigner les aires cérébrales activées lors de différentes tâches fonctionnelles. Il est aussi possible de moduler l'activité cérébrale en stimulant localement le cerveau avec de faibles courants électriques. Une des techniques les plus répandues à cet effet est appelée tDCS pour transcranial direct current stimulation. Il s'agit en fonction de la polarité du courant induit de moduler à la hausse (stimulation anodale) ou à la baisse (stimulation cathodale) l'excitabilité cortico-spinale en dépolarisant ou en hyperpolarisant la membrane des neurones, respectivement. Malgré une démocratisation grandissante de la neuromodulation via tDCS, les résultats rapportés par la communauté scientifique sont relativement hétérogènes. Les travaux initiés au début des années 2000 sont remis en cause par des résultats actuels faisant état d'une variabilité inter et intra individuelle assez importante. Cette pierre d'achoppement nécessite de développer de nouveaux protocoles d'application de la tDCS. Dans cette thèse, nous avons étudié plusieurs modalités d'application de la tDCS afin d'accroître la persistance des effets neuroplastiques induits et d'augmenter les performances comportementales. Deux études ont été menées afin de révéler dans un premier temps les apports induits par le couplage tâche motrice-tDCS pour ensuite mettre en avant les effets cumulatifs de la répétition de sessions de tâche motrice-tDCS avec pré conditionnement sur la performance motrice. La première étude à travers l'utilisation de la spectroscopie dans le proche infrarouge a permis de rapporter des changements hémodynamiques distincts subséquents au couplage tâche motrice-tDCS par rapport à des protocoles tDCS plus conventionnels. La primauté de l'utilisation concomitante de la tDCS à la tâche motrice a été révélée par la moindre activation du cortex sensorimoteur durant la stimulation ainsi que par une activation cérébrale retardée accrue qui pourrait représenter une réorganisation neuroplastique. La seconde étude s'est intéressée aux effets de la polarité du conditionnement lors de sessions répétées avec comme objectif d'améliorer l'apprentissage et la rétention du système sensorimoteur. Le conditionnement par tDCS était plus propice lors de sessions répétées à engendrer des performances motrices supérieures contrairement à la condition sham. La polarité cathodale engendrait une persistance prolongée. Les premiers résultats de ces travaux de thèse ont permis de défendre l'usage concomitant de la tDCS avec

la tâche motrice. De futures recherches sont nécessaires afin d'étudier le transfert de ces résultats dans le monde de l'entraînement ainsi que celui de la réhabilitation.

Mots clés : stimulation transcranienne à courant direct (tDCS), optimisation, couplage fonctionnel tâche-tDCS, conditionnement, répétition, spectroscopie dans le proche infra-rouge.

Abstract

Historically, humans have sought various ways to improve their daily lives. With the current technological advances, this quest is facilitated, especially in the desire to increase their cognitive and / or motor skills. Neuro imagery now makes it possible to inform the areas activated during different functional tasks. Today, it is now possible to modulate brain activity by stimulating the brain locally with weak electrical currents. One of the most common techniques for this purpose is called tDCS for transcranial direct current stimulation. The polarity of the induced current (anodal or cathodal stimulation) allows to modulate upward or downward cortico-spinal excitability by depolarizing or hyperpolarizing the membrane of the neurons, respectively. Despite a growing interest of neuromodulation techniques via tDCS, the results reported by the scientific community are relatively heterogeneous. The work initiated at the beginning of the 2000s is called into question by current results showing a rather large inter and intra variability. This stumbling block requires the development of new protocols for the application of anodal tDCS (atDCS). In this thesis, we were interested in optimizing atDCS protocols in order to increase the persistence of the induced-neuroplastic effects and to increase the behavioral performances. Two studies were carried out in order to first reveal the impact from the motor task/atDCS coupling and then to highlight the cumulative effects of multiple motor-tDCS task sessions with priming atDCS on motor performance. The first study through the use of near infrared spectroscopy allowed to report various hemodynamic changes subsequent to the motor task/atDCS coupling with respect to independent and controlled stimulation protocols. The primacy of the concomitant use of tDCS with the motor task was revealed by the slightest activation of the sensorimotor cortex during stimulation and by an increased delayed cerebral activation which could represent a

neuroplastic reorganization. The second study examined the effects of repeated atDCS sessions with anodal or cathodal tDCS priming in order to improve the learning and retention gains of the sensorimotor system. TDCS priming was more favorable for repeated atDCS sessions to generate higher motor performances contrary to sham. The cathodal polarity produced prolonged persistence. The major findings of this work allow to support the concomitant use of atDCS with the motor task. Future research is needed to study the transfer of these results into the fields of coaching and rehabilitation.

Key words: transcranial direct current stimulation (tDCS), optimization, task-tDCS functional coupling, priming, repetition, functional near infrared spectroscopy.

1

Introduction and outline

Chapter 1: Introduction

“The human brain – the focus of many of the most alluring proposed enhancements – is arguably the most complex thing in the known universe” (Savulescu and Bostrom, 2009). This quote allows us to set out this thesis in a context where humility will be a recurring principle without being fatalistic in view of the magnitude of the task of improving human capacities. This perspective of improvement is to be approached differently according to the definition adopted to conceive the notion of "human enhancement" (Bateman and Gayon, 2012). Beyond the historical, philosophical and factual debates with regard to the number of publications on “human enhancement” referenced on Pubmed, the enthusiasm around this concept is increasing. Neuroscience does not escape this phenomenon, as reflected in the Research Topic published in Frontiers Human Neuroscience entitled Trends in Neuroergonomics (<http://journal.frontiersin.org/researchtopic/3507/trends-in-neuroergonomics>). This special Topic was dedicated to Professor Raja Parasuraman who allowed the emergence of Neuroergonomics as a new scientific field. This exceptional man wanted researchers to develop theories and knowledge that would make life easier for everyone. The aim of this doctorate is totally in line with this desire, that is making it easier for humans to adapt to the growing constraints they encounter. The fields of application are multiple and may seem equally secondary when one focuses on sporting practices that are essential when one is interested in medical perspectives, especially through motor rehabilitation (Homat, 2005). Indeed, to recover the maximum of our previous lost physical capacities in the shortest possible time is a challenge which, beyond being noble, has a real utility in terms of improving the human condition. The work undertaken during this PhD had a main global purpose relative to these therapeutic outlets, notwithstanding that this was not the initial goal because our approach was carried out in healthy subjects. As these two motives are not compartmentalized, the question of ethics becomes, in fact, necessary (Roduit et al., 2015), because if a man is healthy, why seek to improve his performance? The National Advisory Committee on Ethics in Life and Health Sciences recalls in its Opinion No. 122 (Use of Biomedical Techniques for "Neuro-Improvement" in the Non-Sick Person: Ethical Issues) the need to question this issue without defining standards.

The will to try to push back its limits is an immemorial project that has existed since antiquity, as the agony (i.e., Spartan education) shows and remains current with regard to the number of blockbusters like "Lucy". This issue becomes with the advent of some technologies so prevalent that the center of strategic analysis has taken hold of this topic. The improvement

of the capacities of the human being is envisaged as a legitimate aim of research which nevertheless requires an ethical framework as desired by the European Commission as of 2004.

The human movement can be seen as an improvable apparatus. For achieving this aim, non invasive brain stimulation (NIBS) techniques can be used, mainly to modify cortical or corticospinal excitability (Fertonani and Miniussi, 2016) in initiating and regulating motor commands. For that purpose, several techniques, either using magnetic sources such as transcranial magnetic stimulation (TMS) or repetitive transcranial magnetic stimulation (rTMS), or electrical sources such as electroconvulsive therapy (ECT) or transcranial direct current stimulation (tDCS) (Guleyupoglu et al., 2013), can be used. Transcranial electrical stimulation (tES), a category of NIBS, is a candidate to impact neuron activity polarization (Yavari et al., 2017). The changes of cortical excitability and also neurotransmitters activity brought by tES refer to neuromodulation and may modify the outcome of human behavioral capacities. In the present PhD thesis, our studies were focused on the brain-behavior relationship and more particularly the potential of NIBS approaches to influence the brain cortical and associated behavioral responses. As a consequence, the main objective of this PhD targeted on tDCS-induced neuromodulation (see section 2.3) is to contribute to a better understanding of the underlying mechanisms of motor performance.

Indeed, for the time being, proof of concept has yet to be made and the effectiveness of the NIBS techniques must be carefully analyzed (Riggall et al., 2015). In addition, the growing enthusiasm for brain stimulation, particularly tDCS (Dubljević et al., 2014), has yet to be framed (Fitz and Reiner, 2016). This renascent stimulation technique should not be a simple fashion given the possibilities of application are promising (Walsh, 2013). There are many perspectives related to the application of NIBS to improve human behavioral capabilities. However, the long-term effects are not yet appreciable due to the fact that there is a little advances and novelty of the studies regarding the stimulation protocols.

The after-effects of tDCS are mainly reported by using the motor evoked potential (MEP) changes elicited by transcranial magnetic stimulation (TMS) over human motor cortex. However, improvement in motor performance could be dissociated of the increase in corticospinal excitability based on MEP amplitudes (Bastani and Jaberzadeh, 2014). Thus, one interest of this thesis is notably the use of hemodynamic changes measured by functional near-infrared spectroscopy (fNIRS) in the region of the stimulated brain to identify the neural underpinnings of tDCS-action in humans during movement; fNIRS uses optically based

measurements of light intensity, where electrical current-induced artifacts do not influence it. While recent TMS studies have reported a large inter- and intra-variability in response to tDCS protocols (Chew et al., 2015; Li et al., 2015; López-Alonso et al., 2014; Strube et al., 2015; Vallence et al., 2015; Wiethoff et al., 2014), the need to promote new protocols for stimulation is felt. Classically, tDCS is applied before the motor task (adjacent protocol). However some studies have associated the completion of the task and tDCS (concurrent protocol) with encouraging results (Galea and Celnik, 2009; Nitsche et al., 2003c; Stagg et al., 2011b). Yet little is known about the effectiveness between online (tDCS and task are concurrent) and offline (tDCS is adjacent to task) effects from anodal tDCS (atDCS) protocols. This effectiveness is to be considered on a time scale that takes into account for the short-term and long-term effects. It is the notion of plasticity in the sense of remodeling functional networks that is questioned. The issue also lies into the persistence of the effects related to tDCS. Moreover, the effects gathering atDCS- and task-induced modulations in the human brain network, which are afterward reflected in changes of motor behavior, remain incompletely known.

Accordingly, the two experimental studies (chapters 3 and 4) performed in this thesis aimed to examine the added-value for coupling the motor task to the tDCS application (i) during and after a single experimental session combined with fNIRS measurement and then (ii) over repeated sessions with priming tDCS in order to magnify the online and offline effects of the use of the tDCS.

Specifically, study one (chapter 3) compared the time-course of a constant simple finger opposition (SFO) motor task-related modulation of sensorimotor cortex (SMC) activation between concurrent and adjacent atDCS protocols in a within-subjects sham controlled and randomized design.

As study one did not investigate the efficacy of tDCS protocols on motor performance, study two (chapter 4) used a motor tracing task to examine the immediate and after-effects of repeated and priming concurrent atDCS protocol on motor performance. A novel aspect of study two was the quantification of an index of performance underpinning the retention of gains in motor function. Also considering the Bienenstock-Cooper-Munro (BCM) theory which argues for the existence of a “sliding threshold” determined by the conditioning activity (Bienenstock et al., 1982), study two compared the polarity (atDCS vs. cathodal tDCS, ctDCS) of the priming period in order to evaluate the greater persistence of the motor training effects during tDCS on motor performance and its retention.

This manuscript is articulated around three parts. Firstly, we will present the state of current knowledge through a review of the literature on the neuroplasticity within the brain and the mechanisms induced by tDCS to modify the changes of brain activity in the motor and somatosensory areas.

In a second step, we will describe our personal contribution to this field of investigation by presenting the two experimental studies performed. Note that the experiments were conducted with a setup named high definition tDCS (HD-tDCS) which is a specific electrodes montage that will be described in the NIBS section.

Finally, in a third part, we will summarize the main experimental results at the heart of a general discussion of the whole thesis work, and we will discuss prospects and possible applications in the short and medium terms.

1.1 Thesis aims and hypotheses

The overall aim of this thesis was to quantify the cortical and behavioral responses following concurrent motor task and tDCS protocols in healthy subjects in order to optimize the use of tDCS.

Specifically, this thesis aims:

- 1) To examine the effects of HD-atDCS applied over the motor cortex on cortical activation for concurrent and adjacent protocols using fNIRS (study one-chapter 3).
- 2) To investigate the time course of changes in motor performance and retention following the application of repeated priming HD-atDCS (or HD-ctDCS) concurrent / adjacent protocols (study two-chapter 4).

It was hypothesized that

- 1) Concurrent HD-atDCS and motor task protocol would have a greater impact compared to adjacent protocol with a reduced cortical activation of SMC during the stimulation period.

- 2) Concurrent HD-atDCS protocol would impact cortical activation of the stimulated brain regions with an increased delayed activation post stimulation.
- 3) Repeated sessions with the application of HD-ctDCS before concurrent HD-atDCS motor task is a protocol magnifying the effects of atDCS on motor performance.

2

Review of the litterature

Chapter 2: Review of literature

2.1. Overview

This chapter provides a comprehensive review of the literature regarding the physiological effects of tDCS giving a rationale for the research questions addressed in this thesis.

This chapter begins by outlining the neuroimaging techniques which allow to describe the structures and functions of the central nervous system (CNS), highlighting its involvement in motor control. Thereafter, an overview of structural and functional changes of the CNS named neuroplasticity is presented through its different types such as synaptic, intrinsic and metaplasticity. Finally, plasticity is discussed, followed by a thorough review of how this can be modulated through both motor training and non-invasive brain stimulation such as tDCS. The mechanisms of action as well as behavioral changes arising from tDCS application are described so as to emphasize the interest and main purposes of this thesis.

2.2 Imaging the sensorimotor cortex

2.2.1 Neuroimaging possibilities

"*Motor skills are the first mechanisms to interact with the world around us*" (Prichard et al., 2014). These motor skills represent the ability of the individual to develop and achieve an effective behavioral response. Efficacy is judged through the production of movement, which involves a set of neurophysiological mechanisms at different levels (Nakano et al., 1999). From the selection of the adapted response to the execution of movement, several CNS structures are involved. For this thesis, we will limit our scope to the cerebral cortex which is considered the seat of the voluntary movements (Weilke et al., 2001). Neuroimaging methods allow to account for the structural and functional properties of the encephalon. The neurons that compose it are caused to evolve anatomically (structural aspect) and thus modify the networks of connectivity and/or their mode of functioning (functional aspect) with regard to the external stimuli and the peripheral modifications. Advances in functional brain imaging enable visualization of cerebral activity *in vivo* and investigation of activation *foci* during a task. The images obtained represent the aggregated signals of large populations of neurons. Changes in neuronal activity can be measured indirectly by several brain imaging methods (see Table 1).

Electroencephalography (EEG) and magnetoencephalography (MEG) can be considered as imaging techniques *per se*. Nevertheless, EEG and MEG techniques make it possible to reconstruct a topographical mapping of electrical and magnetic activity at the cerebral level, respectively. The EEG is able to collect at the surface of the scalp the electrical activity emitted by a pool of neurons of the cerebral cortex. The EEG measurement at high temporal resolution (the order of one millisecond, ms) represents overall post-synaptic potentials (PSP) activity of a relatively large assembly of neurons. However, as the measured electrical potential is relatively low and diffuse, it *de facto* limits spatial information (Liew et al., 2014). Noteworthy that transcranial alternating current stimulation (tACS) applied in the EEG frequency range is believed to synchronize neuronal networks with the underlying idea to speed up cerebral processing (Butts et al., 2007; Helfrich et al., 2014a, 2014b; Strüber et al., 2014). The synchronous electrical activity of the neurons also produces magnetic fields in infinitesimal proportions. But the MEG makes it possible to collect with accuracy these variations of magnetic fields with the disadvantage of having a low signal-to-noise ratio (Karanasiou, 2012). Accordingly, tasks must be repeated several times before the noise can be mitigated during data analysis.

Beyond the electrical activity produced by the brain at a whole, there is a metabolic activity of neurons that can be detected through the hemodynamic variations that make it possible to infer neuronal activity (Scholkmann et al., 2014). The brain is the seat of an intense metabolic activity, because it is constantly solicited. Paradoxically, the brain has virtually no energy reserve. To compensate for this lack, the brain is strongly irrigated by a capillary system that regulates the flow rate regionally in response to this permanent metabolic demand (Becker Jr et al., 2009; Benton et al., 1996). This demand varies, *inter alia*, according to the genesis of action potentials (AP), which require re-establishing the ionic gradients on both sides of the neuron cell membrane, but also the recycling of glutamate into glutamine to reintegrate the presynaptic button. When an area of the brain is activated, vasodilation of the arteries/arterioles takes place within a time of the order of the second in order to provide the glucose and O₂ intake. The local response is an increase in blood flow to regions of increased neural activity, occurring after a delay of about 3–5 s. This haemodynamic response rises to a peak over approximately 4 to 7 s, then falls and slightly undershoots the initial value for a few seconds, before reaching the baseline again. The functional neurovascular unit is composed of vascular, neuronal and astroglial cells. It is the interface between the CNS and the vascular system. These hemodynamic fluctuations can be

apprehended by different neuroimaging techniques that indirectly inform neuronal activity that impacts cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood inflow, and *de facto* cerebral blood volume (CBV) (D’Esposito et al., 2003) (Fig. 1).

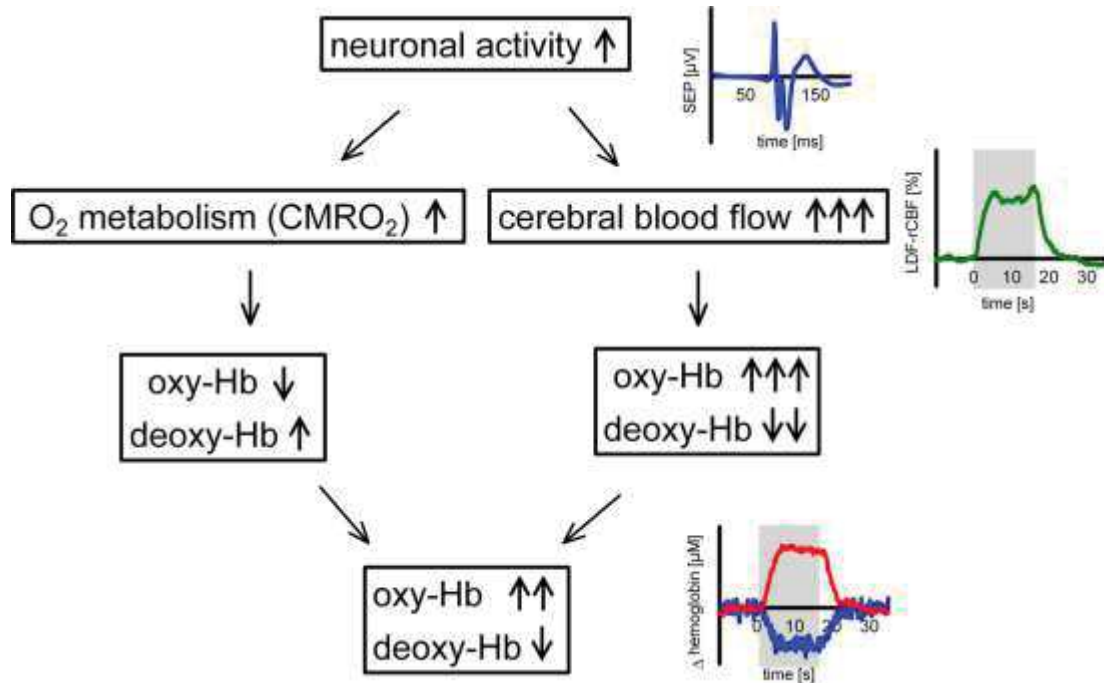


Figure 1 **Physiology of the hemodynamic response related to stimulus presentation.** The neuronal activity assessed by somatosensory evoked potentials (SEP, blue trace) increases resulting from the modification of the excitatory–inhibitory balance and causes hemodynamic changes with an increase in regional cerebral blood flow (rCBF, green trace) and cerebral metabolic rate of oxygen ($CMRO_2$). All these changes are reflected in the oxyhemoglobin (oxy-Hb, red trace) and deoxyhemoglobin (deoxy-Hb, blue trace) fluctuations (Lindauer et al., 2010).

Positron emission tomography (PET) consists of following the polygonation of a tracer injected into the bloodstream. Contrast images allow the localization with accuracy of the metabolic activity to be finely characterized, but the temporal resolution of the order of 2 minutes and the need to have relatively long measurement protocols limit the number of studies available in the literature compared to other techniques (Hiura et al., 2014; van Mier et al., 1998; Winstein et al., 1997).

Functional magnetic resonance imaging (fMRI) consists in recording the hemodynamic variations of the activated brain areas (Cui et al., 2011). The local and transient variations of blood inflow cause changes in blood volume that impacts the amount of oxygen transported by hemoglobin (Ogawa et al., 1990). During this phase of increase in blood inflow and outflow, $CMRO_2$ is also influenced (Fig. 1). fMRI usually measures the changes of blood oxygenation over time and is based on the different magnetic properties of oxygenated and deoxygenated blood that alter the magnetic resonance signal (Raichle, 2009). This technique is known as blood oxygenation level dependent (BOLD) contrast imaging. Beyond its spatial accuracy of the order of mm, fMRI measurement requests the subject to remain stationary in a supine position in an open magnet tunnel.

Similar to its fMRI counterpart, fNIRS is also a non-invasive imaging method that measures the hemodynamic responses to event-related neural activity. By measuring the spectrum of a light beam, fNIRS provides quantitative hemodynamic information for both oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb) (Fig 1). fNIRS is used to monitor even minimal changes in rCBF with good results (Obrig et al., 1996) and has some advantages beyond being non-invasive (Huppert et al., 2009): use in ecological conditions, speed of data acquisition, portability and ability to be not sensitive to electrical and magnetic instrumentation systems. Nevertheless, two major disadvantages have to be reported: a poor spatial resolution especially with continuous-wave NIRS instrumentation and the volume explored by optical imaging only at the surface of the cortex; for more details, see appendix b. It should be noted that superficial hemodynamic changes may mask the optical signals related to brain activity (Takahashi et al., 2011). Solutions have been proposed to counteract this issue by placing short-range optodes (Saager and Berger, 2005) that measure only extracerebral volume and/or using fine analytical analysis methods (Brigadoi and Cooper, 2015). Currently, there is no standard analysis package and data pre-processing is task-dependent.

There are still other neuroimaging techniques such as functional transcranial Doppler ultrasound (Washburn et al., 2012), that we will not develop here. Other techniques to study nervous system at a different scale are available such as light microscopy (Icha et al., 2017), calcium imaging (Wier and Mauban, 2017) or optogenetics (Forcelli, 2017) (see Fig. 2).

Table 1 **Summary of the main neuroimaging methods.**

Neuroimaging method	Activity measured	Temporal resolution	Spatial resolution	Risk	Portability
EEG	Electrical	~1 ms	~10 mm	Non-invasive	Portable
MEG	Electrical	~1 ms	~10 mm	Non-invasive	Non portable
PET	Metabolic	~2 min	~6 mm	Invasive*	Non portable
fMRI	Metabolic	~3 s	~4 mm	Non-invasive	Non portable
fNIRS	Metabolic	~3 s	~10 mm	Non-invasive	Portable

* A contrast medium is injected in order to improve the quality of the images.

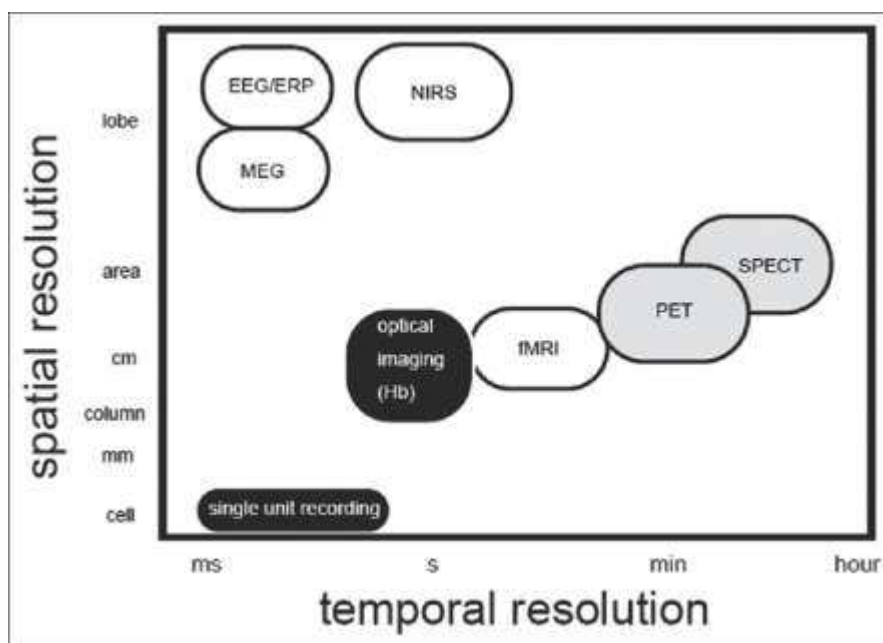


Figure 2 **Comparison of the spatial and temporal resolution of various neuroimaging methods used in neuroscience** (Kameyama et al., 2016). The gray color scale shows invasiveness; low invasiveness is white while high invasiveness is black (including experiments on animal subjects). PET has been colored light gray as there is some radiation exposure. SPECT for single photon emission computed tomography is a nuclear medicine tomographic imaging technique using gamma rays. Optical imaging uses light in the visible and near infrared wavelength to investigate the effects of molecular imaging in tissue. Single unit recording provides a method of measuring the electro-physiological responses of single neurons using a microelectrode system.

2.2.2 Motor areas and movement

During a motor task with regard to the different neuroimaging methods, it is possible to appreciate the active cerebral areas. As shown in Fig. 3, brain areas can be as much the sensory areas where the information is projected as the motor areas, the seat of the genesis of the motor commands, as well as the associative areas where the information resulting from the sensory and motor areas is processed. The movement originating from a muscular activation is generated by a processing of visual and/or sensory information. The information passes through the cerebellum (C) or directly integrates the primary somatosensory cortex (S1) while the visual information is projected onto primary visual cortex (V1) to be integrated into visual cortex (Brodmann Area or BA n°7) and then to the dorsal premotor cortex (dPM). The latter also receives information from the prefrontal cortex (PFC). Also parietal cortex (BA n°5) participates for integrating information from different sensory modalities. At the end, all processes are integrated in the primary motor cortex (M1) which is the seat of motor function, execution as well as planning. The movement is then carried out through loops regulated in particular by basal ganglia (BG) and brainstem regions by transiting through the spinal cord (Fig. 3).

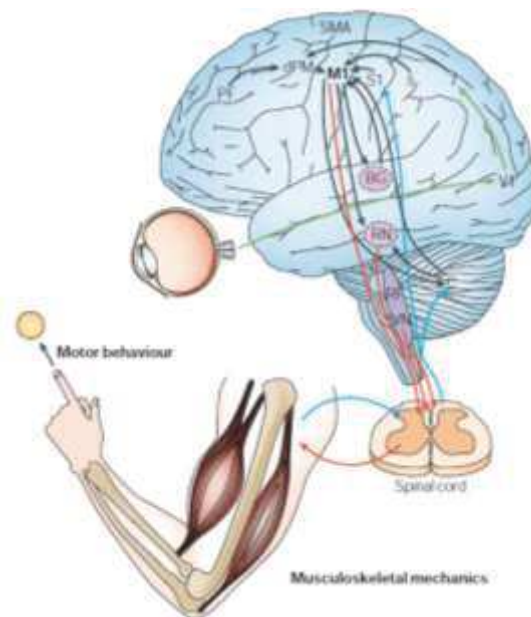


Figure 3 **Motor areas interactions for producing movement.** M1 receives input from other cortical regions that are predominantly involved in motor planning. Somatosensory information is provided through S1, BA n°5 and cerebellar pathways. BG and C are also important for motor function through their connections with M1 and other brain regions (Scott, 2004). See text for more details.

Using multi channel fNIRS when doing finger movements, higher hemodynamic changes have been observed for NIRS optodes centered on M1 (BA n°4) (Watanabe et al., 1996). M1 is to be considered as the neural center of the motor functions (Yousry et al., 1997). Using either MEG or EEG methods, it was shown that M1 is already activated about 100 ms before the onset of the movement. M1 is not only responsible for the execution of voluntary movements, but also for the temporal organization of motor sequences (Gerloff et al., 1998). This area on the precentral anterior gyrus is enclosed at the back by S1 (BA areas n° 1, 2, 3) and at the front by the premotor cortex and supplementary motor area - SMA- (BA n°6). M1 is also strongly connected with the thalamus, the central gray nuclei and the cerebellum. M1 is coupled to S1 for kinesthetic and proprioceptive feedbacks (Rosenblum and Pikovsky, 2001). The functional organization between the different cortical areas for finger-tapping tasks has been reported in a meta-analysis (Witt et al., 2008). Finger-tapping execution reveals usually a hemispherical asymmetry with a predominant activation of the contralateral hand-controlling hemisphere performing the tapping sequence (Colebatch et al., 1991). For more complex finger-tapping tasks, hemispherical asymmetry decreases due to the additional recruitment of the ipsilateral hemisphere (Holper et al., 2009; Rao et al., 1993). An increase in regional cerebral blood flow has been identified using PET for cued sequential finger movements of the right hand in several sensorimotor areas such as primary sensorimotor area, left ventral and right dorsal premotor cortex, posterior SMA, right precuneus, right superior part of the cerebellum and left putamen (Sadato et al., 1996). For these reasons, the main brain regions of interest (ROI) in the present thesis will comprise both the motor and somatosensory areas named SM1 or SMC. Beside, SM1 is highly adaptable to changes in excitability in the early and late stage of neural plasticity (Dayan and Cohen, 2011; Hirano et al., 2015; Muellbacher et al., 2002).

2.3 Plasticity and its different forms

2.3.1 Types of plasticity

The human being constantly accommodates himself to the demands of his environment. These internal adaptations to external constraints are the result of processes initiated mainly within the nervous system (Zilles, 1992). It is mainly CNS remodeling that provides the flexibility of the system to optimize resources to constraints. The CNS has the

ability to modify itself in order to be more efficient (Stephenson, 1993). This capacity, named neuroplasticity, can be defined as the ability of the brain to develop new neuronal and synaptic interconnections and thus develop new functions or reorganize to compensate for such changes (Stuss et al., 1999). However, for these changes to occur, stimuli or their combination should be appropriate (Konorski and Jerzy, 1948). There are several forms of plasticity that can be synaptic or "non-synaptic" with intrinsic and structural plasticity. These different types of plasticity interact in a coherent way through a functional synergy. Synaptic plasticity refers to the efficiency of the synapse. Intrinsic plasticity relates to the excitability of neurons. Structural plasticity indicates the evolution of the neural network. Plasticity is also to be considered in qualitative (i.e., potentiation and depression) and temporal (short and long term) aspects. Short-term plasticity called short-term potentiation (STP) is to be compared with short-term depression (STD) (Zucker and Regehr, 2002). STP is a precursor to long-term potentiation (LTP), as does STD for long-term depression (LTD) (Bliss and Collingridge, 1993). Like the butterfly effect, these local modifications are not without consequence on the whole CNS. The history of the activity of a synapse refers to the notion of metaplasticity (Abraham, 2008). This plasticity of synaptic plasticity (Abraham and Bear, 1996) makes it possible to glimpse the complexity in a global way by integrating the notion of neuronal networks. It is the number of neurons estimated at 10^{11} and the number of synaptic connections of 10^{14} which make the brain the most complex organ to be apprehended (Swanson, 1995). Finally, beyond the balance often sought to ensure pattern stability, there is also a non-homeostatic plasticity. These two forms of plasticity agree to maximize optimization of the organism's adaptation to the environment. Non-homeostatic plasticity will be discussed later, as it relates to the application of tDCS (Ziemann and Siebner, 2008).

2.3.2 Neurophysiology of the neuron

The cortical areas are composed of neurons, interneurons and glial cells, including astrocytes. A neuron collects information from multiple afferences. It is usually composed of a dendritic tree, a cell body also called soma as well as an axon. While the principle of operation may appear relatively simple in appearance, the number of mechanisms involved and their interactions refer to a tangible complexity. The dendrites which are the different points of entry meet at the level of the soma which is extended by the axon as an exit point. There are different types of neurons depending on their location. In the cerebral cortex, two

categories are usually distinguished: projection neurons, mostly excitatory and interneurons, mostly inhibitors. The cells in M1 can be divided into the pyramidal neurons and interneurons. The neurons are the site of many synapses which themselves may be of different nature, namely excitatory or inhibitory (Fig. 4).

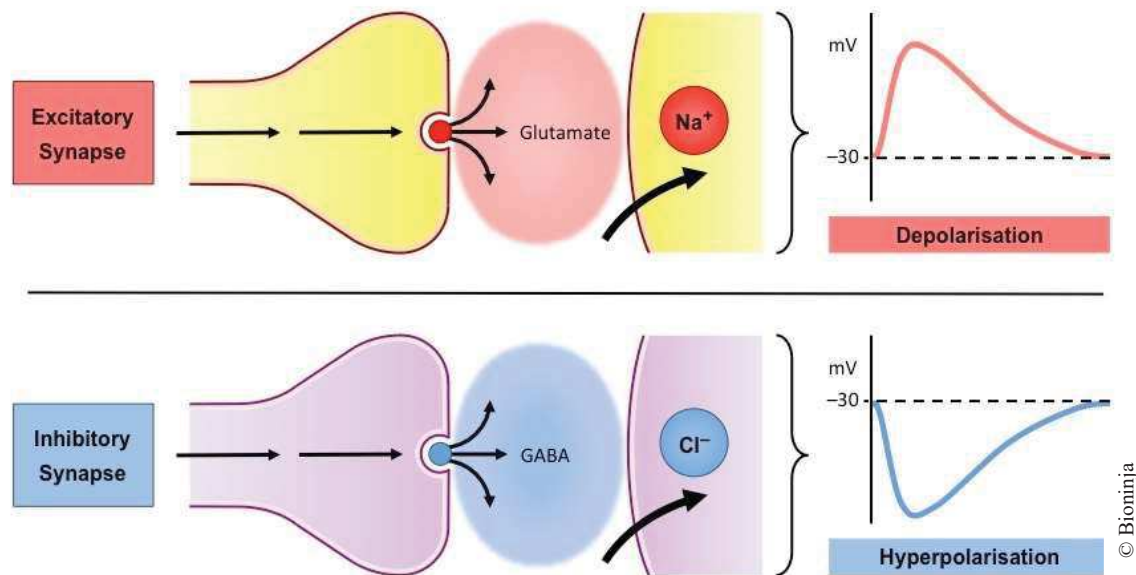


Figure 4 **Representation of excitatory and inhibitory synapses.** Ionic changes (Na^+ sodium or Cl^- chlorine) lead to depolarisation or hyperpolarisation on the neurotransmitters, respectively glutamate or GABA.

Synapses are the connection between a presynaptic axon and a postsynaptic dendrite and have a primary role: the transmission of nerve impulses. A synapse is composed of one or more synaptic buttons located mainly at the tip of the axon. The presynaptic axon contains vesicles of neurotransmitters, which may also be of different types. During depolarization, these vesicles will be fused with the presynaptic membrane in order to allow the release of the neurotransmitters into the synaptic cleft (Fig. 4). Postsynaptic dendrites are provided with different types of neuroreceptors that will be able to capture the neurotransmitters in order to transmit or not the information by modifying their membrane potentials. The neuron behaves like most other cells in the human body, i.e. the membrane is electrically charged. The membrane potential is defined by the polarity resulting from the non-uniform distribution of the ions on either side of the membrane. At the end, ionic motions will allow the transmission of information via electrical signals (Gerstner and Kistler, 2002). It is the variation of the

internal and external concentration of Na^+ , potassium (K^+) and calcium (Ca^{2+}) ions via the ionic channels that depolarizes the membrane to propagate AP (Fig. 5).

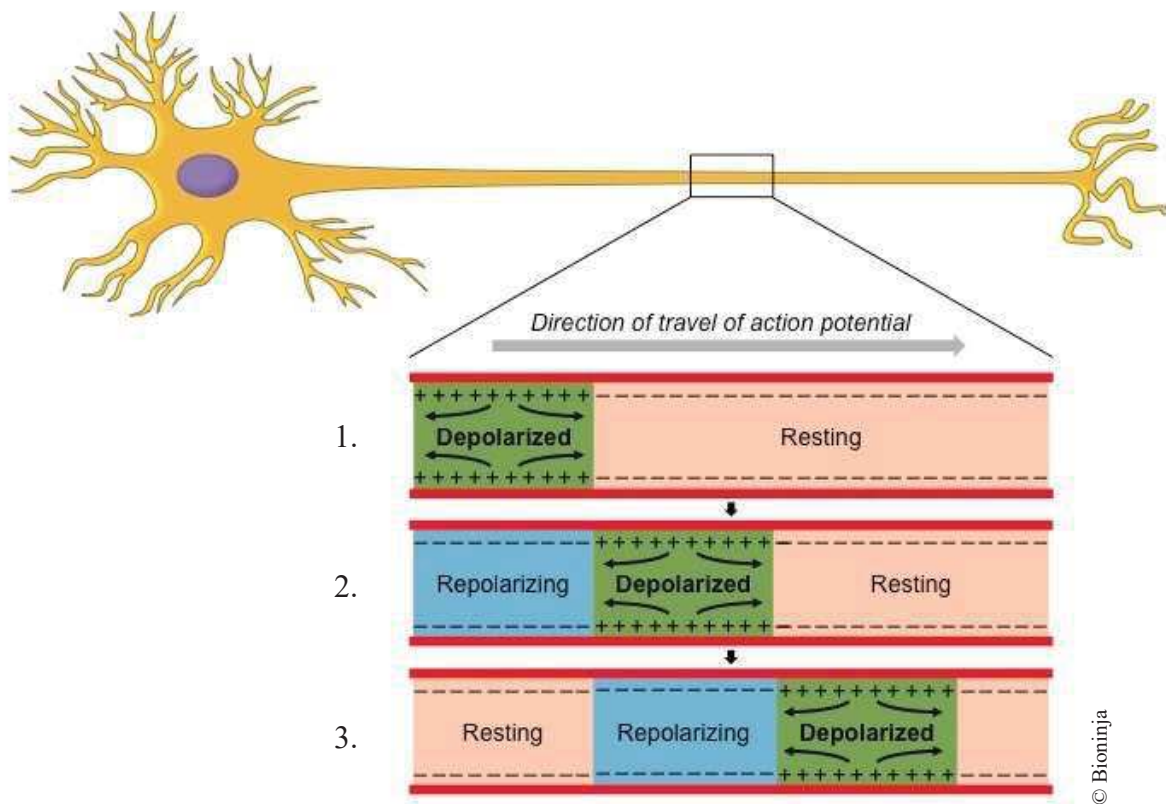


Figure 5 **Travel of action potential.** The depolarization associated with a change in membrane potential (1.) is propagated in the next segment of the axon. After depolarization, the segment is repolarized (2.) before returning to its resting membrane potential (3.).

The channels can also be activated mechanically (i.e., stretched, compressed), chemically with the neurotransmitters. These ionic motions are ensured either by voltage-dependent channels or by chemo-dependent channels. For voltage-dependent ion channels, their opening is controlled by the modification of membrane potentials. For chemo-dependent ion channels, control is governed by the presence of a chemical substance on target receptors.

A neuron being the site of convergence of information coming from presynaptic elements of one or more neuronal populations, the initiation or not of an AP requires a fine treatment. It is at the level of the soma that the excitatory postsynaptic potentials (EPSP) and the inhibitory postsynaptic potentials (IPSP) are integrated by spatial and temporal summation (Fig. 6).

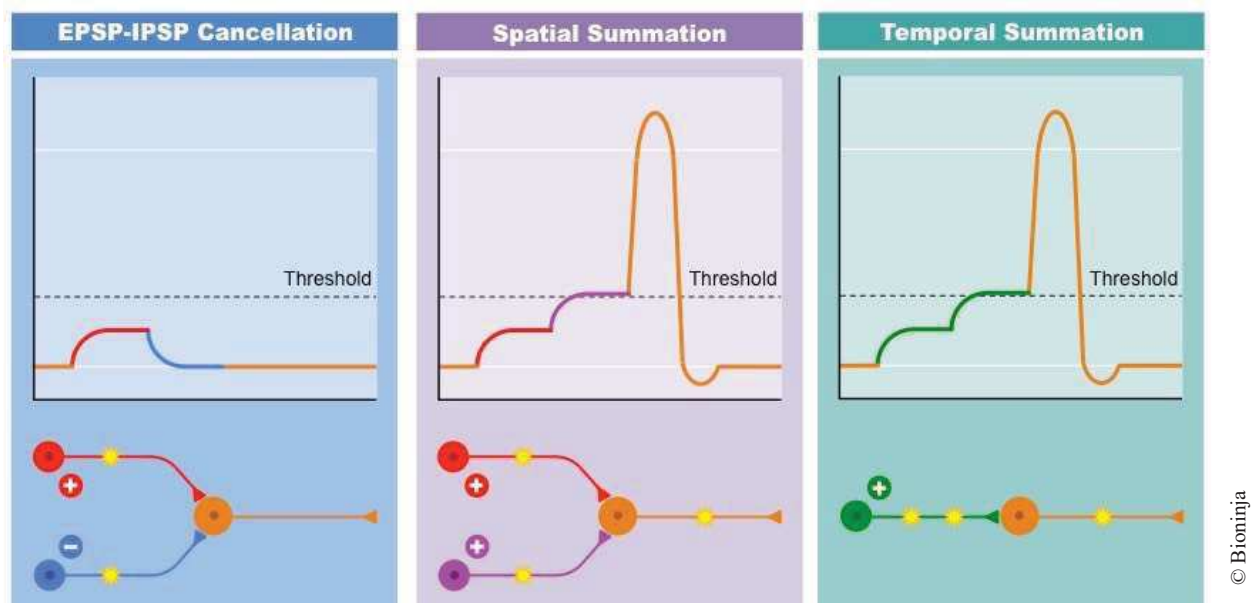


Figure 6 **Sequence of spatial and temporal summation of EPSP and IPSP.** EPSP-IPSP cancellation corresponds to graded excitatory and inhibitory potentials that cancel each other. Spatial summation is related to the fact that excitatory potentials from many neurons trigger threshold point. Temporal summation depends on many excitatory potentials from one neuron that triggers threshold point.

The coupling operation between the EPSP and the PA is also referred to as EPSP-Spike coupling and reflects the level of excitability and participation of a synaptic pathway to the overall network activity. The resting membrane potential of most neurons is more hyperpolarized than the AP initiation voltage threshold. The EPSP + IPSP summation must reach the AP initiation voltage threshold for one or more APs to be triggered at the initial segment of the axon. The value of this potential threshold is not fixed for the different regions of the same neuron. It is more hyperpolarized in the somatic region than in other regions (Coombs et al., 1955). This initiation is generally the result of the summation of several synaptic inputs, which prove to be too small amplitude taken individually. It is a temporal summation of the EPSP and IPSP between 5 and 15 ms which will lead to the generation or not of an AP. The parameters of these spatial and temporal summations will fluctuate as a function of the excitability of the neurons and the duration of exposure to certain stimuli. These fluctuations are the precursors of modifications at the neuronal level which refers to plasticity, in particular by the activation of postsynaptic receptors.

2.3.3 Synaptic plasticity

Below, we will grasp the plasticity through the phenomena of potentiation and depression. With repeated exposure to a stimulus, two cases occur with habituation, which corresponds to a progressive decrease in the neural pathways solicited or, on the contrary, to sensitization with a gradual increase by strengthening networks. Short-term modification (STP / STD) would correspond to an adaptation of the behavior, whereas the long-term modification (LTP / LTD) would be linked to memory that occurs with learning. Nevertheless, changes in short-term excitability should be considered as precursors for further neuroplastic changes. Short-term plasticity is expressed by a transient increase or decrease in the amplitude of the postsynaptic response. Repeated stimulations of the presynaptic neuron, spaced apart by a variable time interval, are one of the commonly means used for estimating short-term plasticity. The characteristics of the second type of response are compared with those of the first. Thus, one speaks of potentiation or facilitation if the second response is greater than the first while depression is used when it is smaller. If STP and STD appear to be associated with a change in the synapse properties at the presynaptic side by an increase in the amount of neurotransmitters for sensitization (STP) and a decrease in habituation (STD), the mechanisms involved for LTP and LTD are more complex and not yet fully elucidated. Hebb in 1949 postulates that when a neuron repeatedly activates a neighboring neuron, the efficacy of the connections between these two neurons is increased (Morris, 1999). The reinforcement of this connection between two neurons leads to a better efficiency of the synaptic transmission; this mechanism called LTP was demonstrated *in vivo* (Bliss and Lømo, 1973). This phenomenon consists of two distinct phases: a first phase called induction or e-LTP (early) (Higashima and Yamamoto, 1985) with Ca^{2+} input controlling the AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (*N*-methyl-D-aspartate) receptor traffic in the post synaptic cell; and a second phase called l-LTP (late) allowing gene activation and protein synthesis (Frey et al., 1988). The first one can be obtained with a single stimulation whereas the second one corresponds to the effects related to multiple stimulation sessions (Reymann and Frey, 2007). There is a reciprocal mechanism in which the reduction of the connection between two neurons decreases the efficiency of synaptic transmission, namely LTD (Ito, 1989). This opposite phenomenon makes it possible to prevent saturation of the system (Laroche, 1994). The distinction between LTP and LTD appears to be related to the Ca^{2+} concentration (Cummings et al., 1996; Yang et al., 1999). A lower intracellular

calcium input leads to the activation of the phosphatases which in turn leads to dephosphorylation of the AMPA and NMDA membrane receptors, which generates LTD. In contrast, activation of kinases will promote phosphorylation of these receptors and generates LTP (Winder and Sweatt, 2001).

Beyond the Ca^{2+} concentration, the arrival time of APs is also an important mechanism for describing the nature of the change to come. The repeated arrival of the presynaptic AP a few milliseconds before the post-synaptic AP production causes the LTP of the synapse concerned. Conversely, the repeated arrival of the presynaptic AP a few milliseconds after the release of the postsynaptic AP causes the LTD. This phenomenon is called spike-timing dependent plasticity (STDP) (Bi and Poo, 1998; Markram, 1997). The sign of the changes in synaptic weight is dictated by the temporal order between the pre-AP and the postsynaptic AP detected by the NMDA receptors. The increase in synaptic current in LTP is related to the increase in the number of AMPA (Malinow and Malenka, 2002) or NMDA (Carroll and Zukin, 2002) receptors. Plasticity can be assessed at the synaptic level through the excitation - inhibition (E / I) balance. This ratio depends on the nature of synapses and neurotransmitters passing through their synaptic clefts. Glutamate is released by the synapses of pyramidal cells when a γ -aminobutyric acid (GABA) is released by interneurons (McCormick, 1992; Nicoll et al., 1990). Glutamate is the main excitatory neurotransmitter and GABA is *a contrario* the main inhibitory neurotransmitter. This E / I ratio is balanced, in particular by the distribution of excitatory and inhibitory neurons; 80% are gabaergic and 20% glutamatergic (Le Roux et al., 2006). It is the ratio between these two neurotransmitters that determines the nature of the PSP, namely EPSP or IPSP.

2.3.4 Intrinsic and structural plasticity

Plasticity is also intrinsic. It can depend on the neuron alone, without necessarily a presynaptic activity. It has been shown that a single neuron (i.e., in culture) met its discharge threshold diminished after two days of deprivation (Desai et al., 1999). Conversely, for neurons involved in muscle contraction, the current required to produce AP is significantly lower when trained (Brons and Woody, 1980). Plasticity affects regions of the neuron specialized in the integration and genesis of the nervous message, particularly in the voltage-dependent conductances at the membrane level (Campanac and Debanne, 2007). The postsynaptic membrane is involved in the regulation of the transmission and storage of

information (Spitzer, 1999). In the cortex, where the neurons are connected to each other, the notion of intrinsic plasticity, parallel to synaptic plasticity, refers to the notion of homeostasis (Turrigiano and Nelson, 2004). Indeed, the neural network must maintain a certain level of activity and connectivity in order to ensure optimal maintenance of the transmission of information. It is carried out via the mechanism of synaptic scaling. In other words the modifications of the efficiency of the excitatory synapses are regulated by neuronal activity. From this level of activity depends on the renewal of receptors (Turrigiano, 2008). These synaptic changes at the scale of a neural network are multiple and tend to compensate for the disturbance (Burrone et al., 2002).

Finally, plasticity is also structural with the integration of new neurons in the network (Lissin et al., 1998), with the change of phenotypes of certain neurons (Gómez-Lira et al., 2005; Liu et al., 2003) or with the apoptosis of certain neurons (Meltzer et al., 2005). There are anthropometric changes observed at the neuronal level (Lamprecht and LeDoux, 2004). Synaptic pimples will undergo morphological changes by gene regulation (Lüscher et al., 2000) with an enlargement of postsynaptic sites with high receptor density (Yuste and Bonhoeffer, 2001). In addition, the amount of dendritic spines varies with glutamate stimulation (McKinney et al., 1999), as do the number of perforating synapses and the surface area of contact between pre- and post-synaptic elements (Matsuzaki et al., 2004). Finally, silent synapses with NMDA receptors under the action of glutamate have the ability to transform into functional synapses (Liao et al., 1995).

2.3.5 Metaplasticity

Nevertheless, this phenomenon of plasticity at the cellular level can only partially suffice when one considers the plasticity of the cortex with all neural networks. The notion of metaplasticity makes it possible to render the complexity of the system by integrating the notion of time, which refers to the "history" of synaptic connections. The BCM model is justified by the desire to place oneself on a scale superior to the neuronal level (Bienenstock et al., 1982) (Fig. 7).

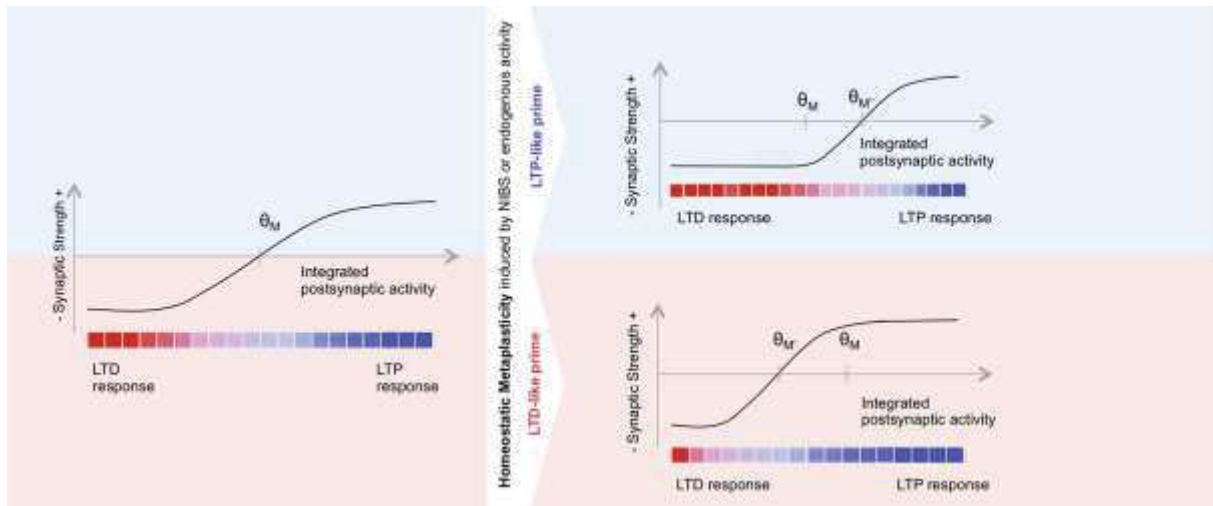


Figure 7 **Metaplasticity apprehended by the sliding threshold concept from BCM model.** Using an LTP-like prime will shift the modification threshold ($\theta_{M'}$) to the right along the x -axis and will hamper LTP response, while using an LTD-like prime will shift the modification threshold ($\theta_{M''}$) to the left on the x -axis and will facilitate LTP response (Karabanov et al., 2015).

This model, which is an improvement of that proposed initially by Cooper-Liberman-Oja (Cooper et al., 1979), presumes the existence of an adaptive threshold that connects together LTP and LTD phenomena. This adaptive threshold determines the possibility of learning, defined as the capacity of the system to acquire, modify or reinforce skills by the formation or the loss of synapses. If the post-synaptic activity is high then the learning is of the LTP type and *a contrario*, a low post-synaptic activity leads to a LTD-type learning. This threshold being adaptive, a strong and prolonged activity of the presynaptic activity will lead to an increase of the threshold which will limit the LTP-type learning. Conversely, a weak but prolonged activity of the presynaptic activity will increase the sensitivity of the network by reducing the threshold and facilitating synaptic reinforcement. This threshold shift as a function of the history of neuronal activity has been validated in rats (Kirkwood et al., 1996). NMDA receptors would only be activated from a certain threshold which determines whether the LTP or LTD phenomenon is induced (Bear et al., 1987). Synapses can be bidirectional (LTP or LTD) depending on the level of post-synaptic activation (Dudek and Bear, 1992) without their nature (excitatory or inhibitory) changing. In fact, this model represents a set of excitatory and inhibitory synapses between two neuronal masses (Girod and Alexandre, 2008) and presupposes that the plasticity is permanent according to the adaptive threshold, depending on the stimuli.

2.4 Noninvasive brain stimulation

2.4.1 tDCS through history

TDCS is not a modern technique as such (Guleyupoglu et al., 2013). The first traces of the use of an electric current to improve the human condition by treating pain go back to the time of the reign of the Egyptian Empire and ancient Greece. Some physicians conducted experiments using electric fish as possible therapeutic treatment (Sarmiento et al., 2016). Scribonius Largus, a Roman physician, who was born 43 to 48 BC, was the first to describe how to apply electric fish to patients' heads to treat their headache (Tarsy et al., 2008). Claudius Galen, Greek physician (129-200) and Pliny the Elder have also conducted investigations with electric fish (Priori, 2003). Other works were carried out in the eleventh century by Ibn-Sidah, an Arab physician concerning epilepsy (Kellaway, 1946).

However, Galvani and Aldini (1792) and Volta (1816), based on the work of Walsh and Seignette (1773) in animals and humans, laid the foundations of electrophysiology. Thus, in 1804, Aldini succeeded in successfully treating a melancholic patient (Lolas, 1977). More recently, Terzuolo and Bullock (1956), Bindman et al. (1962), Purpura and Mc Murtry (1965) and Albert (1966) have contributed to the development of knowledge related to the neurophysiology of transcranial electrical stimulation (tES). Thus, multiple potential effects of the tDCS have revived interest in this technique. In addition, it is painless and does not cause neuronal pain (Nitsche et al., 2003b). Other reasons for its regained use remain pragmatic, such as its inexpensive and small/discrete aspects and the various fields of application on the behavior (Pirulli et al., 2014), the working memory (Dockery et al., 2009; Zaehle et al., 2011), declarative memory (Javadi and Walsh, 2012) and implicit learning (Vries et al., 2010). The current revival for the tDCS is objectivable given the increasing number of articles referenced in PubMed moving from less than 10 per year before 2003 to more than 600 for the year 2015 alone.

2.4.2 Safety of the technique

During this period, progress was made on standards (Agnew et al., 1983; Bikson et al., 2016; Liebetanz et al., 2009; Sundaram et al., 2009), which showed that tDCS does not compromise brain tissue in humans (Nitsche et al., 2004). One schizophrenic patient received one to two stimulations daily for three years (i.e., + 1000 stimulations) without any damage being

reported (Andrade, 2013). In a single stimulation, some mild adverse effects were reported in 567 sessions for 102 patients (Poreisz et al., 2007). These side effects under the active electrode were tingling sensations in 70% of cases and itching for the remaining 30%. The recent development of repeated stimulation protocols also leads to good tolerance in patients with almost the same percentages for over 1900 sessions (Paneri et al., 2016). These effects generally fade within the first 30 seconds (Fregni and Pascual-Leone, 2007). On the other hand, some subjects may feel a sensation of heat for traditional montage whereas it only varies by 0.05 ° C for high density electrodes montage (Minhas et al., 2010).

2.4.3 Mechanisms of action

2.4.3.1 General levels

The work initiated by Priori (Priori et al., 1998) and subsequently relayed by the Department of Clinical Neurophysiology of Göttingen (Nitsche and Paulus, 2000, 2001) has answered some questions that remain relevant (Bikson, 2015). It remains to refine the understanding of the mechanisms of action of the tDCS, especially with regard to the notion of plasticity (Fertonani and Miniussi, 2016). Neuromodulation does not change the nature of the connection between two neurons but alters its intensity. TDCS does not produce EPSP and IPSP but modulates the efficacy of those generated by other synapses. The use of neurostimulation techniques for measuring corticospinal excitability is done with TMS (Barker et al., 1985) and assessing cortical activation is done with functional neuroimaging (Baudewig et al., 2001). The various possible TMS methods (i.e., single pulse, pulse-pulse, etc.) make it possible to obtain information on the level of excitation or inhibition of the descending motor pathways. The TMS technique, which is used extensively for evaluating adaptive neuroplastic changes, may have the disadvantage sometimes of low reproducibility in MEP responses with moderate intra-class coefficient (ICC) (Sankarasubramanian et al., 2015).

TDCS is a neuromodulation technique for manipulating cortical excitability (Nitsche et al., 2008). The current is delivered continuously except during the first 10 to 30 seconds (ramp up), in order to reduce discomfort such as tingling. Note that no electrical current can be strictly continuous and that slight variations in frequencies may occur (Salimpour et al., 2016). This current is monopolar, that is to say, it comes from an active or target electrode to be recovered by a reference or return electrode(s) (Bikson et al., 2010). Both electrodes have

physiological repercussions which can be variable according to their placements and sizes (Moliadze et al., 2010b). If the active electrode is positively charged, the stimulation is anodal. If it is negatively charged then the stimulation is said cathodal.

From this polarity depends the effects of the tDCS in terms of cortical excitability. Anodal transcranial direct current stimulation (atDCS) was shown to increase cortical excitability whereas cathodal transcranial direct current stimulation (ctDCS) would produce the opposite effect, namely a decrease in cortical excitability in healthy humans (Antal et al., 2007; Furubayashi et al., 2008; Nitsche et al., 2005; Nitsche and Paulus, 2000; Priori et al., 1998; Uy and Ridding, 2003). Conventionally, anodal stimulation is shown in red while the cathodal stimulation is shown in blue (Fig. 8).

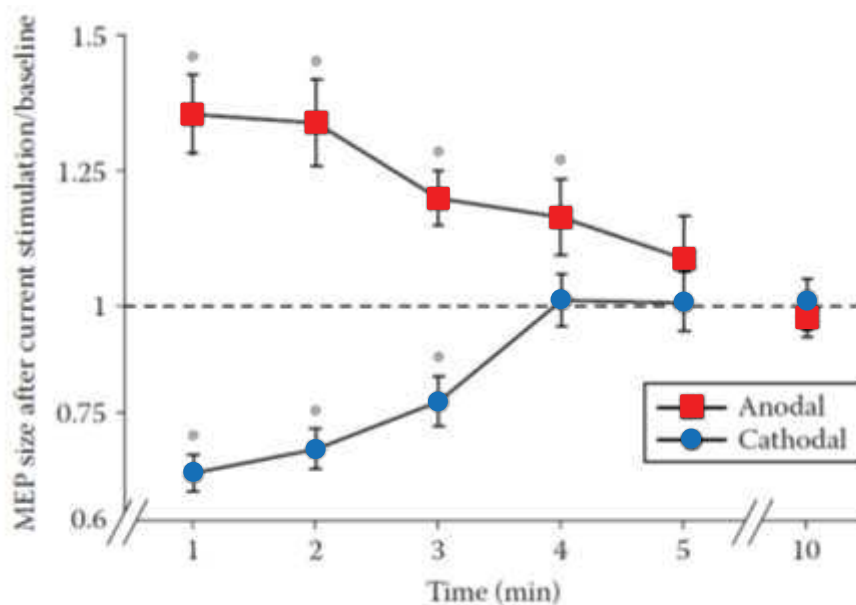


Figure 8 **Time course of cortical excitability of M1 for 10 min after tDCS.** Parameters of stimulation are 5 min tDCS over M1 at 1 mA. MEP are normalized to the baseline (Nitsche and Paulus, 2000).

This anodal-excitation and cathodal-inhibition dichotomy is relatively robust in the literature as regards the motor aspects, but more heterogeneous when the experiments appeal to the cognitive field (Jacobson et al., 2011). It seems logical that the stimulation of a system as complex as the brain can not lead to simple results at the level of MEP changes. In some cases, the effects of tDCS and the behavioral changes are not in line with those expected (Fertonani and Miniussi, 2016). Anyway, a current research topic in *Frontiers Human Neuroscience* entitled “Non-Invasive Brain Stimulation Effects on Cognition and Brain

Activity: Positive Lessons from Negative Findings” indicates that all findings on tDCS effects have to be reported in the literature because some hypothesis remain fragile. Furthermore, some of the subjects are responders to tDCS while others are not (Wiethoff et al., 2014) (see section 2.4.5). Finally, the transferability of the results in healthy subjects to patients can not, in fact, be mechanical, as differences in mechanisms related to the severity of the disease can influence the results (Vallar and Bolognini, 2011).

Half the current delivered would go through the scalp to penetrate the superficial layer of the brain (Miranda et al., 2006). At the neural level for anodal stimulation, the application of a continuous electrical current will lead to a depolarization of the membrane potential (Fig. 9). Conversely, a cathodal stimulation will lead to hyperpolarization. But the electrical current affects different neural tissues (Opitz et al., 2015). Beyond the neuron, tDCS would also stimulate the glial cells without knowing for the moment all the induced-mechanisms (Ruohonen and Karhu, 2012).

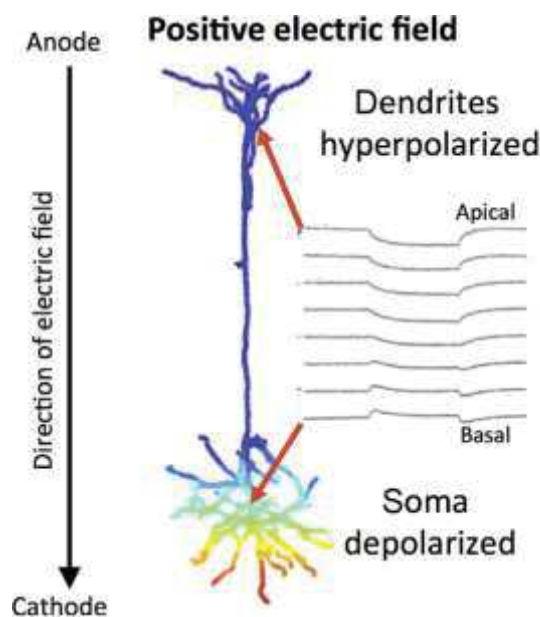


Figure 9 **Different effects of electric field on the neuron** (adapted from Bikson et al., 2004).

Concerning the anodal stimulation, the hyperpolarization of the dendrites generates by conductance a depolarization of the soma and thus produces an increase of the rate of spontaneous discharges (Fig. 10). For cathodal stimulation, the inverse mechanism occurs with depolarization of the dendrites and hyperpolarization of the soma which results in a decrease in the rate of spontaneous discharges (Gartside, 1968). The orientation of the electric field depends on the intensity of the response, due to the impacted neural segments (Kabakov et al., 2012). Indeed, the concentration of ionic channels is thicker at the level of the axon and

the soma. However, the anatomy of cerebral convolutions ultimately produces homogeneous effects (Bindman et al., 1964). Unlike TMS, the tDCS induces a variation in the discharge threshold of membrane potential, but in no case does it induce AP (Creutzfeldt, Fromm, and Kapp 1962).

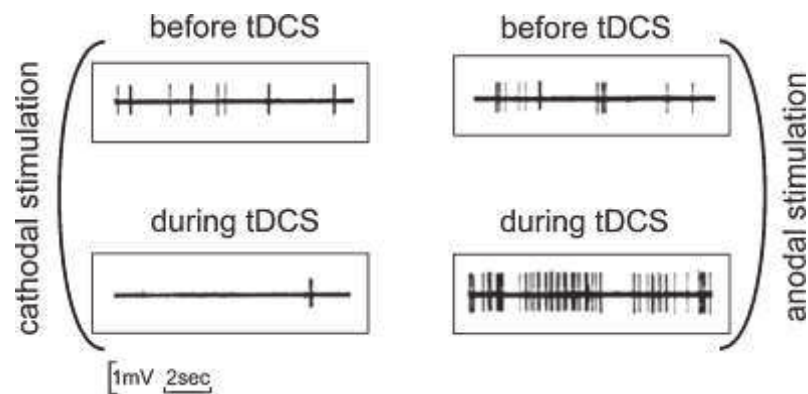


Figure 10 **Spontaneous firing rates during anodal or cathodal tDCS.** The spike activity (vertical lines) was recorded in animals under anodal (right side of figure) and cathodal (left side of figure) transcranial direct current stimulation (Utz et al., 2010).

TDCS modulates the functioning of neurons with immediate effects that occur during the stimulation (online), but also with prolonged effects that are the consequence of the stimulation (Zaghi et al., 2009). This rate of spontaneous discharges persists after stopping the application of the current (Bindman et al., 1964). The effects of tDCS during stimulation are mainly due to direct fluctuations in membrane polarity, whereas effects after stimulation involve more gabaergic and glutamatergic modulation of synapses (Stagg and Nitsche, 2011). Prolonged effects would be due to changes in intracortical inhibition and facilitation, as well as interactions with corticospinal facilitating waves (Nitsche et al., 2005). The prolonged effects of tDCS make it a technique of interest in neuro-rehabilitation units.

2.4.3.2 Molecular and cellular levels

Concerning the intrinsic plasticity, the tDCS modulates, in particular, the activity of the ion channels. An increase in Ca^{2+} has been reported in animals after tDCS (Dubé et al., 2012; Islam et al., 1995; Khatib et al., 2004). The generation of an AP depends in part on the activity of the ion channels as seen previously (Fig. 5). The non-linear effects of tDCS come from the influx of Ca^{2+} (Batsikadze et al., 2013). Ca^{2+} is essential in the induction of

neuroplasticity, whether it is type-LTP or -LTD (Bennett, 2000). The fluctuations of Ca^{2+} will induce either a potentiation at the postsynaptic level if they are brief and significant or a depression when their duration is extended for a small amplitude variation (Lisman, 2001). Post effects are mainly related to the involvement of NMDA receptors that alter the mechanisms of LTP and LTD. These cellular reaction chains have been designed for atDCS to better represent themselves (Fig. 11) (Pelletier and Cicchetti, 2014).

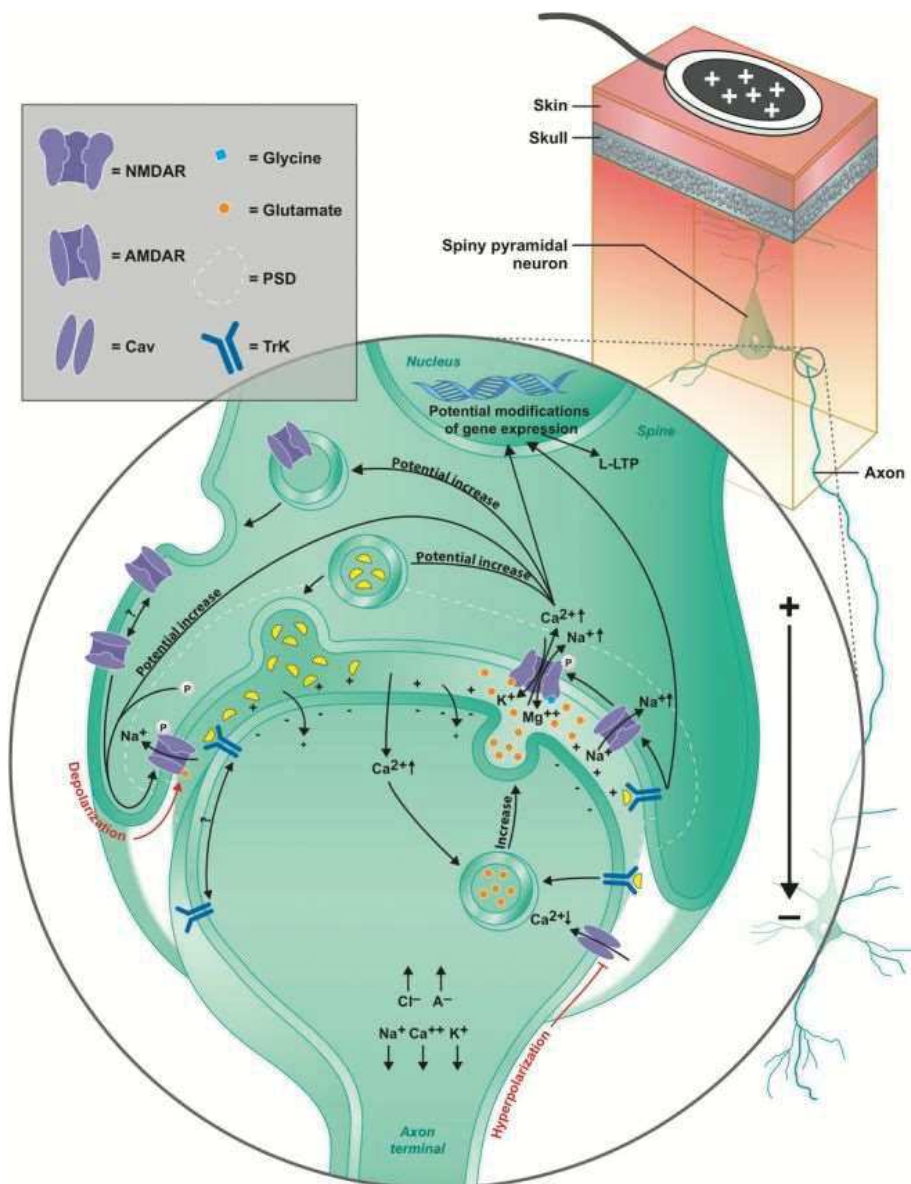


Figure 11 **Cellular and molecular mechanisms induced by anodal tDCS** (Pelletier and Cicchetti, 2014). The synapses of pyramidal neurons in M1 are the site of chain reaction. The hyperpolarization causes an increase in intracellular Ca^{2+} that leads to a greater neurotransmitter release. Cathodal tDCS generates sensibly opposite effects than atDCS,

except for brain-derived neurotrophic factor (BDNF). The activation of Tropomyosin-receptor kinase (Trk) receptors suggests a role for BDNF in anodal tDCS, which further increases the probability of synaptic vesicle docking and neurotransmitter release. The postsynaptic neuron is also affected with either a depolarization of basal dendrites and soma or a hyperpolarization for apical dendrites which are facilitated or inhibited depending on the site AMPA receptor- and NMDA receptor-mediated ionic changes. LTP responses come from an up regulation of neurotransmitter release that facilitates the opening of AMPARs and indirectly that of NMDARs. The Ca^{2+} influx has been demonstrated to increase AMPAR phosphorylation and their incorporation into the membrane. Ca^{2+} further increases the release of neurotrophic factors into the synaptic cleft and its absence decreases it. Once activated, postsynaptic Trk receptor induces later phase LTP (L-LTP) and favors the opening of NMDARs, which also promotes L-LTP; whereas the opposite is involved in cathodal tDCS, promoting later phase LTD (L-LTD). Both L-LTP and L-LTD are dependent on modifications of gene expression. PSD, postsynaptic domain; Cav; voltage-gated calcium channel.

Figure 11 summarizes the molecular chain reaction. Anodal stimulation leads to an increase in the number of NMDA receptors and a decrease in the concentration of GABA (Stagg et al., 2009). The concentration of GABA is positively correlated with the BOLD signal and can be investigated by using fNIRS (Stagg et al., 2011a). The concentration of GABA is also related to short-term learning that is the precursor of lasting changes. The activation of NMDA receptors affects the BDNF, whose secretion increases after atDCS (Kramar et al., 2004; Liebetanz et al., 2002). Interindividual differences may be related to differences in genotypes, especially in relation to the secretion of BDNF, which plays a major role in motor learning, particularly with regard to activation of the TrkB receptor associated with LTP (Cheeran et al., 2008). Also, atDCS for the cerebral cortex of the rat causes an increase in cyclic adenosine monophosphate (cAMP) (Moriwaki, 1991), which is an intermediate in the action of neurotransmitters and thus allowing neuronal hyperactivity. Finally, atDCS also increases dopamine levels in the basal ganglia which together with the cerebellum play an important role in motor control. Recently, it was found that the action of tDCS was mainly on the GABA_A synapses (Amadi et al., 2015). The concentration of neurotransmitters depends on the weight of the synaptic activity. Thus, anodal stimulation with respect to the E / I balance appears to reduce inhibition more than to increase excitation, confirming data on glutamate and GABA levels (Kim et al., 2014; Stagg et al., 2011a).

2.4.4 Motor learning and tDCS

Motor learning is the study of the processes involved in acquiring and refining skills and can be defined as the lasting changes of motor performance caused by training. These changes could be assessed at the cerebral level by neuroimaging methods that are able to divulge the interactions between the areas and the structure of the brain and also the structural and temporal complexity of mechanisms related (Cabeza and Nyberg, 2000; Poldrack and Packard, 2003). To assess learning, subcomponents have been used (Cantarero et al., 2015). The acquisition phase is characterized by fast (within session) and slow learning (between sessions) (Luft and Buitrago, 2005). This is broken down into online learning, offline delayed learning and offline overnight learning (Reis et al., 2015). Online learning represents the gains during the training. Offline delayed learning represents the gain within day and overnight between days of training. Online and offline motor learning (i.e., occurring during and after motor practice, respectively) are still an important topic (Vahdat et al., 2017) and are affected by different factors. Learning can be divided in either implicit learning, a passive process in which people acquire knowledge of new information through exposure or explicit learning, an active process in which people seek out the structure of any information that is presented to them (Doughty and Long, 2003). Any motor programs are tuned from the feedforward strategy and gradual reduction of the variability by using sensory feedback loops (Shmuelof et al., 2012). Three different phases occur at behavioral level termed the cognitive, associative, and autonomous stages (Schmidt and Wrisberg, 2008; Taylor and Ivry, 2012). The early stage corresponds to the first movement representation. During this phase the motor program of the to-be-learned is formed. Changes of regional cerebral activity assessed with PET is associated with early learning of skilled movement (Grafton et al., 1992). The second phase consists of the regulation of the motor program by the detection and the comparison of the discrepancy between inputs and outputs. Overall error and movement variability are improved. During the last stage, the movement is highly automatized.

In all cases, repeated practice is needed to perform better and/or effortless. Procedural learning involves acquisition of a skill through repeated performance and practice (Najarian et al., 2012). The purpose of a workout is to improve and consolidate these gestural patterns. A lot of practice is required to stabilize the neural networks especially by modulating E/I balance. This big amount of practice leads to overlearning that refers to the continued training of a skill after performance improvement has plateaued. Overlearning resulted in a hyperstabilization that causes no disruption between the first-trained task and new learning.

(Shibata et al., 2017). Indeed, it is a question of practicing enormously to fix motor learning. Is it possible to limit this amount of practice that requires a lot of resources knowing that motor abilities can be optimized by the addition of external devices or techniques (Roco and Bainbridge, 2003)? For instance, how can tDCS change the intensity/strength of connections in the motor network?

When tDCS precedes the task, increasing excitability can be potentially disruptive and interferes with neural processes related to learning. Kuo et al. (2008) showed disturbances in implicit sequential motor learning with prior anodal tDCS (1 mA, 10 min), while tDCS (1 mA, 15 min) after motor training appears to improve early consolidation of procedural learning (Tecchio et al., 2010). As a consequence, the timing of tDCS application plays a role in the behavioral changes. The use of tDCS before the task would impair motor learning.

A recent study of Christova et al. (2015) investigated how to optimize online atDCS effects on enhancing motor performance/learning by applying a novel ctDCS priming protocol that harnessed homeostatic metaplastic mechanisms. In the design of this study, healthy subjects were randomly distributed into three priming tDCS groups ($n = 12$) and were required to perform with their non-dominant left hand a grooved pegboard test (GPT) over four training blocks and a retest two weeks later. Three priming tDCS conditions were considered on the right primary motor cortex (M1): (1) Sham: Sham ctDCS (15 min) 10 min before sham online atDCS (20 min); (2) online atDCS: sham ctDCS (15 min) 10 min before online atDCS (1 mA, 20 min); (3) ctDCS priming: ctDCS (1 mA, 15 min) 10 min before online atDCS (1 mA, 20 min). TMS parameters (MEP, intracortical facilitation-ICF, and short interval intracortical inhibition-SICI) were assessed before and up to 60 min after the three tDCS conditions. The results indicated that although both online atDCS conditions improved GPT performance (i.e., faster completion time) over sham after the four training blocks, only the priming ctDCS/online atDCS condition further enhanced GPT performance two weeks later. These latter findings were explained in relation to homeostatic metaplastic mechanisms based on the Bienenstock-Cooper-Munro theory that postulates a “sliding threshold” (see Fig. 7) for bidirectional synaptic plasticity (Bienenstock et al., 1982). Accordingly, priming with ctDCS, which reduced cortical excitability (reduced MEP amplitude and ICF) and increased cortical inhibition (increased SICI) after the ctDCS session, would have reduced post-synaptic activity in the activated neural network. Based on the BCM model, this ctDCS-induced reduction in post-synaptic activity would be expected to reduce the modification threshold for LTP-like plasticity during subsequent online atDCS, and thus further enhanced GPT performance two

weeks later. The prolonged increase in ICF and reduced SICI for at least 60 min afterwards provides some evidence for this homeostatic metaplastic effect enhancing offline learning of the GPT. However, the authors acknowledged that a limitation of the study design was that a priming ctDCS followed by sham online atDCS condition was not tested, which could confirm that the results of the priming ctDCS/online atDCS condition were primarily due to homeostatic metaplastic mechanisms. Nevertheless, Christova et al.'s (2015) novel methodology and findings give an interesting background to optimize tDCS priming protocols in order to modulate neuroplasticity and enhance motor performance/learning.

An important tDCS parameter that requires further investigation is the influence of the time delay between priming and tDCS application on homeostatic metaplasticity and its effects on motor performance/learning (Karabanov et al., 2015). A few studies have investigated the effects of altering the delay between repeated tDCS applications with the same polarity on cortical excitability (Bastani and Jaberzadeh, 2014; Fricke et al., 2011; Monte-Silva et al., 2013) and motor performance/learning (Bastani and Jaberzadeh, 2014). However, no clear evidence of the optimal time delay could be ascertained from their respective priming tDCS protocols. Christova et al. (2015) considered a 10 min delay between ctDCS and online atDCS to be sufficient to allow homeostatic metaplastic mechanisms to take hold. But it is still not known if a shorter or longer time delay between priming ctDCS and online atDCS would differentially modify homeostatic metaplasticity and motor performance/learning. We (Muthalib et al., 2016) have previously postulated a non-homeostatic approach of priming with atDCS immediately before online atDCS to further facilitate the neuroplastic effects of online atDCS. We reason that since sub-threshold neuronal membrane depolarization induced by atDCS has an intensity- and time-dependent effect to strengthen synaptic efficacy (Nitsche and Paulus, 2001), performing atDCS (2 mA, 10 min) immediately before online atDCS would boost the already strengthened synaptic connections through a further “gating” mechanism induced with the concurrent motor task. Gating is a strategy used to weaken intracortical excitability that inhibits neural networks when performing motor tasks (Karabanov et al., 2015). The tDCS induces transient disinhibition or depolarization which increases the cortical excitability and also the synaptic strength to LTP (Ziemann and Siebner, 2008). This regulation is realized via the threshold change of the membrane as a function of the preceding post-synaptic activity. During surimposition of anodal tDCS during a motor task, it can be speculated that the amount of current entering the motor cortex becomes larger (Kwon and Jang, 2011). The cortical activity

at the proximity of the anode is increased in the combination of stimulation-task compared to the motor task alone (Kim and Ko, 2013). This is likely due to the suppression of magnesium (Mg^{2+}) on the post-synaptic NMDA receptors which allows a massive intake of Ca^{2+} (Moriyoshi et al., 1991).

We have recently shown that this priming atDCS/online atDCS protocol on the left M1 can reduce bilateral M1 activation to perform a unilateral simple finger sequence task at the same tapping rate (Muthalib et al., 2016). These results could be explained by a non-homeostatic mechanism following the “gating” theory, such that the reduced motor task related bilateral M1 activation during the atDCS suggests a greater efficiency of neuronal transmission (i.e., less synaptic input for the same neuronal output) in the activated neuronal network. Whether this priming atDCS/online atDCS protocol would enhance motor performance/learning greater than a priming ctDCS/online atDCS or online atDCS protocol still requires to be investigated and neuroimaging could report this changes due to priming (Henson et al., 2000).

2.4.5 tDCS parameters

The effect of tDCS depends on several parameters such as the region stimulated, the intensity of the current, the duration of stimulation, the placement and size of the electrodes, the number of sessions, the state of the brain and the type of task. The effects of the stimulation are the result of a particular combination of the parameters and any modification even of a single parameter modifies the effects of the tDCS.

Beyond the polarity, the intensity of the current and the duration of stimulation are two important parameters to induce particular effects. For the intensity, most studies use between 1 and 2 mA (Bikson et al., 2016) in healthy adults. The amount of the current decreases exponentially with the distance between the electrodes (Rush et al., 1968). The latter should therefore to be taken into account. There are safety recommendations in this regard (McCreery et al., 1990). However, this intensity is mainly to be considered by relating it to the surface of the electrodes (Nitsche et al., 2007). By comparing 3 sizes of electrodes (i.e., 12, 24 and 35 cm^2), it was shown that those of 12 cm^2 produced the most important changes for the same current density (Bastani and Jaberzadeh, 2013; Bikson et al., 2016). The unit to be considered is not just the amperage in mA, but rather the current density in mA / cm^2 . The magnitude of changes in excitability depends on the density of the current (Bikson et al., 2009). However, results are heterogeneous with regard to the neuroplasticity. Three different

current densities (0.032, 0.04 and 0.048 mA/cm², 10 min) for atDCS lead to no significant changes in cortical excitability and short-interval intracortical inhibition (Kidgell et al., 2013). For atDCS, 2 mA would be the most likely intensity to induce increase in cortical excitability (Ammann et al., 2017).

Regarding the duration of stimulation, most studies report a period of time between 10 and 20 minutes (Bastani and Jaberzadeh, 2012). The duration of stimulation depends on the persistence of prolonged effects (Fig. 12). For 5 and 7 minutes of atDCS, the effects in terms of excitability changes after stimulation do not persist for more than 5 minutes. However, with 9 minutes of stimulation, MEP elevations were reported for 30 minutes and over 90 minutes for 13 minutes of atDCS (Nitsche and Paulus, 2001).

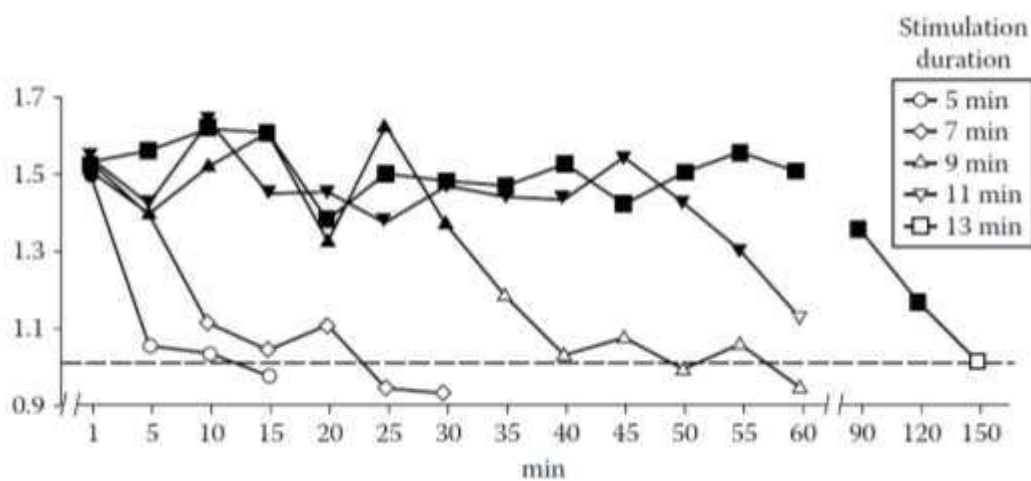


Figure 12 **Time course of anodal tDCS on cortical excitability of M1 as a function of the duration of stimulation.** 5–7 min anodal stimulation induces short-lasting after-effects, while prolonged anodal tDCS increases the duration of the aftereffects over-proportionally (Nitsche and Paulus, 2001). The black symbols show significant differences whereas symbol without filling is corresponding to no significant difference. Dotted line is the 1:1 ratio from baseline.

The tDCS should be applied over a sufficiently long time to alter the synaptic strength by modulating the activity of NMDA receptors (Nitsche et al., 2003a). This relation between the stimulation time and the duration of the effects is not linear and can be reversed beyond a certain time. In multiple stimulation protocols investigated with the aim to inform the duration of application and rest between two stimulation sequences, Monte-Silva et al. (2013) reported that 26 minutes of stimulation completely reversed the benefits of cortical excitability. Indeed,

Fricke et al. (2011) had shown different effects between a short rest time and a longer rest time. In this multiple experience study, MEP were reported for two periods of 5 minutes of tDCS intersected by different times (i.e., 0, 3 and 30 minutes). With 0-min break, the aftereffects were prolonged. With 30-min break, the effects of the 2nd period were identical to the 1st period. With 3-min break, the effects were opposite to the results of 1st period. This work was completed by Bastani and Jaberzadeh (2014) with up to three stimulation sessions. However, there is no clear consensus on resting time between two stimuli, because the experimental paradigms differ (Besson et al., 2016).

Note that the tDCS has the advantage of being able to perform so-called "sham" stimulations, which turn out to be control situations. Indeed, anodal, cathodal or sham stimulations are virtually indistinguishable for subjects as for the experimenter, if the manipulation takes place in double-blind (Gandiga et al., 2006). During a sham stimulation, the current will be applied for about 30 seconds, the subject will feel the possible tingling related to the phase of increase in intensity and will get used to it in a very short time. As a result, the current will be decreased for 30 seconds to arrive at a situation where the subject thinks to be stimulated while no current is applied. Questionnaires to monitor the perception of participants are almost always fulfilled (Kessler et al., 2012).

TDCS suffers in comparison with repeated TMS (rTMS) of a lower spatial resolution. However rTMS stimulation at 1 Hz on M1 also decreases cerebral blood flow in remote regions (Siebner et al., 2003). Although there are different electrode positions with tDCS (Moliadze et al., 2010b; Nitsche and Paulus, 2000), the return electrode will always interact with the underlying areas for cephalic placement (Purpura and Mcmurtry, 1965) and an interaction with the brainstem for extracephalic placement (Bindman et al., 1964; Lippold and Redefearn, 1964). The remote effects reported by several studies (Lang et al., 2005; Notturmo et al., 2014) finds its main cause in the conductivity of the cerebrospinal fluid which disperses the induced currents (Miranda et al., 2013). HD-tDCS montage for high density or high definition is a promising type of montage for tDCS. The active electrode is surrounded by several return electrodes. Alam et al. (2014, 2016) tested different configuration from 1x1 to 8x1. Findings showed that 4x1, that is one active electrode surrounded by 4 return electrodes, provides more electric field generated to the cortex layer during tDCS. Distances have also be tested with better results for a distance of ± 3 cm. If the current is less diffuse with 4x1

(Dmochowski et al., 2011; Muthalib et al., 2017), the effects are a higher increase and more delayed and prolonged MEP amplitude (Kuo et al., 2013).

2.4.6 tDCS and inter- and intra-variability

It is now well documented that the effects of tDCS are variable (Labruna et al., 2015; Li et al., 2015; López-Alonso et al., 2014; Ridding and Ziemann, 2010; Strube et al., 2015; Vallence et al., 2015). The ICC reported by Labruna et al. (2015) is of 0.242. This represents a poor reliability. The effects of tDCS are dependent on the anatomical structure of the region of interest (Bikson et al., 2012; Datta et al., 2009). There are other intrinsic reasons, such as gender, age and genetic aspects, and also extrinsic reasons such as stimulation site, the level of attention (Wiethoff et al., 2014). In view of the results from the literature, some authors have questioned the use of tDCS on a single session (Horvath et al., 2014b). However, the method used for this meta-analysis has been called into question (Antal et al., 2015; Chhatbar and Feng, 2015). In order to reduce this variability, repeated sessions can be envisaged. The interest of multiplying the sessions is that one increases the probabilities that the participants become more responders (Fig. 13). López-Alonso et al. (2015) reported that 18 out of 45 participants did not respond with one session. This figure drops to 10 when presented at two sessions. However, the converse is also possible as responders become non-responders. The persistence of effects after 5 sessions of atDCS on the speed-accuracy compromise for a visuomotor task beyond 3 months is encouraging (Reis et al., 2009). The same is true for the pain that is significantly reduced after 5 days of stimulation (Brietzke et al., 2016).

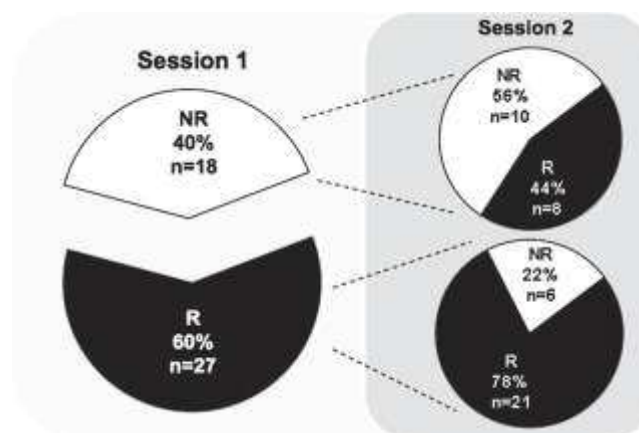


Figure 13 **Percentage of responders and non-responders after 2 tDCS sessions.** The average of MEP amplitude after anodal tDCS between 0 and 30 minutes was used to characterize the participants (López-Alonso et al., 2015)

Also, in order to reduce the variability of the effects of tDCS, it has been recently considered to fuse tDCS and task (Stagg and Nitsche, 2011). The task is a parameter to be further considered (Learmonth et al., 2015; Tseng et al., 2012) because the tDCS affects the neurons that are closest to their discharge threshold (Siebner et al., 2009b). Combining task and brain stimulation appears to be a promising approach to magnify the effects of tDCS. In addition, performing a task that engenders relationships with other parts of the brain involved in the task should strength the ongoing networks (Miniussi et al., 2013a). Finally, the interest of the use of concurrent atDCS with motor task is that if neuroanatomically two networks overlap then the one that is activated by the task will benefit from the tDCS based on the principle: "the winner takes the bet".

All these elements from this literature review show that the concurrent paradigms have more noticeable effects than other paradigms, but this must be reported more clearly in the field. Beyond the underlying theories, using neuroimaging techniques has the advantage to highlight the effects of anodal stimulation during motor task.

3

Functional targeting with anodal HD-tDCS leads to a delayed increase in motor task-related sensorimotor cortex activation

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Chapter 3:

Functional targeting with anodal HD-tDCS leads to a delayed increase in motor task-related sensorimotor cortex activation

Abstract

Functional targeting with online anodal high-definition transcranial direct current stimulation (HD-atDCS) and motor task performance is a promising protocol to magnify sensorimotor cortex (SMC) neuroplasticity compared to performing the motor task after HD-atDCS (offline). The aim of this study was to benefit from functional near-infrared spectroscopy (fNIRS) to compare the time course of motor task-related SMC activation modulation between online and offline HD-atDCS. We hypothesized that online HD-atDCS will impact motor task-related SMC activation to a greater extent than offline HD-atDCS. In a withinsubject sham controlled and randomized study design, 9 healthy participants underwent 3 HD-atDCS sessions targeting the left SMC (online, offline, and sham) separated by 1 week. fNIRS hemodynamic changes were measured from the left SMC during a simple opposition (SFO) motor task before (Pre), immediately (T1) and 30 min (T2) after each session. The SFO movement rates were not different between (online, offline, sham) or within (Pre, T1, T2) sessions. The SFO task-related hemodynamic changes showed that compared to sham the online HD-atDCS session induced a significant ($p < 0.001$) delayed (T2) increase in SMC activation to perform the same SFO task while there was only a trend between offline and sham session ($p = 0.05$). Functional targeting with online HD-atDCS was more effective in modulating motor-task related SMC activation and hence neuroplasticity with a delayed time evolution, which may represent some process of motor memory consolidation.

3.1 Introduction

Improvement in human motor capabilities can be boosted by converging technologies (Roco and Bainbridge, 2003). For achieving this aim, noninvasive brain stimulation (NIBS)

techniques can be proposed as an alternative or in addition to other training methods (Parasuraman and McKinley, 2014). Transcranial direct current stimulation (tDCS) is a NIBS technique that applies low-level electrical currents through the brain, which modulates cortical excitability by altering neuronal membrane thresholds and synaptic strengths (Nitsche et al., 2008; Stagg and Nitsche, 2011). TDCS-induced neuromodulation is known to produce both immediate- and delayed after-effects (Zaghi et al., 2009). Polarizing neurons during tDCS has immediate-effects on cortical excitability due to the alteration of resting membrane potential, leading to modulation of spontaneous firing rates (Miranda et al., 2006). This tDCS polarization-induced modulation of spontaneous firing rates also induces long lasting after-effects on cortical excitability (minutes to hours after tDCS) that is related to the activity of excitatory and inhibitory neurotransmitters on their synaptic receptors altering the excitatory/inhibition balance (Liebetanz et al., 2002; Michael et al., 2004).

In human studies, anodal tDCS (atDCS) is believed to increase cortical excitability as reflected in transcranial magnetic stimulation (TMS) motor evoked potentials (MEPs) (Jacobson et al., 2011). However, recent reports suggest around half of healthy subjects do not show an expected excitatory neuroplastic effect after atDCS (Chew et al., 2015; Li et al., 2015; López-Alonso et al., 2014; Strube et al., 2015; Vallence et al., 2015; Wiethoff et al., 2014). It is noteworthy that these recent reports highlighted studies that measured MEPs in a resting-state after tDCS without looking at motor task-related changes in their design. Novel experimental protocols (or designs) need to be developed for reducing inter-individual variability in atDCS responses. Functional targeting protocols using online atDCS and motor task, where the motor task is performed during the stimulation period (i.e., online effect), could have greater facilitative effects on motor performance/learning than if the motor task is performed offline or after the stimulation period (i.e., offline effect) (Stagg et al., 2011b). These greater facilitative effects of online atDCS on motor performance/learning might be due to the impact of atDCS on decreasing gamma aminobutyric acid (GABA) neurotransmitter levels at inhibitory synapses (Amadi et al., 2015). Furthermore, synaptic efficacy at NMDA receptors is enhanced in the simultaneously engaged neural network through a “gating” mechanism (Ziemann and Siebner, 2008). The decrease of inhibition at GABA receptors and increased synaptic efficacy at NMDA receptors will theoretically result in greater neuronal efficiency with less neuronal activation to perform the same motor task (Levinson and El-Husseini, 2005). While the interaction of the timing of tDCS application and motor task appear crucial parameters to optimize atDCS physiological benefits, the effects underlying concomitant atDCS- and motor task- induced modulations in the

functionally target brain region, which are afterward reflected in changes of behavior, remain incompletely known.

Combining tDCS with functional neuroimaging methods allows tracing the alterations at the stimulation site during (online effects) or after (after effects) stimulation (Siebner et al., 2009a). Based on neurovascular coupling (NVC) mechanisms, different functional neuroimaging techniques can be used to determine changes in task-related activation of neural networks modulated by tDCS (Paquette et al., 2011). Some early functional magnetic resonance spectroscopy (fMRI) studies investigating offline (20 min, 1 mA) and online atDCS protocols (short periods of stimulation from 20 s to 2 min, 1 mA) with motor tasks have reported contrasted findings in motor task related activation patterns (Antal et al., 2011a; Jang et al., 2009; Kwon and Jang, 2011). Offline atDCS (20 min, 1 mA)-hand grasp-release movements induced an increase of activation in the targeted sensorimotor cortex (SMC) compared to sham (Jang et al., 2009). But online atDCS (8x20s, 1mA)-finger-tapping movements induced a decrease in activation of the supplementary motor area (SMA) without notable changes over the targeted SMC (Antal et al., 2011a). The inability to measure alterations of activation in the targeted SMC during online atDCS might be due to the low intensity (1 mA) and the short duration (20 s) of the stimulation protocol used. Conversely, it was observed that online atDCS (2 min, 1 mA) - hand movements induced more SMC activation than sham (Kwon and Jang, 2011). These contradictory findings using short duration and lower intensity atDCS protocols stem from the technological limitation of combined atDCS and fMRI studies that cause distortions in fMRI signals by the tDCS electrical/magnetic fields, as well as subject safety due to heating of tDCS cables/electrodes by the fMRI magnetic field. Therefore, these limited combined tDCS-fMRI studies invite for future functional neuroimaging investigations to determine the effect of functional targeting with atDCS on motor task-related SMC activation.

In contrast to fMRI, motor-task related changes in the concentration of oxygenated (O₂Hb) and deoxygenated (HHb) hemoglobin in the SMC measured by functional nearinfrared spectroscopy (fNIRS), reflect NVC with good sensitivity the hemodynamic response to neural activity (Leff et al., 2011) without interference from the tDCS environment. The combined use of atDCS with fNIRS as a relatively simple and safe method offers the possibility to investigate the immediate- and delayed after-effects of atDCS on resting-state (Muthalib et al., 2017) and task-related SMC activation/hemodynamic response (Choe et al., 2016; Gözenman and Berryhill, 2016). atDCS using a high-definition (HD-atDCS) electrode montage (4x1) has been shown to increase the stimulation focality and

intensity at the M1 target (Datta et al., 2009). Our recent preliminary fNIRS study (Muthalib et al., 2016) applied online HD-atDCS (2 mA, 20 min)-sequential finger opposition (SFO) task and found immediate effects with a decrease in task-related activation in the targeted left SMC compared to a pre-stimulation. However, since the after-effects of HD-atDCS show peak changes in cortical excitability after a delay of ~30 minutes from the cessation of the stimulation (Kuo et al., 2013), it is not known whether task-related SMC activation would also show greater neuromodulatory effects at a delayed time point. Moreover, the effectiveness between online and offline HD-atDCS protocols to modulate motor task-related SMC activation needs to be clarified in order to propose the most optimal protocol.

Therefore, the aim of the present study was to compare the time-course of SFO motor task-related modulation of SMC activation between online and offline HD-atDCS protocols in a within-subjects sham controlled and randomized design. It was hypothesized that online HD-atDCS will modulate SFO motor task-related activation in the targeted SMC to a greater extent than both sham and offline HD-tDCS application.

3.2 Methods

Participants

Fifteen healthy men adults (mean age \pm SD, 33.4 \pm 12.2 yr) voluntarily participated in this study. Subjects were right handed (laterality index 82.8 \pm 14.0, range from 58 to 100) as determined by the Edinburgh handedness inventory (Oldfield, 1971). All subjects had no history of neurology or physical disorders or any upper extremity muscle or joint injuries. The study was approved by the local Research Ethics Committee and was in accordance with the Declaration of Helsinki, and all participants gave written informed consent after a description of the study procedures and associated risks.

Study design

In a single blind randomized within-subjects design, subjects participated in three HD-atDCS sessions (online, offline, and sham, see Fig. 1). The order of the sessions was randomized and counterbalanced using an online algorithm (<http://www.randomization.com/>). Sessions were separated by a least 1-week and were performed at the same time (\pm 1 hour) of the day in a quiet and dimly light-room.

Protocol

The subjects were seated in an adjustable armchair at a table in front a LCD monitor. Both forearms were placed in supination position upon the surface of the table. Subjects were then familiarized to perform a self-paced SFO task (i.e., sequential tapping of the index, middle, ring and fourth finger against the thumb) with their left and right hand at a rate of 2-3 Hz.

Following the familiarization and a 3 min rest period the subjects were required to perform the SFO task before the stimulation with their right and left hand in an alternative block design (30-s rest and 30-s task, repeated five times for each hand). The start hand was randomized and counterbalanced across the subjects. The start and the stop of the SFO task was displayed on a LCD monitor for each block to better control the duration of the task and task-related hemodynamic response (Colier et al., 1999). The experimenter counted the number of SFO taps during each of the experimental task blocks.

Three min after the pre-stimulation SFO task, subjects received one of 3 HD-atDCS sessions. Each session consisted of four phases (see Fig. 1): (i) Pre: SFO task before tDCS (ii) tDCS: 20min tDCS or sham, (iii) Time 1: SFO task with Online, Offline, or Sham tDCS, and (iv) Time 2: SFO task at 30 min after tDCS. For sham tDCS, 50% underwent online and 50% underwent offline. The current was always ramped up or down over the first and last 30 s of stimulation. All of the subjects were instructed that they would feel senseless or a mild tingling sensation under the electrodes that fades over seconds depending on the variability of individuals, who were blinded to tDCS protocols. The current was turned off after 30 s in the two sham protocols or continued for a total of 20 min during HD-atDCS sessions (with online- or offline-motor task). Even if HD-tDCS is well tolerated (Turski et al., 2017), a questionnaire containing rating scales of 11 unpleasant sensations compared to resting state was filled out after the stimulation sequence and at the end of the session. As variability in physiological measures can be due to psychological states (Wehrwein and Carter, 2016), the State-Trait Anxiety Inventory (Spielberger et al., 1970) for assessing levels of state anxiety was completed at the beginning of each session.

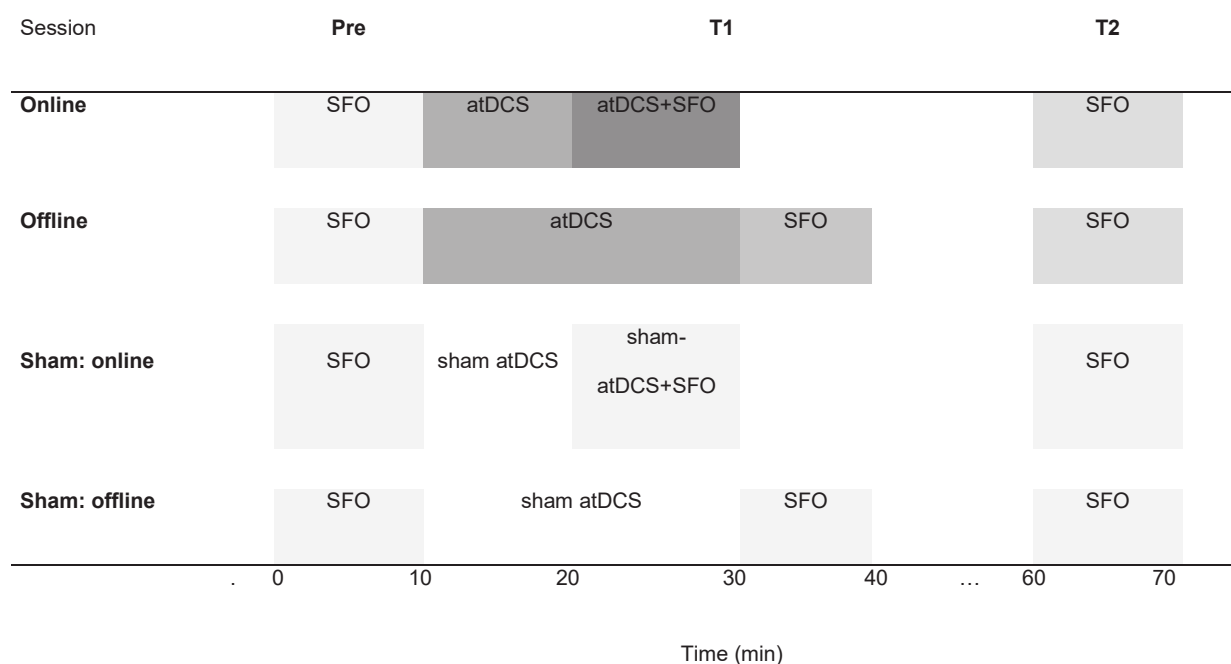


Figure 14 **Experimental timeline**. All subjects underwent three HD-atDCS (2mA, 20min) sessions (online, offline and sham) with 1 week washout between each session. For each session, subjects performed a simple finger opposition (SFO) motor task before (Pre), immediately (T1) and 30 min (T2) after cessation of stimulation. For the online protocol at T1, SFO was performed during the stimulation (online) whereas for the offline protocol, SFO was performed after the stimulation (offline). T1 represents immediate effects of HD atDCS-SFO task, whereas T2 represents the delayed effects (see Methods for further details).

Transcranial direct current stimulation

Direct current was generated by a current stimulator (Startim®, Neuroelectronics NE, Spain) and delivered to the left SMC of the subject through a 4x1 anodal HD-tDCS montage (active anode electrode on C3 surrounded by four return electrodes on FC1, FC5, CP5 and CP1; each at a distance of ~4 cm from the active electrode (Muthalib et al., 2016)). The five electrodes (3.14 cm² AgCl electrodes) were secured on the scalp in the offline 10-10 EEG electrode system positions using conductive paste (Ten20®, Weaver and Company, USA) and held in place using a specially designed plastic headgear to arrange the HD-tDCS electrodes and fNIRS probes on the head (see Fig. 2. for layout).

Functional near-infrared spectroscopy

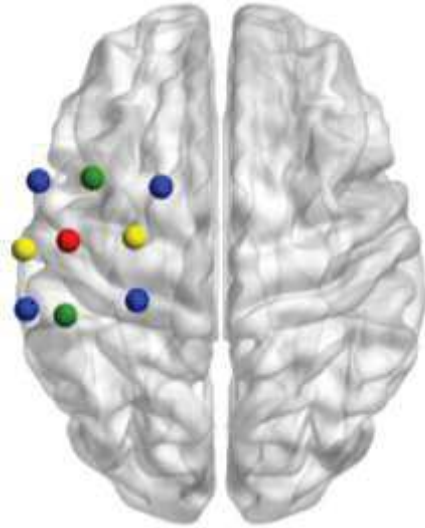
Hemodynamic responses during rest and SFO task periods were recorded continuously using a continuous wave multi-channel fNIRS system (Oxymon MkIII Artinis, Medical Systems,

The Netherlands) utilizing two wavelengths (~765 and 856 nm) at a sampling of 10 Hz. NIR light was delivered via fiber optic cables to a customized plastic headgear. Two receivers (avalanche photodiode) and two transmitters (pulsed laser) probes were placed, creating a 4 channel array (each channel represented by a receiver-transmitter combination separated by ~3 cm). Based on 10-20 EEG electrode system (Klem et al., 1999), the headgear was aligned with the vertex (Cz) and channels covered the stimulated SMC regions (see Fig. 2).

The oxymon calculates the changes in O₂Hb and HHb concentration values (expressed in μM) according to a modified Beer-Lambert Law and including an age-dependent constant differential pathlength factor (Duncan et al., 1996). During the data collection procedure, the time course of changes in O₂Hb and HHb concentration values were displayed in real time, and the signal intensity was verified for each channel before data collection.

Location of fNIRS probes and HD-atDCS electrodes

A 3-dimensional digitizer (Fastrack, Polhemus, USA) was used to measure the location of each fNIRS optode probe and tDCS electrode with a stylus marker in relation to the veridical landmarks of the participant's head (nasion, Cz, the pre auricular points anterior to the left and right ears). Subsequently, these coordinates were registered over a reference MRI atlas in the Montreal Neurological Institute (MNI) coordinates system (Singh et al., 2005), and the points on the scalp were projected over a three-dimensional reconstruction of the brain cortex (see Fig. 2) using the NIRS-SPM toolbox (Ye et al., 2009). The Brodmann areas corresponding to the region were further determined using the Anatomy 1.8 toolbox for SPM (Eickhoff et al., 2005). No difference in the location of fNIRS probes and HD-tDCS electrodes was found for the locations between sessions for each subject.



		MNI coordinates			
		X	Y	Z	BA
fNIRS probes	R1	-43	11	58	3-4-6
	T1	-66	-13	42	4-6
	R2	-29	-9	71	1-2-3-40
	T2	-52	-35	59	1-3-4
HD-atDCS	A1	-51	-10	58	1-2-3-4
electrodes	C1	-20	8	68	6
	C2	-28	-30	75	7
	C3	-61	10	35	6
	C4	-65	-33	38	40

Figure 15 Locations of the functional near-infrared spectroscopy (fNIRS) transmitter (T, in yellow) and receiver (R, in green) probes and anodal high-definition tDCS (HD-atDCS) anode (A, in red) and cathode (C, in blue) electrodes on the left hemisphere (Left panel). Each fNIRS channel was located midway between the T and R probe. MNI coordinates (x,y,z) and Brodmann areas (BA) of the 4 fNIRS channels and 5 HD-atDCS electrodes are reported on the right panel. BA1,2,3,4: sensorimotor cortex (SMC); BA6: Supplementary motor area (SMA)/Premotor cortex (PMC); BA7: superior parietal lobule (SPL); BA40: Inferior parietal lobule (IPL).

Data Analysis

SFO Movement rate

SFO Movement rate at each time point for each subject was calculated as the average of the number of SFO taps completed by the left and right hand divided by 300s. Three participants out of 15 with an intra-individual coefficient of variation (CV) up to 5% for the movement rate were excluded from further analysis because they did not follow correctly the instructions of the experimental design.

fNIRS

Pre-processing

Since the presence of cardiac pulsations in fNIRS O₂Hb signals is indicative of a good contact between the optical probes and the scalp (Themelis et al., 2007) the quality of each of the four channels was checked using two pre-processing methods. First, we analyzed the power

spectrum of each time series, where the detection of a peak value around 1Hz reflects the presence of the cardiac pulsations in the fNIRS signal at rest. Then we used the continuous wavelet transform (Grinsted et al., 2004) which is a time-frequency analysis of the signal, where the presence of a strong powerband around 1Hz reveals a good signal over time. After these preliminary pre-processing steps, 3 participants out of 12 were removed from further analysis due to many bad channels along sessions.

Data processing

The data processing was performed for each subject using some of the Homer2 processing package functions (<http://homer-fnirs.org/>) based in MatLab (version 2014a, Mathworks, USA) (see supplementary file). The fNIRS values retained for statistical analysis were changes in the channel averaged O₂Hb and HHb computed over the 10 task blocks using the integral between 5 to 25 seconds out of the 30 seconds of the task. This integral analytic approach allows quantifying the concentration changes over time while being sensitive to task-related changes on O₂Hb and HHb regardless of the shape of the hemodynamic response profile (Näsi et al., 2010; Safi et al., 2012). An index of hemoglobin differential (Hbdiff = O₂Hb – HHb) was also used to evaluate the level of cortical activation (Lu et al., 2015). The SMC activation (O₂Hb, HHb and Hbdiff) and movement rate for the two sham sessions (sham online and sham offline conditions) were not significantly different, so we pooled the data to represent one sham session.

Statistical Analysis

We used the Kolmogorov-Smirnov test to check for normal distribution. A repeated measures ANOVA (ANAOVARM) was used to compare the SMC activation (O₂Hb, HHb and Hbdiff) and movement rate with two within-subject factors (Time: Pre, T1, T2 and Session: online, offline and sham). In case of a significant main or interaction effect, follow-up ANOVAs with *post-hoc* LSD Fisher tests for multiple comparisons were conducted. All statistical analyses were performed using Statistica version 7.1 (StatSoft France, 2006). In all statistical tests a significance level of 0.05 was used. The effect sizes reported in the results section reflect partial-eta squared values (η^2_p) (Lakens, 2013).

3.3 Results

Subjective scalp sensation and Anxiety

A two-way ANAOVARM indicated that no differences were observed among the sessions for the resting state sensation over the scalp during HD-atDCS, indicating that the participants were unable to differentiate real HD-atDCS from sham sessions. There was no significant difference in State-Trait Anxiety Inventory between the sessions.

Movement rate

As indicated in Table 2, there were no significant differences in the SFO movement rate between the experimental sessions or over time for both the right and the left hands.

Table 2 Mean (SD) simple finger opposition (SFO) movement rate (Hz) for the online, offline and sham HD-atDCS sessions before (Pre), immediately (T1) and 30 min (T2) after stimulation.

Session	Right hand			Left hand		
	Pre	T1	T2	Pre	T1	T2
Online	2.4 (0.2)	2.4 (0.2)	2.4 (0.2)	2.4 (0.2)	2.4 (0.2)	2.4 (0.2)
Offline	2.3 (0.2)	2.4 (0.3)	2.4 (0.2)	2.3 (0.2)	2.4 (0.2)	2.4 (0.2)
Sham	2.5 (0.2)	2.4 (0.2)	2.4 (0.2)	2.4 (0.2)	2.4 (0.2)	2.4 (0.2)

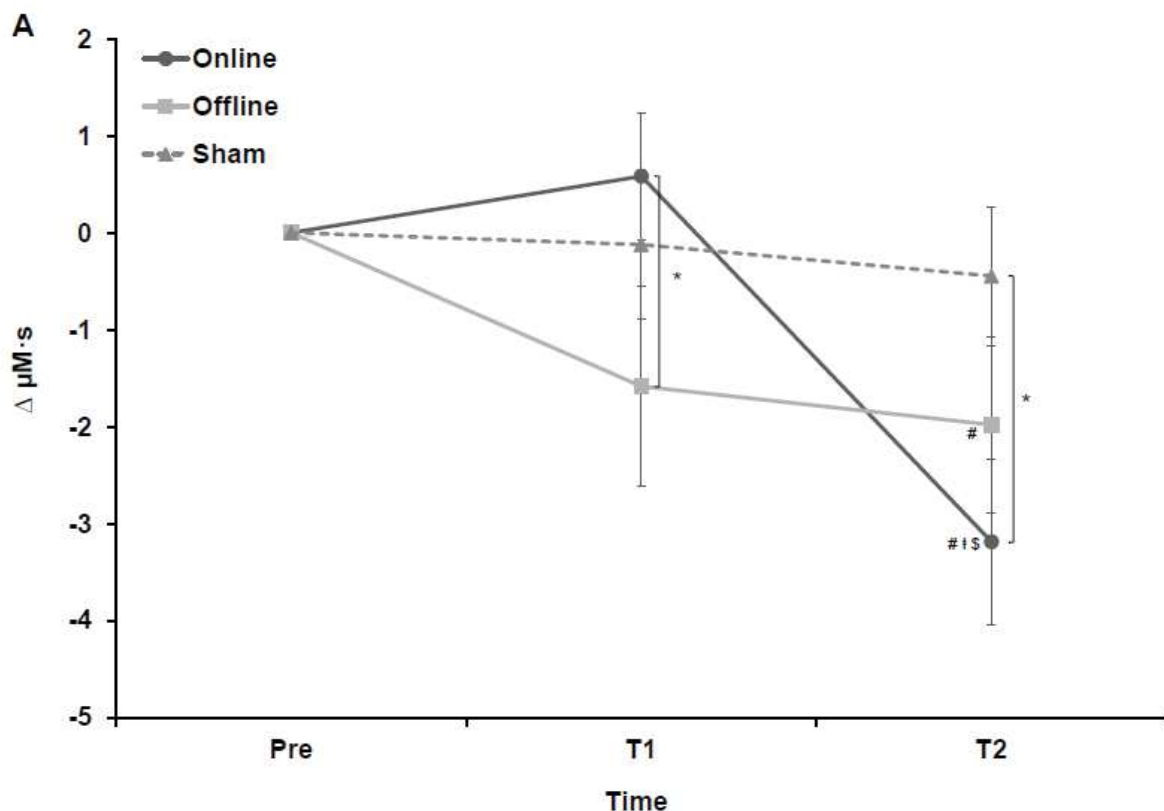
fNIRS

Figure 3 shows the changes in HHb and Hbdiff -for the online, offline, and sham sessions over time. For HHb (Fig. 16A), there was no Session main effect ($F(2,16)=0.098$, $p=0.907$), but there was a Session x Time interaction effect ($F(4,32)=3.228$, $p=0.025$, $\eta^2p=0.288$) and Time effect ($F(2,16)=9.616$, $p=0.002$, $\eta^2p=0.546$). *Post hoc* analysis revealed significantly lower HHb (i.e., increased SMC activation) from Pre to T2 for both the online ($p<0.0006$) and offline ($p<0.02$) sessions, while there was no significant change from Pre to T2 for sham. Moreover, HHb for the online session at T2 was significantly ($p<0.01$) lower than the sham session, but there was no significant difference in HHb between online and offline or between

offline and sham sessions at T2. Although HHb at T1 was significantly ($p < 0.02$) higher (i.e., decreased SMC activation) for the online than offline session, these changes in HHb were not significantly different to sham.

For Hbdiff (Fig. 16B), there was no main Session effect ($F(2,16)=1.640$, $p=0.225$), but there was a Session x Time interaction effect ($F(4,32)=2.860$, $p=0.039$, $\eta^2p=0.263$) and a main Time effect ($F(2,16)=5.802$, $p=0.013$, $\eta^2p=0.420$). *Post hoc* analysis revealed significantly lower Hbdiff (i.e., decreased SMC activation) from Pre to T1 ($p < 0.03$) and higher Hbdiff (i.e., increased SMC activation) from Pre to T2 for the online ($p < 0.02$) session, while there was no significant change from Pre for the offline and sham session. Hbdiff was significantly higher (i.e., increased SMC activation) for the online ($p < 0.0004$) session at T2 compared to sham, and there was a trend at this T2 time point for Hbdiff in the online session to be higher than offline ($p=0.061$), as well as for offline to be higher than sham ($p=0.053$).

For O₂Hb, there was no Session x Time interaction effect ($F(4,32)=1.713$, $p=0.171$) or Session main effect ($F(2,16)=2.000$, $p=0.168$), but there was a trend for the Time main effect ($F(2,16)=3.570$, $p=0.052$, $\eta^2p=0.309$).



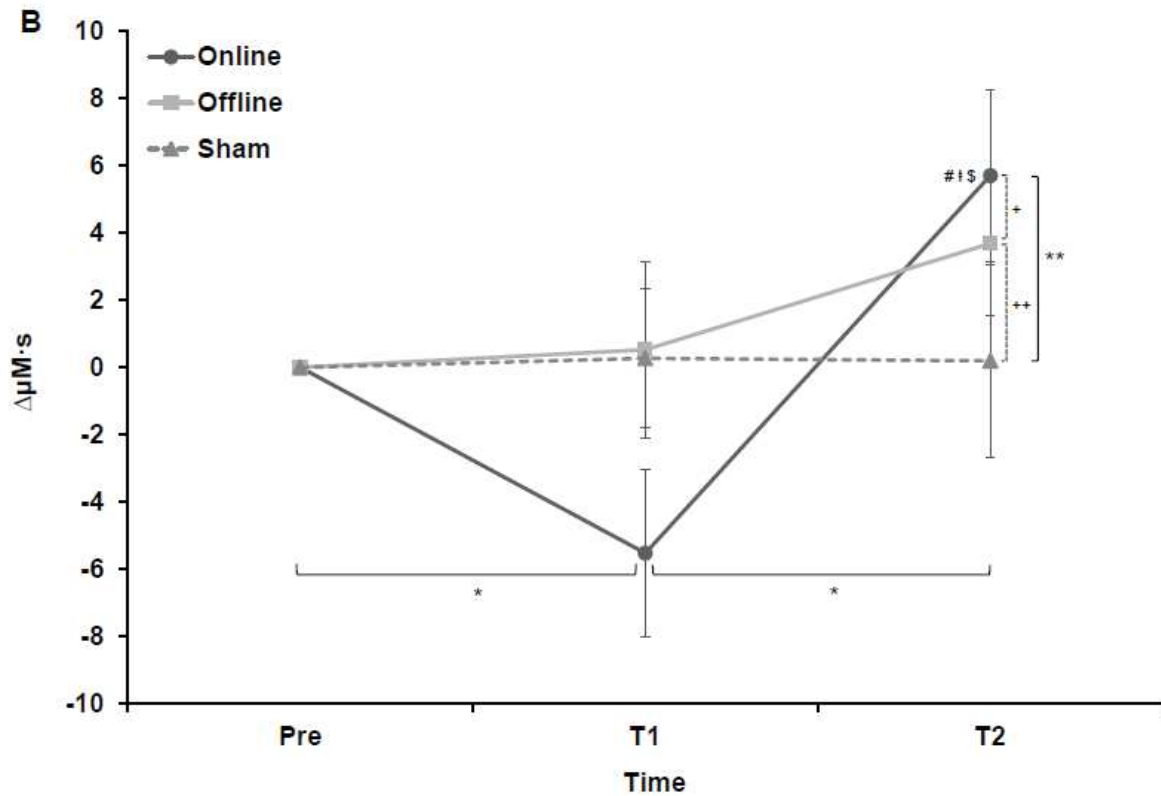


Figure 16 Group mean (\pm SEM) motor-task related changes normalized to the respective baseline values (Pre) in deoxygenated (HHb, panel A) and differential (Hbdiff, panel B) hemoglobin concentration in the left sensorimotor cortex for the online, offline and sham HD-atDCS sessions immediately (T1) and 30min after (T2) stimulation. * $p < 0.05$; ** $p < 0.001$; + $p = 0.053$; ++ $p = 0.061$; # T2 > Pre for Online; † T2 > T1 for Online; \$ T1 < Pre for Online.

3.4 Discussion

This study for the first time utilized fNIRS neuroimaging of motor task-related sensorimotor cortex (SMC) activation to provide a surrogate marker of neuroplastic modulation by functional targeting with HD-atDCS. We wanted to determine whether performing a simple finger opposition (SFO) motor task during (online) than after (offline) HD-atDCS (2mA, 20min) will modulate to a greater extent task-related SMC activation. Our main novel finding was that both online and offline HD-atDCS sessions induced a delayed (30 min after stimulation) increase in SMC activation to perform the same SFO task; however, only the online session was significantly greater than sham.

During SFO motor task performance, specific sensorimotor cortical networks are engaged such as the SMC, supplementary motor area, and premotor cortex with the SMC showing the most consistent effects (Witt et al., 2008). We chose a SFO task since it is a well learned motor task, so no changes in performance was expected over the experimental period. We confirmed this by the similar movement rates within and between the three experimental sessions (see Table 2).

In the present study, we employed fNIRS as a relatively simple and safe method to investigate the immediate and delayed neuroplasticity effects of HD-atDCS on SFO motor task-related hemodynamic responses, which is a proxy of SMC activation. Based on the neurovascular coupling mechanism, the hemodynamic response measured by fNIRS is usually characterized with an increase in O₂Hb and a concomitant smaller reduction in HHb in the cortical microcirculation, and these patterns of O₂Hb and HHb changes can be used to identify the level of cortical activation, which is correlated well to the fMRI BOLD signal (Leff et al., 2011). Due to the greater influence of superficial blood vessels on O₂Hb signals (Kirilina et al., 2012), HHb changes (Muthalib et al., 2016) and an integrated measure combining O₂Hb and HHb (i.e., Hbdiff = O₂Hb – HHb) (Lu et al., 2015) are likely more suitable metrics for accurately detecting task-related changes in SMC activation. Indeed we found much larger variability in the O₂Hb integral values between subjects, which could account for the non-significant ANOVA effects. However, normalizing O₂Hb to HHb (i.e., Hbdiff that is driven by increases in O₂Hb with a smaller contribution from decreases in HHb) reduced this variability, which allowed Hbdiff to better detect task-related changes in SMC activation. Hence a greater SMC activation was reflected in an elevated Hbdiff and reduced HHb. Based on this relationship, we observed that when a SFO motor task is performed concurrently with HD-atDCS (i.e., online session) it induced a delayed increase in SMC activation (time T2) that was greater in magnitude than when the SFO task was performed after the stimulation (i.e., offline session). Since the sham session did not induce any changes in task-related SMC activation over the three time points tested (Pre, T1 and T2) and only the online session was significantly greater than sham at the delayed measurement time (T2), we consider that online HD-atDCS induced greater neuroplastic effects than offline HD-atDCS that outlast the stimulation period and evolves over time.

This striking finding reinforces the fact that HD-atDCS elicited neuroplastic effects in the stimulated region of the SMC under the electrodes (Lang et al., 2005) that was evident only after a 30min delay and depended on when the SFO task was performed in relation to the stimulation (i.e., online vs offline). This delayed neuromodulatory effect on task-related SMC

activation induced by online and offline HD-atDCS is in agreement with the time course of cortical excitability reflected in MEP changes in which peak values occur after 30 minutes with HD-atDCS in resting conditions (Kuo et al., 2013). It appears that when the SFO task is performed immediately after HD-atDCS (i.e., offline session) compared to online HD-atDCS it is less effective in modulating task-related SMC activation and hence neuroplasticity measured both immediately (T1) and after a 30 min delay (T2). These findings would confirm previous tDCS and motor learning studies (Stagg et al., 2011b) that showed reduced learning when the motor task is performed offline than concurrently with stimulation (Amadi et al., 2015).

In the online session, the SFO task-related sensorimotor network engagement during HD-atDCS could sensitise the impact of the electric fields on the stimulated SMC region through polarization and subsequent synaptic efficacy mechanisms. This provides further evidence that synaptic modifications are more pronounced when the task and tDCS are concurrent (Karok et al., 2013). In the present study, this greater increase of SMC activation in the online than offline session after a delay period could be the consequence that HD-atDCS seems to be more efficient at inducing neuroplasticity when networks are already involved in the task, since active networks are preferentially sensitive to neuromodulation (Bikson et al., 2013; Reato et al., 2010). Moreover, atDCS alone increases the driving force of synaptic activity due to the synergistic effects of dendritic hyperpolarization and somatic depolarization (Lafon et al., 2016). The fact that we combined both motor task and electrical stimulation may have induced a “gating mechanism” that increased the calcium levels above a threshold to induce synaptic plasticity (Saucedo Marquez et al., 2013), and this neuroplastic effect was greater for the online than offline session.

In our previous study (Muthalib et al., 2016) that only investigated online HD-atDCS, we found a lower SMC activation at the immediate time point, which was evident in both the online and offline (3min delay) assessment. We argued that the significant reduction in SMC activation (i.e., smaller decrease in HHb) for a similar motor output (i.e., SFO tap rate) could be related to HD-atDCS inducing a greater efficiency of neuronal transmission in the SMC to perform the same SFO task. In the present study, although we showed that online HD-atDCS induced a numerically reduced SMC activation at T1 that was significantly smaller than offline HD-atDCS, the changes were not different to sham. Nevertheless, we consider that there were modifications in the excitation/inhibition balance (Levinson and El-Husseini, 2005) for both online and offline sessions at this time point. In the present study, we utilized the integral of the HBdiff and HHb of 4 fNIRS channels surrounding the anode to infer the

level of SMC activation, while in our previous study we utilized the peak changes of one channel, and this difference in fNIRS analysis may account for the discordant findings. Furthermore, it should be noted that similar to the fMRI BOLD response, fNIRS hemodynamic response measurements are limited in the ability to differentiate excitatory vs. inhibitory activity, and it is not possible to completely separate changes in cortical excitability or metabolism from changes in NVC.

The present study extends our previous study (Muthalib et al., 2016) by showing that after a 30 min time delay from stimulation, neuroplastic changes occur that magnify the level of SMC activation for both the online and offline HD-atDCS sessions with the online session showing a more pronounced effect. This is a novel finding and it is not easily apparent why there would be an increased SMC activation to perform the same SFO task. However, based on the theory of homeostatic plasticity (Turrigiano and Nelson, 2004), the increase of SMC activation after a 30min delay (T2) could be a consequence of the modification of excitation/inhibition balance at T1 requiring adjusting of their synaptic strengths (Pozo and Goda, 2010) after a 30min time delay. This increase in SMC to perform the same motor task 30min after both online and offline HD-atDCS could represent a reduced efficiency, which is counterintuitive to the known enhancements of motor learning after tDCS and motor task application (Reis and Fritsch, 2011). We would rather consider that the delayed increase in SMC activation after HD-atDCS could represent a type of motor memory consolidation process (Galea and Celnik, 2009). Previous work (Reis et al., 2009; Saucedo Marquez et al., 2013) highlighted the beneficial effect of online tDCS and motor task training on consolidation of the motor task after a delay period from stimulation (i.e., offline gains). This consolidation results in part from memory stabilization and as such requires energy with subsequent increases in blood flow (Lisman et al., 2002).

3.5 Conclusion

This study highlights the crucial role timing of HD-atDCS and motor task performance has on modulating motor task-related activation of the targeted SMC. The novel finding suggests that functional targeting with online HD-atDCS is more effective to induce neuroplasticity changes that evolves over time after stimulation as revealed by an increase in SMC activation. The increase in activation of the functionally targeted SMC could represent several neuroplastic mechanisms that modify excitation/inhibition balance. Future research with

combined neurophysiological and neuroimaging techniques are needed to fully understand this phenomenon at a larger scale.

Supplementary File

The data processing was performed for each subject using some of the Homer2 processing package functions (<http://homer-fnirs.org/>) based in MatLab (version 2014a, Mathworks, USA) as following:

- 1) Concatenation of the three periods of interest (i.e., Pre, T1 and T2).
- 2) Conversion of the raw optical intensity signals into changes in optical density (*hmrIntensity2OD* Homer2 function).
- 3) Motion artefact removal on changes in optical density time-series using the moving standard deviation and spline interpolation methods (Grinsted et al., 2004) (with $SDThresh = 20$, $AMPTresh = 0.5$, $tMotion = 0.5s$ and $tMask = 2s$ and $p = 0.99$ as recommended by Cooper et al (Cooper et al., 2012); Homer2 functions *hmrMotionArtifactByChannel* and *hmrMotionCorrectSpline* were used for this step.
- 4) Application of a wavelet motion correction filter (with a $iqr = 0.1$ as recommended by Molavi et al (Molavi et al., 2012); Homer2 function *hmrMotionCorrectWavelet* was used.
- 5) Conversion of changes in optical density into concentration changes using the *hmrOD2Conc* Homer2 function based on the modified Beer-Lambert law.
- 6) Application to the data of a band-pass filter (fourth order Butterworth filter) with cut-off frequencies of 0.009-0.08 Hz in order to remove physiological components and reduce very low drifts (Molavi et al., 2012); Homer2 function *hmrBandpassFilt* was used.
- 7) Recovering of the hemodynamic response by block averaging all trials related to the same motor task type. A 10-s rest period was included at the beginning of each block for baseline correction in order to obtain the relative changes in O₂Hb and HHb.

4

Multiple sessions of concurrent anodal tDCS and motor task training temporarily boost plateau learning

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Chapter 4:

Multiple sessions of concurrent anodal tDCS and motor task training temporarily boosts plateau learning

Abstract

Online tDCS (i.e., tDCS concurrent to the task) and priming tDCS are proposed to have cumulative effects on motor performance. However, the impact of the tDCS polarity for priming remains unclear. The aim of this study was to enhance more motor learning and retention of a tracing-motor circular task with multiple online anodal tDCS (atDCS) sessions using cathodal tDCS (ctDCS) as compared to atDCS priming and sham. In a between double blind sham controlled and randomized study design, 22 participants separated in 3 independent groups underwent for 3 consecutive days high definition-atDCS (HD-atDCS) training sessions targeting the left sensorimotor cortex, preceded by a baseline measurement (day 0) and followed by two retention tests (day 4 and day 18, one day and two weeks after training, respectively). A circular tracing-task of 5 trials of 1 min intersected by 1 min rest was performed at pre, during and post- HD-atDCS for each training session and for day 0, 4 and 18. The motor performance increased significantly at the end of training for both atDCS and ctDCS priming ($p < 0.001$) but not for sham. This increase had also been revealed at day 4 for a-tDCS ($p = 0.05$) and for c-tDCS at day 4 and 18 ($p < 0.001$). The combination of priming tDCS and multiple sessions of concurrent a-tDCS was beneficial for improving performance during training and for the first day of retention, without being superior to sham. The cumulative effects of priming and repetition persisted only for c-tDCS priming during the second retention test two weeks after the end of the training.

4.1 Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive neuromodulation technique that can increase or decrease cortical excitability depending on the polarity of the induced

electric field (Dissanayaka et al., 2017). Anodal tDCS (a-tDCS) of the primary motor cortex (M1) has generally been shown to enhance motor performance and learning, but this depends on the specific motor task utilized (Saucedo Marquez et al., 2013), as well as tDCS parameters (electrode position, Schambra et al., 2011; current intensity, Cuypers et al., 2013) and the timing of application (Reis et al., 2015). However, even with strict control of these parameters, important intra- and inter- individual variability of responses to tDCS have been reported in several studies (Li et al., 2015; Wiethoff et al., 2014). Although anatomical differences between subjects will always be a major factor influencing tDCS responses, one way to enhance tDCS responses is to develop new tDCS protocols where personalization of stimulation parameters is the ultimate goal (Cancelli et al., 2015). Regarding the tDCS equipment and setup, high-definition (HD)-tDCS montage can be one solution to improve optimization of the technique due to the expected focality of the induced-current (Edwards et al., 2013; Muthalib et al., 2017) and the persistence of the after-effects on cortical excitability (Datta et al., 2009; Kuo et al., 2013).

For either motor or cognitive tasks, concurrent application of a-tDCS and task training is a potential way to enhance the performance and learning (Cohen Kadosh et al., 2010; Stagg et al., 2011). The greater facilitative effect of concurrent a-tDCS on motor performance/learning is likely due to enhanced synaptic efficacy in the simultaneously engaged neural network through a “gating” mechanism (Ziemann and Siebner, 2008). A possible reason why offline a-tDCS (i.e., tDCS before the task) may limit motor performance/learning compared to concurrent or online a-tDCS has been suggested to be related to homeostatic metaplastic mechanisms based on the Bienenstock-Cooper-Munro (BCM) theory that postulates a “sliding threshold” for bidirectional synaptic plasticity (Ziemann and Siebner, 2008). Accordingly, a-tDCS, which increases the likelihood of (long term potentiation or LTP)-like plasticity, would increase the modification threshold for LTP during the subsequent motor task and thus adversely affect motor performance/learning. Antal et al. (2004) using a visuo-motor coordination task, have showed that the effects of a-tDCS during the tracking task enhanced online motor performance gains compared to sham. Recently, a meta-analysis concluded that multiple sessions of a-tDCS is more efficacious than a single session for enhancing motor learning and retention (Hashemirad et al., 2016). The seminal study by Reis et al. (2009) reported that after 5 days of concurrent M1 a-tDCS and visual pinch task training performance, greater effects on retention of performance gains were found for more than 3 months after training (Reis et al., 2009). In a more recent study, the

same group has showed that 3 days of concurrent a-tDCS and tracing task training induced mainly online skill acquisition gains over the 3 days (Prichard et al., 2014). Furthermore, Reis et al. (2015) have showed that 3 consecutive days of concurrent a-tDCS and visual pinch task training interact with the physiological consolidation process in the hours after the tDCS-training rather than overnight sleep (Reis et al., 2015). These findings suggest a time-dependent development of consecutive offline gains in the first few hours after each concurrent a-tDCS and training session.

The sequence and timing of the tDCS polarity are parameters that can also be manipulated to enhance motor performance and learning with regard to the homeostatic metaplasticity phenomenon (Karabanov et al., 2015). Sub-threshold neuronal membrane depolarization induced by a-tDCS has an intensity- and time-dependent effect to strengthen synaptic efficacy (Nitsche and Paulus, 2001). Performing a-tDCS (2 mA, 10 min) immediately before concurrent a-tDCS was proposed to boost the already strengthened synaptic connections through a further “gating” mechanism induced with the concurrent motor task (Besson et al., 2016). Reducing corticospinal excitability with cathodal tDCS (c-tDCS) before concurrent HD-a-tDCS and motor task training is another way to induce homeostatic metaplastic mechanisms to enhance motor performance and learning (Christova et al., 2015; Fujiyama et al., 2016). Concerning the timing for two tDCS sessions with the same polarity, Bastani and Jaberzadeh (2014) have reported that a break of 5 min is deleterious for motor performance. For a-tDCS priming, having no rest would allow a greater chance for neuroplasticity to take hold via gating mechanisms. By applying priming c-tDCS followed 10-min later by concurrent a-tDCS and pegboard motor task training, Christova et al. (2015) have showed enhanced motor learning and a greater retention of this skilled motor task 2 weeks later compared to sham and training with concurrent a-tDCS. Using a similar homeostatic metaplastic protocol, Fujiyama et al. (2016) have showed a significantly greater enhancement in online skill acquisition of a unimanual isometric force control task for the group with priming c-tDCS followed by concurrent a-tDCS-training compared to only concurrent a-tDCS-training in both young and older adults. However, it is not known if multiple sessions of priming c-tDCS combined with concurrent a-tDCS-training would enhance more learning and retention of a tracing-motor task compared to multiple sessions of concurrent a-tDCS-training.

Therefore, the aim of this study was to enhance learning and retention of a tracing-motor circular tracing task with multiple (3 consecutive days) concurrent a-tDCS-training

sessions with or without priming tDCS. Based on the known effect of practice and on the results of concurrent tDCS combined with multiple sessions (Gomes-Osman and Field-Fote, 2013; Reis et al., 2009), we hypothesized an increase day after day owing to training with a larger magnitude of change with priming c-tDCS. We also hypothesized that the two conditions of priming for the follow-up would disclose a retention of the improvement in performance with a larger magnitude of change for c-tDCS priming.

4.2 Methods

Participants

Twenty five healthy subjects (9 females, 19-45 years old, mean age \pm SD: 31 ± 9.9) voluntarily participated in this study that has received Ethics approval by IRB of Euromov (University of Montpellier, France) and in accordance to the Declaration of Helsinki. The laterality quotient (LQ) for right handers ($n=21$ with a-tDCS=6, c-tDCS=8 and sham=7) and left handers ($n=4$ with a-tDCS=3 and c-tDCS=1) assessed with the Edinburg handedness inventory (Oldfield, 1971) was 75 ± 23 and -70 ± 33 , respectively. All subjects had no history of neurology or physical disorders or any upper extremity muscle or joint injuries and gave written informed consent after a description of the study procedures and associated risks. The respect of safety recommendations associated with the use of tDCS was strictly respected (Bikson et al., 2016).

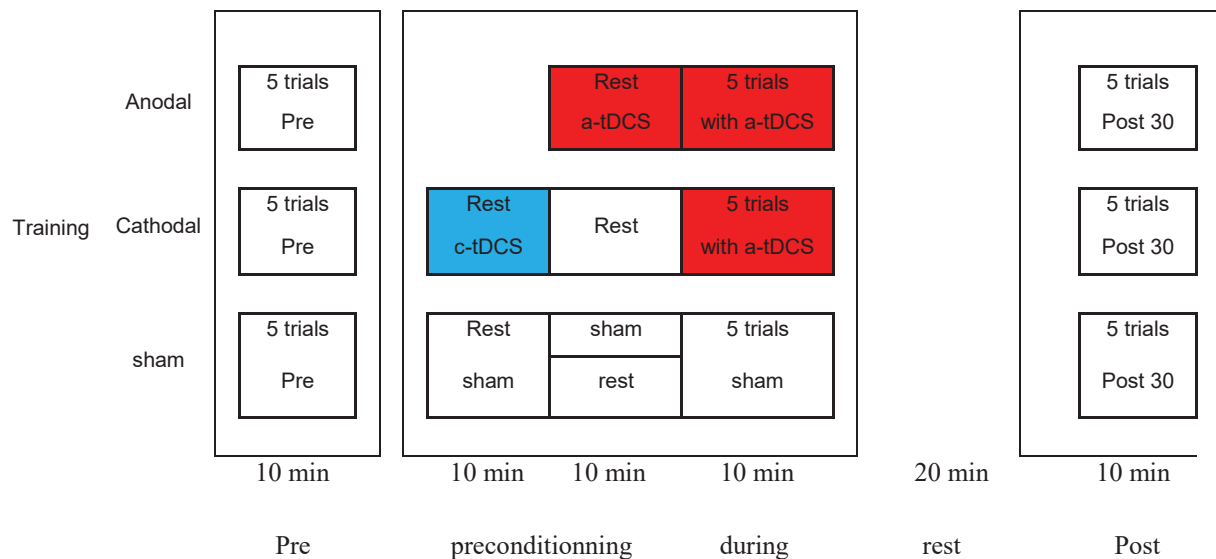


Fig 1. **Schematic representation of the experimental design.** The subject performed the motor task three times intersected by 20 min of preconditioning or delay. Pre and post are without tDCS while during tDCS depends on the specific tDCS parameters of the 3 groups with different polarity for the preconditioning phase.

Study Design and Protocol

Figure 1 presents the schematic of the experimental design. 3 participants were excluded because they did not respect the instructions (see below). In a double blind randomized study, the 22 subjects were randomly distributed into 3 groups: anodal priming/anodal-task (a-tDCS, n=8 whose 2 females); cathodal priming/anodal-task (c-tDCS, n=8 whose 4 females); sham (n=6 whose 3 females). For sham, 50% underwent anodal priming/anodal-task and 50% underwent cathodal priming/anodal task. All subjects were required to undertake 6 testing days (5 successive days and 1 day 2 weeks later for a retention test). For the baseline (Day 0) and the 2 retention (day 4 and day 18) testing days, no tDCS was applied and only the tracing-motor task consisting of 1 block of 5 trials (1 minute task intersected by 1-minute rest, total 10 min duration) were performed. Days 1, 2, 3 were training days that included sham or real tDCS, and each training day comprised of 3 training blocks of 5 trails: Pre-tDCS block, tDCS-block, and Post-tDCS block. In the pre-tDCS block, no tDCS was applied to all groups during the tracing-motor task. In the tDCS-block, the specific tDCS parameters were set and concurrent tDCS and tracing-motor task training were

undertaken. a-tDCS priming (10 min) was adjacent to online a-tDCS task (10 min) while c-tDCS priming (10 min) was intersected by 10 min of rest before online a-tDCS task (10 min) (Fig. 1). In the Post-tDCS block, tDCS was off and the tracing-motor task was performed again after 20 min rest to assess within-day offline effects. Subjects were informed to perform the tracing-motor task as fast as possible while maintaining accuracy. In order to minimize practice effects on baseline performance, no practice was provided.

All participants and one experimenter (CV) undertaking the tDCS applications/assessment were blind to the tDCS parameters and settings. Even if tDCS is well tolerated (Turski et al., 2017), a questionnaire containing rating scales of 11 unpleasant sensations compared to resting state (i.e. sitting quietly without tDCS electrodes over the head) was filled out after the stimulation sequence and at the end of each session. In order to control certain parameters that may affect the effects of tDCS, a questionnaire on the quality and quantity of sleep was recorded at the beginning of each testing day (Snyder-Halpern and Verran, 1987).

Transcranial direct current stimulation

A 4x1 ring montage with HD electrodes (3.14 cm²) was used to deliver the direct current to the left (right handers, n=19) or right (left handers, n=3) M1 (Starstim, Neuroelectronics, Barcelona, Spain). With regards to the handedness of the participant, the active electrode was placed on the scalp overlying the dominant M1 (C3 or C4) based on the 10-20 EEG system. The 4 return electrodes surrounded the anode or cathode electrode at a centre-to-centre distance of 3.5cm. For the anode on C3, return electrodes were placed on FC1, FC5, CP1 and CP5. For the anode on C4, return electrodes were placed on FC2, FC6, CP2 and CP4. To reduce the variability of placements of the electrodes with multiple sessions, the same experimenter (CV) always marked the site of the electrodes. For each session, the use of a plastic piece ensured to respect the electrodes distance and location. To fix the montage, a headband was placed to maintain also the tDCS device.

For a-tDCS, constant current was delivered for 20 min at an intensity of 2 mA with a ramp up and down phase of 30 seconds duration. For sham tDCS, a ramp up of 30 s followed by a plateau of 30 s at 2 mA, then 30 s ramp down were applied (Gandiga et al., 2006). For the c-tDCS/a-tDCS group, c-tDCS was applied for 10 min with 30 s ramp up/down, then after a 10 min rest, a-tDCS was applied for 20 min with 30 s ramp up/down. In all sessions, the

impedance was monitored at the beginning and the end of each period of stimulation for all electrodes.

Tracing-motor task

The tracing-motor task was a computerized version of the circular tunnel task shown to be highly reliable over testing days (Accot and Zhai, 2001). Subjects were required to do circular traces using a hand stylus within the boundaries of a circle of an 80 cm length and 0.8 cm width from 12.3 to 13.1 cm (see Figure 2). The index of difficulty (ID) defined by the length of circle (A) divided by the channel's width (W) was set to 100 (i.e., 80/0.8) (Kulikov et al., 2005). The line tracing was recorded with a computerized tablet Wacom Intuos (gd1218U, Japan) at the sampling frequency of 100 Hz. For data acquisition, a homemade script was built with MATLAB® (version R2012b – MathWorks, MA, USA).

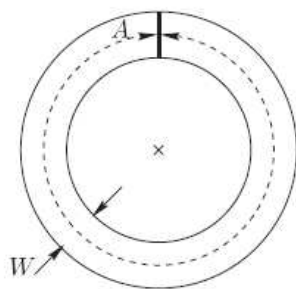


Fig 2. **Representation of the circular-tracing task.** A is the perimeter (dotted line) of the circle's center (X) and W stands for the path width (continuous lines). From Accot and Zhai (2001).

Data analysis

We defined an index of performance (IP) for the task based on previous related studies (Bonnetblanc, 2008; Kulikov et al., 2005).

$$IP = TED60 / WVT60$$

Where TED60 represents the total Euclidean distance achieved during the 60-second task and WVT60 represents the width of the virtual circular tunnel, including all the trajectories of the subject during the 60-second task.

To calculate IP, we developed a Matlab script taking in input raw data from the Wacom Intuos tablet. The first step in pre-processing raw data was calibration. For this we used a controlled data set and transformed the pixel indexes (X and Y positions) into Euclidean distance (in mm) from the center of the circular tunnel. The second step consisted in re-sampling the data to obtain a fixed sampling period at 100 Hz; the `interp1` function of Matlab with the 'pchip' method of interpolation was used. We calculated IP from the pretreated data,. TED60 is calculated by summing the Euclidean distances between 2 consecutive points for all points acquired during the motor task. WVT60 is calculated as the difference between the distance from the farthest point to the center and the distance from the nearest point to the center for all points.

With regards to the purposes of the study, IP values were assessed in trials 45 (i.e., the last trial of training with tDCS use), 55 (i.e. the last trial one day after training, short retention) and 60 (i.e. 14 days after training, long retention).

Statistical analysis

We used the Kolmogorov-Smirnov and Levene test to check for normal distribution and homogeneity of variances. A two-way repeated-measures ANOVA (ANOVA_{RM}) was used to compare IP for each trials (from trials 1 to 60) as the within-subject factor and groups (a-tDCS, c-tDCS and sham priming) as the between-subject factor. The Tukey test was used as a post hoc test to determine the between-group differences at specific points from the design: t1, t45, t55 and t60. All statistical analyses were performed using Jamovi software version 0.7.5.6 (Jamovi project, 2017). In all statistical tests a significance level of 0.05 was used. The effect sizes reported in the results section reflect partial-eta squared values (η^2_p) (Lakens, 2013).

4.3 Results

Subjective scalp sensation, sleep and perception of difficulty

The 25 participants conducted the study to the end. A two-way ANOVA_{RM} indicated that no differences were observed among the sessions for the resting state sensation over the scalp, indicating none of them were unable to differentiate real tDCS from sham. No significant differences between groups were found for time and quality of sleep.

Changes in performance

Figure 3 shows the evolution of IP over time for the 3 groups of priming stimulation conditions. There was no significant main group effect ($F(2,19)=0.306$ $p=0.740$) for IP. However, the results of two-way repeated measures ANOVA revealed a significant main effect for trials ($F(59,1121)=6.950$, $p<0.001$, $\eta^2p=0.268$) and a significant interaction effect between groups and trials ($F(118,1121)=1.440$, $p=0.002$, $\eta^2p=0.131$). *Post hoc* analysis showed that IP values at trials 45 and 55 were significantly higher than trial 1 for both a-tDCS and c-tDCS priming groups. Only for c-tDCS priming, IP values were still significantly higher in trial 60.

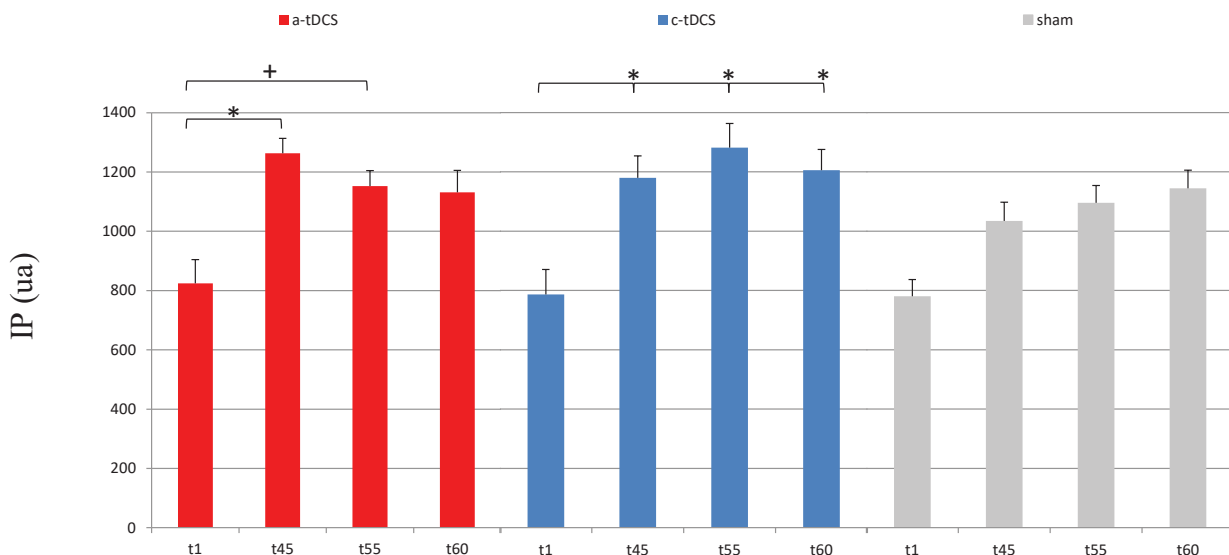


Fig 3. Index of performance (IP, mean + SE) at different time points for each priming polarity condition. t1 represents the 1st trial, t45 is the last trial with tDCS. t55 and t60 are the last trials of the short (i.e., 1 day) and long (i.e., 2 weeks after) retention test, respectively.

In red a-tDCS, in blue c-tDCS and in grey sham. All the comparisons were related to trial 1. + $p < 0.05$; * $p < 0.001$ from t1.

4.4 Discussion

The purpose of this study was to examine the enhancing effects and retention of a tracing-motor task with 3 consecutive days of a-tDCS-training sessions with two different polarities of priming tDCS. Our findings for all combination of priming and concurrent a-tDCS conditions showed compared to the beginning of training an increase in motor performance at the end of 3-days training (i.e., trial 45) and in the first day of retention (i.e., trial 55) while only the group using c-tDCS priming maintained its performance level two weeks after (i.e., trial 60), without superiority compared to sham whatever the polarity.

The choice of a circular tracing-task with low learning reserve was made to isolate the tDCS impact compared to the learning effect. Indeed circular tracing-task based on the steering law derived from the Fitt's law (Accot and Zhai, 1999) might provide limited improvement in performance despite training (Gibbs, 1962). The participants had to manage jointly two parameters: speed and accuracy. To prevent misinterpretation in the variation of these two parameters the motor performance was calculated with IP (Bonnetblanc, 2008). No significant increase in IP was revealed for sham group at each specific time points as compared to trial 1 (Fig. 3). This confirmed the result of a previous study (unpublished data) where an index of difficulty of 100 did not produce increase in performance in a unique session. Thus the changes in performance could be more influenced by tDCS effect than practice. Beyond the will to propose a task to quickly reach the relative "ceiling" levels to be in line with highly skilled individuals (e.g., elite athletes, expert operators), the important use of the upper limbs in everyday life could disrupt the neuroplastic changes. Learning is so plastic that it is vulnerable to disruption by subsequent new learning (Shibata et al., 2017).

As expected, at the end of the training period (t45), IP increased significantly for the two polarities of cumulative effects of priming and repetition tDCS. The lack of difference between groups especially between a-tDCS and c-tDCS do not allow confirming that priming is a key parameter for training. This result was partly in accordance with Christova et al. (2015) that reported an improvement in grooved pegboard task (GPT) for all conditions. Also no difference was revealed between sham priming/a-tDCS online and c-tDCS priming/a-tDCS

online but both priming conditions were different from sham. Priming c-tDCS in single session was not totally responsible of the improvement. Moreover, cumulative effects of priming and repetition of the present study induced important performance changes from baseline as reported in previous studies using only multiple sessions of concurrent tDCS (Prichard et al., 2014; Reis et al., 2009). Thus to evaluate the interest to introduce priming, the replication of study without enhancement in performance after multiple training sessions is required with the adding of priming. For example, in a visuomotor grip force tracking task with stroke patients, no improvement at the end of training with concurrent a-tDCS was revealed (Pavlova et al., 2017). In addition, the lack of a condition with sham priming followed by online a-tDCS motor-tracing task prevents to conclude that the increase was due to priming.

The second aim of this study was to assess the effect of priming on motor performance retention. Two retests were made on days 4 and 18 (i.e., one day and two weeks after the training). Lowering excitability during priming should have increase LTP according to BCM theory and so increase IP (Karabanov et al., 2015). Our results supported partly this statement since c-tDCS priming group has significant greater performance in day 4 (t55) and 18 (t60) as compared to the beginning of training (t1). Increasing excitability should have opposite effect (i.e., promote LTD). Similar results with improvement in performance for retention tests were observed in Christova et al. (2015) and Fujiyama et al. (2017) studies despite differences in stimulation parameters. However, the question of intensity especially for c-tDCS and the duration of the rest period before online a-tDCS remains unclear. The variability of motor response reported especially for c-tDCS (Wiethoff et al., 2014) was likely attenuated with multiple sessions (López-Alonso et al., 2015). However, the standard deviation of IP with c-tDCS was 25% more important than sham. Once again the necessity to individualize the intensity to ensure that excitability has been lowered with c-tDCS is necessary (Berryhill et al., 2014). The lack of significant difference for the main group/priming effect limited the current interpretation. However the changes we observed within each priming condition are promising. Motor performance retention was improved by adding external stimulation like c-tDCS with a more persistent phenomenon. Future researches with more complex task are needed to confirm the interest of priming on retention.

4.5 **Conclusion**

The main finding suggests that priming prior to completion of the task is beneficial for performance and short retention for both tDCS polarities. For long retention (i.e., two weeks after the training), only c-tDCS appears beneficial. Future research with combined neurophysiological and neuroimaging techniques are needed to fully understand the priming phenomenon at a larger scale.

5

General discussion

Chapter 5: General discussion

During the two last decades, several studies have shown that tDCS could have beneficial effects in the aim of “human enhancement”. Consistent with a neuroergonomics approach, task performance can be facilitated by non-invasive neuromodulation techniques, such as tDCS (Clark and Parasuraman, 2014; McKendrick et al., 2015). However, robust stimulation parameters and protocols need to be developed for applying tDCS to enhance motor performance in clinical and healthy populations, because the results are heterogeneous whatever the protocols tested (Dedoncker et al., 2016; Elsner et al., 2016; Westwood and Romani, 2017). The first challenge is to increase the number of responders to tDCS protocols. When it will be resolved, then the persistence of the effects could only be studied. Our work made it possible to underline that coupling tDCS and motor task appeared as a promising protocol to magnify the effects of tDCS while a conditioning phase was a means of further developing long-term motor performance. However, these two aspects should not be limited to the only ways for optimizing the tDCS protocols. There is also an advantage in repeating the stimulation sequences. One purpose more and more utilized by a lot of research laboratories is to switch from single to repeated tDCS sessions. This point will be not discussed as it appears obvious (see Montero and Lundby, 2017). There is a large number of studies providing evidence for efficacy of multiple-sessions of atDCS over M1 (Reis et al., 2009; Saucedo Marquez et al., 2013; Schambra et al., 2011; Waters-Metenier et al., 2014). Moreover, a meta-analysis conducted by Hashemirad et al. (2016) indicates that application of multiple sessions of atDCS (i.e., 3 or 5 days of training) compared to single atDCS session induced a significant improvement in skills for visual isometric pinch task, sequential finger tapping and serial reaction time task. It fits with evidence-based analysis in medical field where only studies based on repeated tDCS sessions are included (Lefaucheur et al., 2017). Repetition of specific motor tasks is recognized as a key element in post-stroke rehabilitation, in particular so that the expected behavioral changes persist. What happens when the tDCS is superimposed? If one wants to solicit the individual with the addition of an anodal tDCS stimulation during the execution of a motor task, protective mechanisms could be expected in the biological tissues. The modification of the GABA / glutamate balance linked to an excessive stimulation time due to repeated stimulations can lead to excitotoxicity and cause neuronal apoptosis. However, the results of the various clinical studies (Bolognini et al., 2011; Hesse et al., 2007; Kim et al., 2010; Lindenberg et al., 2010) are encouraging because they report no side-effects and significant functional improvements in Fugl-Meyer motor score,

Jebsen-Taylor test, Barthel index or grooved Pegboard test (Ar et al., 1974; Goldstein and Samsa, 1997). Moreover, some teams (Saposnik et al., 2011) are soliciting even more the participants by adding virtual reality, recognized to accelerate the neurorehabilitation (Cameirão et al., 2012; Holper et al., 2010). The cumulative / combined effects of these different techniques appear at a first glance to be positive. Nevertheless, it is necessary to better define the changes induced by the tDCS at the neurophysiological level before being able to systematize and individualize the rehabilitation protocols.

During this thesis, two main questions have guided our thinking. Primarily, the necessity to have concurrent tDCS and motor task in order to magnify the expected effects of tDCS. Since the beginning of our work, this topic has interested more and more researchers, specifically in the cognitive field. Secondly, the notion of priming with multiple sessions has been questioned in order to evaluate the possibility of having cumulative effects. Beyond these two main points, the question of the dosage arose. A part of time has been dedicated to this question that remains crucial for having the best dose-reponse relationship when applying tDCS protocols. All these points are resumed below.

5.1 The promise of concurrent tDCS protocol

After having detailed the work carried out during this PhD, we will synthesize the knowledge and findings of our studies and compare them with the literature that has evolved since our first experimentation started during the Master year. First, according to Hebb's theory (Hebb, 1955), reinforcement is possible only if neurons fire together and tDCS is only a neuromodulation technique without being able to induce AP. Therefore, in order to develop neuroplasticity, it is necessary to use a task, a motor task in our case. This research work has been positioned on the premise that a protocol coupling motor task and cerebral stimulation by anodal tDCS is more advantageous than other traditional protocols. Regarding the preliminary study conducted (Muthalib et al., 2016), the effects of tDCS-task coupling were measured both during task execution and immediately afterward. The main new finding of this first study was a significant reduction in bilateral SMC activation (based on smaller HHb_{\min} values) for a similar motor behavior (i.e., a constant rate of a finger sequence opposition task) in the online and offline conditions compared to baseline. Although O_2Hb_{\max} increased significantly only when HD-atDCS was active for the stimulated left SMC, we have considered that changes in O_2Hb were likely contaminated by anodal HD-tDCS induced local

skin blood flow changes in the vicinity of the HD-tDCS electrodes. However, the NIRS instrumentation used (i.e., continuous wave NIRS) makes it possible to capture changes other than those located only in the superficial layers. Indeed, in a comparative study with a time domain (TD) NIRS, it was reported that CW- and TD- fNIRS showed a similar time course in the stimulated left SMC over the 10 min of HD-atDCS. The TD-fNIRS replicated the time course of NIRS-derived parameters in the cortical layer of the stimulated left SMC, but the magnitude of changes were much smaller than those observed at the superficial layer (Muthalib et al., 2015). Changes in HHb are considered less affected by skin blood flow changes (Kirilina et al., 2012) and we found less variability in HHb responses during the five trials of the SFO task than with O₂Hb responses. Therefore, we propose that HHb may be a more reliable marker of HD-tDCS induced effects on task related cortical activation.

The findings of smaller bilateral SMC HHb_{min} values during the SFO task in the online and offline conditions compared to baseline levels could be related to a greater efficiency of neuronal transmission (Holland et al., 2011) in the bilateral SMC (i.e., less synaptic input for the same neuronal output) that reduced SFO task-induced regional blood flow and thus produce smaller changes in fNIRS-derived HHb in the bilateral SMC. Furthermore, since the effect of HD-atDCS on SFO task related SMC activation was similar for both the online and offline conditions, we suggest that synaptic neuroplastic modifications are necessary to induce these motor task-related reductions in SMC activation. One possible reason for the reduction in SMC activation could be related to neurotransmitters. Several studies have highlighted that atDCS leads to a reduction in GABA with little to no significant changes in glutamate (Kim et al., 2014; Stagg et al., 2011a). The decrease in GABA concentration could be the cause of this facilitation by limiting the amount of inhibition (Iversen and Johnston, 1971). The more important facilitating effects when atDCS stimulation is added to the motor task are probably attributable to greater synaptic efficacy in the entire neural network engaged simultaneously through the gating mechanism. This reinforces the idea that atDCS may act more on the reduction of the inhibition than on the increase of the excitation which is only a consequence of the modification of the E / I balance (Levinson and El-Husseini, 2005). Moreover, the decrease in the GABA concentration accompanying atDCS should lead to a lesser need for glutamate and energy, in particular to synthesize glutamine into glutamate at the astrocyte level (Watkins, 2000).

This reduction of SMC activation reported in our first pilot study is appealing when regarding the brain activation related to the level of athletes. In a fMRI study, Naito and Hirose (2014)

have highlighted less activation for the top level of professional football players compared to other players and other sports during foot movements (Fig. 20). The possibility to decrease cortical oxygenation by coupling motor task and atDCS could be in favor to increase efficiency in the networks involved in task, while several years of practice are needed. The question of the acceleration of learning with online atDCS may find some clarifications in neural correlates, but efficiency of behavioral modifications have to be assessed to validate the use of tDCS during motor task. For sport application, it is necessary to remain humble because the performance is well known to be multifactorial and the dynamic aspect of game actions limits the scope of laboratory results.

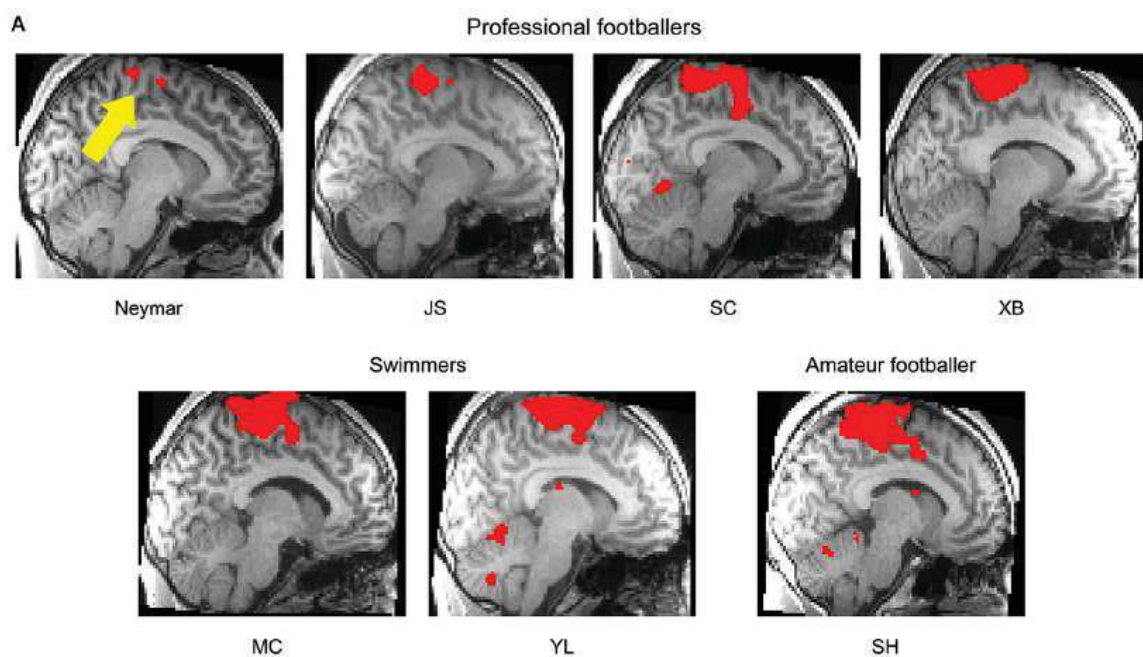


Figure 20 **Cerebral activity in medial-wall motor regions during foot movements for sport participants of different levels** (Naito and Hirose, 2014). Red represent the voxels with a greater activity than voxel-wise threshold. The size of medial-wall activity was smallest in Neymar's brain (yellow arrow). The largest activity was reported for amateur footballer and swimmers.

Despite the attempt of a focal stimulation to the left SMC by anodal 4x1 HD-tDCS, the effects on motor task-related cortical activation were bilateral, probably because intervening in one part of a distributed neural network system has effects on many nodes in the system (Lang et al., 2005). It should also be noted that we found the same effect on bilateral SMC activation during SFO movements with the left and right hands. Although it would have been more expected to observe a difference in ipsilateral and contralateral SMC activation between the

left and right hands, evidence exists from recent studies that unilateral tDCS intervention on the SMC can have bilateral effects (Hendy and Kidgell, 2014; Roy et al., 2014).

For instance, protocols using online atDCS, where the motor task is performed during the stimulation, has greater facilitative effects on motor performance/learning than if the motor task is performed after the stimulation (i.e., offline atDCS) (Stagg and Nitsche, 2011). These greater facilitative effects of online atDCS on motor performance/learning are likely due to enhanced synaptic efficacy in the simultaneously engaged neural network through a “gating” mechanism (Ziemann and Siebner, 2008). Despite the lightening of the physiological mechanisms related to gating as the removal of a magnesium block on post synaptic NMDA receptors, resulting in stronger NMDA receptor-mediated postsynaptic responses by increased intracellular calcium entry (Moriyoshi et al., 1991), there are still many cellular approaches to be carried out. The recent works conducted by the team of Bikson reported for example that cathodal DCS enhanced LTP in apical dendrites while anodal DCS enhanced LTP in basal dendrites. Both anodal and cathodal DCS reduced LTD in apical dendrites (Kronberg et al., 2017). From the same perspective, they reported that opposing polarization of soma and dendrite may have a synergistic effect for anodal stimulation, increasing the driving force of synaptic activity while simultaneously increasing spiking probability at the soma (Lafon et al., 2016). These findings promote the fact that tDCS is a modulator rather than an inducer and so reinforce the necessity to couple tDCS with motor task.

One of the advantage of using tDCS during motor task (online protocol) is the more homogeneous hemodynamic response across subjects compared to other conditions (i.e., offline and sham protocols) (Fig. 21). Indeed, all participants had an increased cortical oxygenation in post conditions only when the tDCS had been coupled to atDCS. In the two other sessions, the results were more disparate with increases, decreases and stagnations. Note that this way to represent the data is more informative with individual responses (Weissgerber et al., 2015).

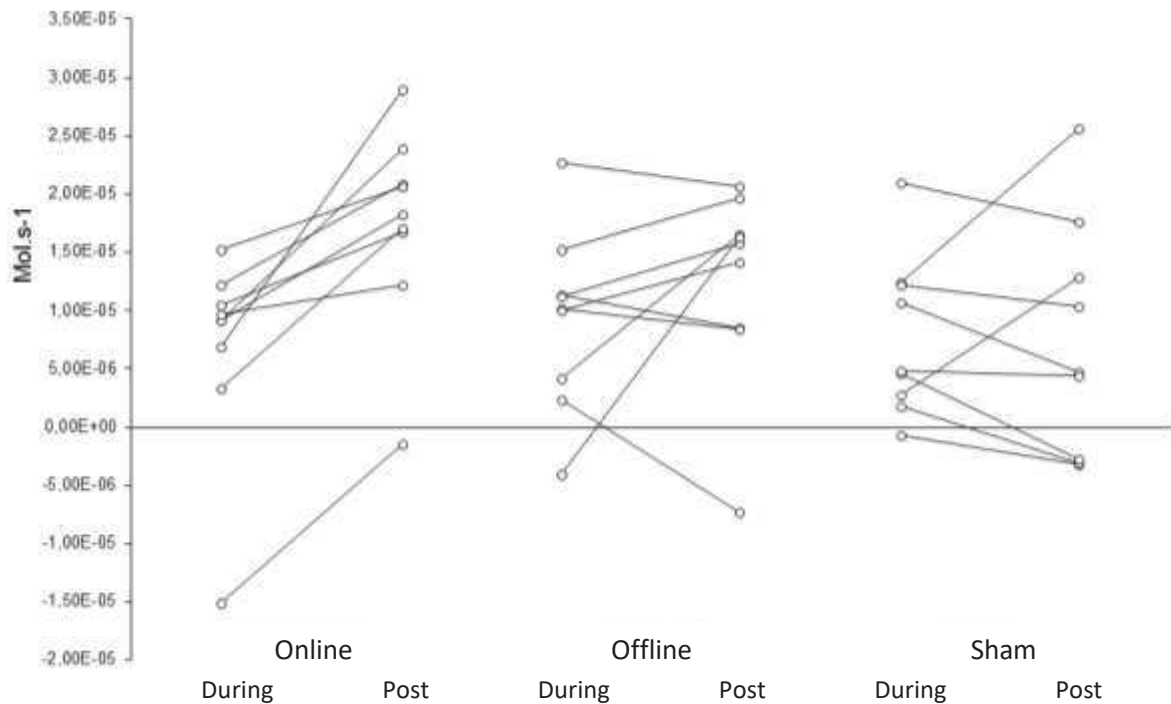


Figure 21 **Changes in the cortical oxygenation response measured by fNIRS from during (tDCS and finger task, online effect) to post (after tDCS, offline effect) epochs.** Participants (n=9) underwent three different tDCS protocols. A simple finger sequence opposition task was used. Findings obtained from the study 2 (chapter 4)

During the motor task, neuronal networks are activated for the production of the movement. Kronberg et al. (2017) showed in an animal study that without activation of the networks, the effects of tDCS were less. These results can be applied to human. It is possible to support this conclusion. In Fig. 15, there is a significant difference between the slope ($F(2,16)=3.970$, $p=0.040$, $\eta^2p=0.332$). *Post hoc* analysis revealed with Bonferroni correction a steeper slope for the online than the sham protocol ($p=0.042$). An increase in the slope between During and Post means a large activation related to modifications of the E / I balance, which is likely a hallmark of neuroplastic rearrangements. Beyond the mechanisms engendered by the tDCS, what is important comes from the similar response patterns of all participants. This result suggests that coupling motor task and atDCS uniformizes the impact of the latter and in fact may reduce the variability of these effects.

Overall, current works showed that the timing of the application of the tDCS and the motor task is a crucial parameter for optimizing the effects of tDCS on motor performance and motor learning. If finally the inhibitory synapses would be more impacted by atDCS then it is even more appropriate to take an interest on conditioning, and in particular the polarity of the stimulation during this phase.

5.2 Priming effects of tDCS

The results of our first study reported, among others, a significant decrease in cerebral activity during the motor task - atDCS coupling with respect to the basal state followed by a significant delayed increase in cerebral activity 30 min later. This shape reinforces the advantage of adopting a conditioning phase with respect to the observed time course of changes. A conditioning operating on the synaptic activity carried out before the tDCS protocol coupled with the motor task appears as a second promising approach in order to optimize the facilitating effects of tDCS on both performance and motor learning. Unfortunately the results are as too often heterogeneous for cathodal stimulation. Lang et al. (2004) reported for 1 mA an inhibitory effect. Batsikadze et al. (2013) corroborated this finding for 1 mA, but reported that with 2 mA opposite effect occurred with an increase in MEP. With the same intensity (i.e., 2 mA) Wiethoff et al. (2014) went deeper in the analysis and revealed that 41% of the participants had an inhibitory profile after 10 min of stimulation while the remaining 59% was a facilitatory profile. Taken together, the conclusion can go in different direction knowing that some researchs argued for higher intensities (Liebetanz et al., 2009; Nitsche and Bikson, 2017).

Anyway the recent studies of Christova et al. (2015) and Fujiyama et al. (2017) aimed to optimize online atDCS effects on enhancing motor performance/learning by applying a novel ctDCS priming protocol. Priming ctDCS protocol could harness homeostatic metaplastic mechanisms. TMS parameters (MEP, ICF and SICI) were assessed in the aforementioned studies. In both Christova et al. (2015) and Fujiyama et al. (2017) studies, priming with ctDCS (1 mA during 15 min and 1.5 mA during 10 min, respectively) reduced cortical excitability (reduced MEP amplitude and ICF) and increased cortical inhibition (increased SICI) after the ctDCS session. These findings suggest likely a reduced post-synaptic activity in the activated neural network. Based on the BCM model, this ctDCS-induced reduction in

post-synaptic activity would be expected to reduce the modification threshold for LTP-like plasticity during subsequent online atDCS, and thus further enhance performance. We lack knowledge on the ability of the nervous system to “rebound” after a decrease in excitability and further studies using single unit recording (see Fig. 2) have to be carried out. This would ensure that changes in the primary sensory cortex indicated in the BCM model and based on visual cell reactions are transferable to the motor aspects.

An important tDCS parameter that requires further investigation is the influence of the time delay between priming and tDCS application on homeostatic metaplasticity and its effects on motor performance/learning (Karabanov et al., 2015). Similarly to the well-recognized effect of overcompensation at the muscular level depending on the necessary rest time, we could envisage an influence of conditioning at the cortical level. A consensus exists at present on hypotheses that have not been verified when the excitability is decreased in contrast to positive or anodal conditioning. A few studies have investigated the effects of altering the delay between repeated tDCS applications of the same polarity on cortical excitability (Bastani and Jaberzadeh, 2014; Fricke et al., 2011; Monte-Silva et al., 2013) and motor performance/learning (Bastani and Jaberzadeh, 2014). However, no clear evidence of the optimal delay time period could be ascertained from their respective priming tDCS protocols. Christova et al. (2015) considered a 10 min delay between ctDCS and online atDCS to be sufficient to allow homeostatic metaplastic mechanisms to take hold. But it is still not known if a shorter or longer time delay between priming ctDCS and online atDCS would differentially modulate homeostatic metaplasticity and motor performance/learning. We (Muthalib et al., 2016) have previously postulated a non-homeostatic approach of priming with atDCS immediately before online atDCS to further facilitate the neuroplastic effects of online atDCS. We reason that sub-threshold neuronal membrane depolarization induced by atDCS has an intensity- and time-dependent effect to strengthen synaptic efficacy (Nitsche and Paulus, 2001). The results reported in chapter 4 are not totally in line with the two previous studies (Christova et al., 2015; Fujiyama et al., 2017). At the end of the 3-days training and for the first day of retention, priming (i.e., atDCS and ctDCS) lead to higher results compared to trial 1 in motor performance, however they were not superior to sham. Likewise two after, ctDCS priming IP value were higher than trial 1 without superiority to atDCS priming and sham (see Fig. 19). In a perspective of clinical application, the statistic could be presented differently with the score changes in %. Indeed, the increase from trial 1 to trial 55 (i.e., the last trial of the first day of retention) was of 49%, 71% and 45% for atDCS, ctDCS and sham, respectively. From trial 1 to trial 60 (i.e., the last trial two weeks after

training), the increase was of 47%, 64% and 51%. These results for practitioners are relevant especially with the task chosen that allow to quickly reach the relative “ceiling” levels. tDCS priming or “warm down” concept could be replicated with pathological population and also sportmen for whom a slight advantage can make it possible to win the bet.

In conclusion, priming tDCS protocols are promising ways to optimize tDCS facilitatory effects on motor performance/learning, and have relevance from a neuroergonomic standpoint. Nevertheless, future studies are necessary to determine the optimal polarity and timing of tDCS applications to modulate neuroplasticity and enhance performance in clinical, sports, and real-world settings.

5.3 Dosage considerations for tDCS

It is always complicated to optimize the stimulation protocols (Brunoni et al., 2016). For the purpose of augmenting motor skills, tDCS is usually applied to scalp overlying M1 with a current intensity of 1-2 mA over 10-20 min duration. Very recently two leaders in the neuromodulation field argued to extend the parameter range for tDCS until 4 mA (Nitsche and Bikson, 2017). Most research groups have used a conventional electrode montage of two large (7 cm x 5 cm) rectangular rubber-sponge electrodes with the anode electrode placed on the M1 and return electrode on the supraorbital region (Nitsche and Paulus, 2000) or extracephalic region such as the shoulder (Muthalib et al., 2013). However, the imprecise understanding of the specific neurophysiological changes induced by scalp-applied electric fields limits the current efforts to understand its precise mechanisms of action. Consequently, tDCS parameters and montage are commonly applied uniformly among subjects without consideration for anatomical and physiological differences between individuals, which may account for partly the variability of responses to tDCS that was recently reported in the literature (Li et al., 2015; Wiethoff et al., 2014). This is a growing concern among researchers as the number of tDCS studies increases and reproducibility is an important concern (Berryhill et al., 2014; Jacobson et al., 2011). In order to circumvent the limitations for directly measuring the tDCS electric field, studies have attempted to optimize tDCS applications using computational modeling of current flow between the electrodes in order to predict brain regions where the tDCS current passes through or directly engages. Although modeling approaches have been applied to derive optimal electrode montage and current dosage for tDCS (Kessler et al., 2013; Turski et al., 2017), the estimates of tDCS current distribution remain theoretical and await experimental validation. Therefore, in order to

optimize potential applications of the tDCS to enhance motor and cognitive performance, there is a critical need to identify a neurophysiological correlate of the electric field spatial distribution from the scalp-applied current. Within this context, neuroimaging methods can be used to provide information about the brain-tissue effects of the tDCS electric fields when measured in a resting-state during (Muthalib et al., 2015; Zheng et al., 2011) and/or after (Amadi et al., 2014; Sood et al., 2016) neurostimulation. Since the strength of the electric field diminishes exponentially with distance from the electrode (Sood et al., 2016), the larger fNIRS O₂Hb values found within the spatial boundary of the 4x1 HD-tDCS electrodes compared to outside (Muthalib et al., 2017) would suggest that there was a stronger electric field distribution in the stimulated hemisphere, more specifically inside the square formed by the electrodes. It is interesting to note that the sham session in our study also induced a numerically larger increase. This indicates that sham HD-atDCS (2 mA current applied for 1.5 min duration, including 30 s ramp up/down) induces scalp skin blood flow increases that are spatially bound to the 4x1 HD montage and outlasts the period of stimulation. These sham tDCS findings corroborate with a recent study (Hoshi, 2016) that showed increased skin blood flow changes (erythema) within the boundaries of the scalp attached conventional (25cm²) rubber/sponge electrodes after both atDCS (2mA for 30min duration) and sham tDCS (2 mA current applied for 1.5 min duration); but the extent of the erythema with sham was significantly lower than HD-atDCS. Based on these results and those from Nikolin et al. (2017) who reported that sham may alter neuronal function, future researches have to be carried out on both the dosage, but especially by focusing on the true effect of sham condition. Indeed, the effects of tDCS being systematically compared to sham, it is necessary to ensure that only the effects of the motor (or cognitive) task are evaluated in this condition. If this is not the case, then the effects of tDCS are underestimated. Although at a group level O₂Hb results showed in our study (Muthalib et al., 2017) a significant influence of the spatial distribution of HD-atDCS effects, at a single subject level there were differences in the time course of O₂Hb in the left stimulated hemisphere region of interest between the subjects. These differences are most likely due to anatomical and physiological differences between subjects, which are known to be a contributor to variability in tDCS effects. However, a within-subjects comparison showed that the O₂Hb in the stimulated hemisphere was consistent between two atDCS sessions at rest (Muthalib et al., 2017). Therefore, fNIRS may provide an indirect measure of the HD-tDCS-induced electric field. The benefits of a neurophysiological (fNIRS) correlates to the HD-tDCS electric field compared to modelling are that different HD-tDCS current intensities, durations and montages can be compared on

the same subject and between subjects on a targeted cortical region. This will allow for optimizing HD-tDCS parameters individually. This is based on the assumption that the spatial distribution of the fNIRS O₂Hb changes overlying the targeted cortical region provides a surrogate marker of the spatial distribution of the electric field applied to the scalp.

The indications provided by the NIRS make it possible to apprehend the hemodynamic variations which inform only partially and indirectly on the mechanisms underlying the use of the tDCS which impacts both the neuronal activity and the extracortical haemodynamic activity. Therefore, combining neuroimaging techniques (fNIRS, fMRI and EEG) with tDCS is needed. However, analytical methods still raise many questions. A collaborative research work undertaken in this PhD allowed to integrate the use of Kalman filtering to report on the evolutions related to the effects of the tDCS (Sood et al., 2016). Nevertheless, beyond the autoregressive character of the model relating to mathematical transformations linked to the non-stationarity of cerebral signals (EEG and fNIRS), the explanations remain based on hypotheses. The combination of neuroimaging methods could be used with every time promises and caveats (Bergmann et al., 2016; Fabiani et al., 2014; Thut et al., 2017; Woods et al., 2015).

5.4 Limitations

Finally, before examining the perspectives of this thesis work, let us underline some limits. As often in neuroscience, the results are dependent on tasks (Saucedo Marquez et al., 2013; Shirota et al., 2017). Yet, the results of the study 1 (chapter 3) based on a simple motor task that did not require learning led to better identification of the effects of tDCS when associated or dissociated from the task. However, fNIRS limits the explanations to metabolic aspects and does not make it possible to determine the impact of the tDCS/motor task coupling on the level of excitability variations. Does the slightest activation during T1 (i.e., SFO task with online, offline or sham) due likely to less GABA play a crucial role in motor cortical plasticity and so in human motor learning (Floyer-Lea et al., 2006; Ziemann et al., 2001)? Or is it related to more glutamate?

Therefore, an interpretation of the phenomena at a larger scale could have promoted the motor task / tDCS coupling (Russo et al., 2017). When focused on the dynamics of activation patterns (see Fig. 16), questions on the time course of activation emerge such as:

has the peak values been reached? Will the return to baseline have the same dynamics? The answers remain unresolved.

A lot of precautions have been taken, particularly in the treatment of the signal, but shall not prevent the large variability inherent in the complexity of the human brain and the state (i.e., resting state or occupied) in which the subject is located. The inter-individual variability is usually a serious concern to prove concept that the tDCS is a reliable tool. Current evidence does not allow for a Level A (defined effectiveness) recommendation for any medical applications as indicated by the International Federation of Clinical Neurophysiology (Lefaucheur et al., 2017). The variability was pointed out in the MEP measurement of the tDCS effects (Horvath et al., 2014a). What alternative is available to measure excitability? The use of resonance magnetic spectroscopy would allow a more precise illumination GABA and glutamate concentrations, however this technique remains confidential as to the complexity of the methods still to be developed. Also, the use of TMS that provides information on the level of excitability contaminates the interpretations, due to the sending of magnetic pulse that interacts with the effects of tDCS. The same questions may arise for fNIRS. The results presented at the second brain stimulation conference in 2017 suggest that fNIRS O₂Hb time course appears to be a reliable marker for identifying atDCS-induced hemodynamic effects in the stimulated sensorimotor cortex region at rest (Besson et al., 2017). However future researches are needed for considering diffuse correlation spectroscopy techniques (Giovannella et al., 2016). It will be possible to obtain a precise local measurement of the CBF which is a biomarker of brain health and function (Durduran and Yodh, 2014).

5.5 Future directions

The possible applications of this work require closer contact with practitioners. The transfer to clinical applications, in particular neuro-rehabilitation seems quite obvious. The use of rTMS is constraining because the patient must remain motionless during the stimulation sequence. This could leave room for the use of the tDCS whose effects are magnified when coupled to the performance of the task itself as reported by our first results. Concretely, protocols with tDCS could be carried out with the help of clinicians with stroke patients in order to speed up recovery of motor functions. The interest of our results in optimizing the effects of tDCS is to advocate also prior to any learning a reduction in brain

activity. This "warm down" which seems counter-intuitive for many practitioners is, on the contrary, an additional asset to prolong the effects of rehabilitation or training. Once again, new researches based on more ecological approach assessed with behavioral variables are needed to convince the practitioners to adopt these protocols. Also with healthy population, the same application could be set up with the perspective to speed up the learning.

Based on a neuroergonomic approach with binding tasks due to the information to be collected and processed, the links between tDCS and mental load will be investigated through the recent obtained funding from the ANR MODEX project (Modulation and Evaluation of the Mental Flexibility of the Risk Systems Operator) led by the Institut Supérieur de l'Aéronautique et de l'Espace (Toulouse). This will involve identifying brain networks of mental flexibility and proposing new training modalities in the field of risk management using, for example, multimodal intervention (i.e., cognitive-motor task coupled to the tDCS).

Finally, recent works have investigated functional connectivity in regard to the modifications of the cortical networks from haemodynamic signals (Anwar et al., 2016; Vergotte et al., in press). TDCS modifies the functional organization of the brain that is characterized by an optimal compromise between integration (i.e., areas connected to become statistically interdependent) and segregation (i.e., areas tend to organize into independent clusters) (Sporns, 2011). These changes have to be reported in order to inquire clinicians and trainers the better way to manage training. The possibility to use fNIRS for functional connectivity has already been proved (Medvedev, 2014). However, there is no study on functional connectivity when tDCS is applied on M1. This lack will be filled soon. Preliminary own results indicated that tDCS appears to decrease the exchange of information on the stimulated area.

6

Conclusion

Chapter 6: Conclusion

From human assistance to the development of human performance, "human enhancement" is and will be a continuing concern. Advances in cerebral stimulation appears in this perspective as an opportunity. The interest aroused by the results of the first work has *de facto* led to a phase of disillusionment, however the enthusiasm around the tDCS has not slowed down with the will to demonstrate concept regarding this technique. The work carried out during this thesis allowed to defend the notion of coupling between motor task and tDCS, and this, through an original approach by the use of the spectroscopy in the near infrared. Behind the idea that any exogenous aid must be accompanied by an endogenous solicitation under penalty of disappearing function is the notion of neuroplasticity. The hypothesis that functional targeting leads to a delayed increase in cerebral activation with respect to dissociation has been verified. This implies an increased reorganization of the networks involved to carry out the same task. To paraphrase Maupertuis, when a change occurs in nature, the quantity of action employed in this change is always the smallest possible. This increase in fact suggests that this increase is aimed at greater efficiency in the future when this task is carried out.

If the notion of repetition is no longer discussed to increase motor performance, the concept of conditioning remains confidential. For the BCM model, reducing the cortical excitability prior to the action would be more conducive to engendering a better retention of the learning. The results obtained during the second study showed the dominance of the anodal and cathodal priming without yielding any significant difference with the placebo condition. There are therefore still studies to be carried out to tune the parameters of this conditioning in order to further magnify the effects of the tDCS.

All the results of our work made it possible to clarify the supremacy of the coupling on the dissociation and also the interest of modulating the cortical excitability before coupling motor task and tDCS. Of course, other studies are awaited in order to better identify the neuroplastic mechanisms involved, notably by combining neuroimaging techniques, but also other methods of analysis will have to be developed in order to understand the connectivity of the various brain areas as well as a wider time scale to explain the dynamics of the phenomena.

7

Résumé substantiel en français

Résumé substantiel de la thèse en français

Coupler tâche motrice et stimulation transcranienne à courant continu pour un meilleur résultat

Introduction

De tout temps, l'être humain a aspiré à améliorer son quotidien. Le « human enhancement », pour les Anglo-saxons, a pris une place telle qu'un nouveau champ scientifique est apparu. Il s'agit de la neuroergonomie qui couronne les efforts du Prof. Raja Parasuraman qui souhaitait que les chercheurs développent des théories et des savoirs permettant de faciliter le quotidien de tous. De nombreuses techniques permettent aujourd'hui du fait des avancées technologiques de fournir une aide par assistance à l'homme dans ses tâches quotidiennes. Parmi elles, certaines (exemple des Interfaces cerveau machine) ont porté leur attention sur la commande centrale, autrement dit le cerveau. Dans ce domaine, les connaissances ne cessent de croître afin de mieux rendre compte des mécanismes neurophysiologiques lors de tâches fonctionnelles, notamment en ayant recours aux techniques de neuroimagerie. L'ensemble de ces techniques a mis à jour la complexité du fonctionnement du cerveau qui reste difficile à « mesurer ». Pour autant, le monde de la recherche s'efforce de « capturer » l'activité cérébrale inhérente au paradigme proposé pour explorer certains processus cognitivo-moteurs, tout en restant prudent sur les interprétations des premiers résultats disponibles. L'usage grandissant de techniques non-invasives de stimulation cérébrale concourt à ce but d'appréhender le fonctionnement du cerveau, notamment en venant le perturber. Le développement des techniques de stimulation cérébrale a conduit à considérer davantage la stimulation transcranienne à courant continu (tDCS) qui est devenue une technique de neuromodulation très en vogue. Les premiers travaux de neuromodulation utilisant la tDCS dans sa version contemporaine datent du début des années 2000. La tDCS s'est rapidement répandue du fait de son faible coût, de sa facilité apparente d'utilisation et de sa transportabilité. Elle permet d'envoyer un courant électrique continu à faible intensité (1-2 mA) à travers deux électrodes positionnées sur le cuir chevelu dans le but de moduler l'excitabilité corticale. La polarité anodale pour l'électrode active permet d'augmenter cette excitabilité alors que la polarité cathodale engendre une réduction de cette

excitabilité. Plusieurs paramètres dont l'intensité, la durée de stimulation, le placement et la taille des électrodes sont à prendre en compte pour que la séquence de stimulation soit la plus efficace possible. Dans le cas de tâches motrices, la notion du timing d'application de la tDCS apparaît aussi comme un élément majeur, si ce n'est primordial pour optimiser les effets potentiels apportés par la stimulation. Le rôle de la tDCS est davantage un modulateur qu'un inducteur de plasticité cérébrale ce qui renforce la nécessité de coupler l'action motrice à la tDCS. Aussi la persistance des effets de la tDCS est une marotte dès lors que l'on s'intéresse à l'apprentissage moteur. La neuroplasticité, c'est-à-dire la modification des réseaux neuronaux se traduit notamment par une réorganisation corticale objectivable par des techniques de neuroimagerie indirectes combinées à la tDCS, comme la spectroscopie dans le proche infrarouge (NIRS). La théorie développée par Bienenstock, Cooper et Munro (BCM) soutient l'existence d'un seuil de dépolarisation neuronal adaptatif qui régulerait la capacité à modifier positivement ou négativement l'ensemble des processus de consolidation ; ce seuil étant déterminé par l'activité présynaptique. Il apparaît qu'une réduction de l'activité présynaptique préalablement à l'accomplissement d'une tâche (i.e., conditionnement) augmenterait les effets potentialisateurs au niveau de la plasticité alors qu'une augmentation de l'activité présynaptique lors du conditionnement réduirait la capacité à conserver l'information. Dans cette thèse, les changements immédiats et retardés de l'activité cérébrale induits par tDCS couplés ou non à ceux de la tâche motrice ont été évalués par le biais de la NIRS dans une première étude alors que la rétention, et par conséquent les changements à moyen terme ont été inférés à partir d'un index de performance motrice dans une seconde étude. Ces études visaient à (i) examiner les modifications de l'activité cérébrale en couplant tâche motrice et tDCS en modalité anodale lors d'une session unique, puis à (ii) évaluer l'influence du type de conditionnement (i.e., passif ou actif avec polarité anodale ou cathodale en tDCS) lors de sessions répétées tâche motrice-tDCS anodale sur le gain des réponses motrices.

Ainsi, le but général de cette thèse était de quantifier les réponses corticales et comportementales suite au couplage tâche motrice-tDCS anodale chez des sujets sains afin de mieux discriminer les effets apportés par la tDCS. Les hypothèses émises portaient sur l'impact plus important de protocoles ayant recours à un couplage tâche motrice-tDCS sur l'activité cérébrale de la région motrice. Au regard du conditionnement, la polarité cathodale devrait engendrer un surcroît de performance à court terme (< 24h) et aussi à moyen terme (< 15 jours) par rapport à la polarité anodale.

Revue de littérature

Les différentes techniques de neuroimagerie permettent d'identifier les aires cérébrales actives lors de tâches motrices, ainsi que leurs relations. L'activité électrophysiologique révélée par l'électroencéphalographie ou la magnétoencéphalographie apporte une information sur l'activité des potentiels post-synaptiques avec une haute résolution temporelle. L'activité hémodynamique tissulaire étudiée par la tomographie par émission de positons, l'imagerie par résonance magnétique ou encore la NIRS renseigne sur la réponse métabolique induite par l'activité neuronale. Une augmentation de l'activité neuronale engendre une augmentation du flux sanguin cérébral régional, ainsi que du volume sanguin et dans le même temps impacte à la hausse la consommation d'oxygène au niveau cérébral. Concernant la NIRS, ces phénomènes se traduisent par une augmentation de la concentration d'oxyhémoglobine (O₂Hb) concomitante à une légère diminution de la concentration de désoxyhémoglobine (HHb). L'apport de ces différentes techniques de neuroimagerie a permis d'identifier la temporalité ainsi que l'intensité d'activation cérébrale lors de tâches motrices, notamment manuelles. Il est reconnu lors d'une tâche rythmique de doigts que le cortex moteur primaire est le siège de la plus importante activité cérébrale, quand bien même le cortex somatosensoriel primaire est activé préalablement.

La répétition de mouvements conduit à une réorganisation du système nerveux central. Ce phénomène est appelé neuroplasticité et permet d'optimiser les ressources par rapport aux contraintes d'une tâche à réaliser. Différentes formes de plasticité coexistent : synaptique ou « non-synaptique », intrinsèque ou structurelle. La plasticité synaptique renvoie à l'efficacité des synapses, alors que la plasticité intrinsèque est relative à l'excitabilité des neurones. La plasticité structurelle renseigne de l'évolution neuroanatomique du réseau neuronal. Au niveau qualitatif, on peut noter des effets potentialisateurs ou dépresseurs. Dans le premier cas, cela se traduit par un renforcement du réseau alors que dans le second cas, cela conduit à une diminution de l'efficacité de ce réseau. Au niveau temporel, la plasticité est envisagée à court ou à long terme, sachant que les modifications à court terme sont un préalable pour obtenir des effets à long terme. On parle dans ce cas de potentialisation (LTP) et de dépression (LTD) à long terme. Si l'activité post-synaptique est élevée alors l'apprentissage est de type LTP et *a contrario*, une activité post-synaptique faible conduit à un apprentissage de type LTD. Au-delà de ce mécanisme dichotomique et au regard de la complexité du système, la notion de métaplasticité qui intègre la dimension temporelle en renvoyant à « l'histoire » des connexions synaptiques permet de mieux appréhender certains processus

sous-jacents. Le modèle développé par Bienenstock, Cooper et Munro (BCM) présuppose l'existence d'un seuil de dépolarisation adaptatif afin de faire coexister les effets LTP et LTD. Ce seuil étant adaptatif, une stimulation induisant une activité présynaptique forte et prolongée entraînera une hausse du seuil qui limitera l'apprentissage de type LTP. Inversement, une activité faible, mais prolongée, augmentera la sensibilité du réseau de par la diminution du seuil et la facilitation du renforcement synaptique. Toujours au regard du large panel de situations auxquelles l'être humain peut être confronté, il s'agit de rendre compte de la notion de « gating » qui est un processus relatif à l'adjonction d'une stimulation exogène durant une tâche. L'activation de ce mécanisme non-homéostatique engendre une diminution de l'efficacité des circuits inhibiteurs intracorticaux. Il s'agit d'une désinhibition qui pourrait renforcer la neuroplasticité.

L'usage de la tDCS pourrait impacter favorablement les connexions neuronales eu égard à deux situations qui demandent à être investiguées davantage : le couplage avec la tâche motrice et le conditionnement de l'activité synaptique précédant l'usage de la tDCS. Cette technique de stimulation cérébrale consiste à appliquer une faible intensité (1-2 mA) de courant en continu à travers des électrodes placées sur le cuir chevelu dans l'objectif de moduler *in fine* l'excitabilité cérébrale. Lors d'une stimulation dite anodale ou positive, l'excitabilité corticale évaluée par la mesure des potentiels évoqués moteurs augmente. *A contrario*, une stimulation dite cathodale ou négative engendre généralement une diminution de l'excitabilité corticale. Cette neuromodulation via tDCS facilite, en polarité anodale, la génération de potentiels d'action sans pour autant le déclencher comme le permet la stimulation magnétique transcrânienne (TMS). Si une partie des mécanismes neurophysiologiques inhérents à la tDCS commence à être caractérisée, il reste encore nombre de recherches à mener, notamment du fait des différents paramètres à prendre en compte lors d'une stimulation exogène.

Les effets de la tDCS sur l'excitabilité corticospinale apparaissent non linéaires, notamment concernant l'intensité du courant. L'amplitude et la persistance des effets induits par tDCS dépendent pour partie de la durée de stimulation. Néanmoins, une durée trop prolongée peut provoquer des effets inverses voire délétères au but recherché. La taille des électrodes impacte la densité de courant induite par tDCS. Le placement de ces mêmes électrodes conduit également à des effets plus ou moins ciblés et intenses, bien que de nouveaux montages (utilisation de multiples électrodes ou HD-tDCS) permettraient de palier à ces effets. Le nombre de sessions de tDCS influence aussi la persistance des effets tout

comme le niveau d'activité cérébrale en fonction que le participant soit dans un état de repos ou en train d'effectuer une tâche. Si la plupart des études ont été menées avec l'application de tDCS avant la tâche à effectuer, il apparaît que les résultats seraient supérieurs lors du couplage tâche motrice-tDCS lors de sessions d'apprentissage. Pour autant, très peu d'études se sont intéressées à comparer couplage *versus* dissociation de l'application de la tDCS avec la tâche motrice alors que le protocole avec couplage présenterait le bénéfice de cibler davantage les réseaux activés. Très récemment ont été investigués les effets sur la performance du type de conditionnement par tDCS suivi d'une période courte d'entraînement moteur où la tâche motrice était couplée à une tDCS anodale. Les résultats prometteurs liés à un conditionnement de polarité cathodale renforcent la réflexion menée lors de la genèse de cette thèse sur l'intérêt d'altérer l'excitabilité corticale préalablement à l'action motrice.

Par conséquent, les deux études expérimentales réalisées dans le cadre de cette thèse avaient pour ambition d'apporter des connaissances nouvelles sur les réponses corticales lors de l'usage du couplage (étude 1) et des précisions sur les évolutions comportementales lors du conditionnement (étude 2) dans l'application de protocoles de tDCS en polarité anodale.

Contributions personnelles

Étude 1 : Augmentation retardée de l'activité du cortex sensorimoteur induite par le couplage tâche motrice - stimulation anodale transcrânienne à courant continu

Le ciblage fonctionnel résultant d'un protocole couplage stimulation anodale/tâche motrice est prometteur pour magnifier la plasticité du cortex sensorimoteur (SMC) comparativement à la dissociation tâche motrice et tDCS. Le but de cette étude était de comparer l'évolution des modifications hémodynamiques révélées par spectroscopie dans le proche infrarouge (NIRS) du SMC lors de protocoles avec couplage ou dissociation entre tâche motrice et tDCS. L'hypothèse retenue était que le couplage tâche motrice-tDCS anodale impacterait davantage l'activation cérébrale comparativement à la dissociation. Dans cette étude randomisée, neuf sujets adultes sains droitiers ont participé à trois sessions (couplage, dissociation, placebo) séparées d'une semaine.

Les variations hémodynamiques ont été mesurées par NIRS au pourtour du site de stimulation (SMC gauche controlatéral au mouvement) lors d'une tâche rythmique de doigts

d'une minute entrecoupée d'une minute de repos et répétée cinq fois alternativement pour chaque main. Les mesures ont été reproduites à trois reprises lors de chaque séance, à savoir à un état basal (T0), pendant la tâche (T1) et trente minutes (T2) après la tDCS en anodal.

La fréquence de mouvements n'était pas significativement différente entre les trois temps (T0, T1, T2), ni entre les trois sessions (couplage, dissociation, placebo). Les variations hémodynamiques relatives à la tâche motrice ont montré que comparativement à la condition placebo, la session avec couplage tâche motrice-tDCS entraînait une augmentation significative ($p < 0,001$) de l'activation du SMC à T2. Concernant la condition avec dissociation, il a été rapporté une tendance ($p = 0,05$) pour l'augmentation d'activation du SMC à T2 comparativement à la condition placebo.

En conclusion, cette étude a souligné que le couplage tâche motrice-tDCS anodale est plus efficace pour moduler l'activation du SMC relative à une tâche motrice dans un délai de trente minutes. Cette augmentation pourrait représenter plusieurs mécanismes neuroplastiques qui modifient l'équilibre excitation/inhibition au niveau du SMC. Le couplage stimulation anodale-tâche motrice pourrait influencer sur les processus de consolidation de la mémoire motrice.

Étude 2 : La répétition de sessions de traçage couplées à une stimulation anodale transcrânienne à courant continu déplace temporairement le plateau des performances.

Le couplage tDCS-tâche motrice et l'amorçage de tDCS sont proposés pour avoir des effets cumulatifs sur la performance motrice. Cependant, l'impact de la polarité du tDCS pour l'amorçage reste éclaircir. L'objectif de cette étude était d'améliorer davantage l'apprentissage et la rétention d'une tâche de traçage circulaire avec de multiples sessions tDCS anodale (atDCS) avec un conditionnement cathodal (ctDCS) comparativement à un conditionnement anodal et sham. Dans une étude à double aveugle simulée contrôlée et randomisée, 22 participants séparés dans 3 groupes indépendants ont subi pendant 3 jours consécutifs des sessions d'entraînement sur stimulation anodale à haute définition (HD-atDCS) ciblant le cortex sensorimoteur gauche, précédées d'une mesure de référence (jour 0) et suivi de deux tests de rétention (jour 4 et jour 18, un jour et deux semaines après l'entraînement, respectivement). Une tâche de traçage circulaire de 5 essais de 1 minute entrecoupée par 1 min de repos a été effectuée au temps pré, pendant et après pour chaque séance d'entraînement

et au temps pré pour le jour 0, 4 et 18. La performance motrice a augmenté significativement à la fin de l'entraînement ($p < 0,001$) pour les conditions de conditionnement a-tDCS et c-tDCS, mais pas pour sham par rapport au premier essai. Cette augmentation a aussi été relevée au jour 4 pour a-tDCS ($p=0.05$) et pour c-tDCS au jour 4 et 18 ($p < 0.001$). Le conditionnement par tDCS a été bénéfique pour l'amélioration de la performance pendant l'entraînement et pour le premier jour de rétention, sans pour autant être supérieur à sham. Cependant, les effets cumulatifs du conditionnement et de la répétition n'ont persisté que pour le conditionnement c-tDCS lors du second test de rétention deux semaines après l'entraînement.

Discussion générale

Conformément à une approche neuroergonomique, la performance lors de tâches fonctionnelles peut être facilitée par des techniques de neuromodulation non invasives, telles que la tDCS avec polarité anodale. Cependant, des paramètres et des protocoles de stimulation robustes doivent être développés pour appliquer la tDCS afin d'améliorer la performance motrice dans des populations saines et chez les patients. Dans cette perspective, ces travaux de thèse ont été positionnés sur le postulat que le protocole de couplage entre tâche motrice et stimulation cérébrale par tDCS anodale est plus prometteur que d'autres typologies de protocole plus traditionnelles. Une étude préliminaire^[1] antérieure aux travaux de thèse avait rapporté une réduction significative de l'activation bilatérale du SMC pour une réponse motrice similaire (i.e., fréquence de mouvement constante pour une tâche rythmique d'opposition des doigts de la main dominante) à la fois lors du couplage tâche motrice-tDCS anodale et aussi immédiatement après la stimulation comparativement à une condition sham. Ce résultat pourrait être lié à une plus grande efficacité synaptique au niveau des SMC. La diminution de la concentration de GABA pourrait être la cause de cette facilitation en limitant la quotité de l'inhibition. Ces effets facilitateurs plus importants lorsque la stimulation tDCS anodale est couplée à la tâche motrice sont probablement attribuables à une efficacité synaptique plus importante dans l'ensemble du réseau neuronal engagé simultanément grâce au mécanisme de «gating». Cela renforce l'idée que l'on agit davantage avec une stimulation

[1] Muthalib M, **Besson P**, Rothwell J, Ward T, Perrey S. Effects of Anodal High-Definition Transcranial Direct Current Stimulation on Bilateral Sensorimotor Cortex Activation During Sequential Finger Movements: An fNIRS Study. *Adv Exp Med Biol* 2016;876:351–9. doi:10.1007/978-1-4939-3023-4_44.

tDCS-a sur la réduction de l'inhibition que sur l'augmentation de l'excitation qui n'est qu'une conséquence de la modification de la balance excitation/inhibition. De plus, la diminution de la concentration de GABA devrait engendrer un besoin moindre de glutamate et de fait un besoin moindre d'énergie pour notamment synthétiser la glutamine en glutamate au niveau de l'astrocyte. À côté de cela, il s'agit de s'intéresser au cerveau dans son ensemble lors de la réalisation de tâche motrice, car malgré la tentative de stimulation focale sur le SMC controlatéral au mouvement avec un montage 4x1 tDCS-a-HD, les effets sur l'activation corticale associée étaient bilatéraux, probablement parce que l'intervention sur une partie du système du réseau neuronal distribué a des effets inter et intra hémisphère de par les nombreux nœuds du système. Dans l'ensemble, les travaux actuels montrent que l'interaction du moment de l'application de la tDCS et de la tâche motrice est un paramètre crucial pour optimiser les effets de la tDCS sur les performances motrices et l'apprentissage moteur. Si finalement les synapses inhibitrices seraient davantage impactées par la tDCS anodale alors il convient plus encore de s'intéresser à la notion de conditionnement, et notamment la polarité de la stimulation lors de cette phase. En effet, les protocoles actuels privilégient un conditionnement tDCS anodale.

Les résultats de notre étude principale ont rapporté entre autres une diminution significative de l'activité cérébrale lors du couplage tâche motrice/tDCS anodale par rapport à l'état basal suivie d'une augmentation significative retardée lors de la répétition de cette même tâche. Cela renforce l'intérêt d'adopter une phase de conditionnement vis-à-vis de la dynamique observée. Un conditionnement opérant sur l'activité synaptique réalisée préalablement au protocole tDCS couplé avec la tâche motrice apparaît comme une seconde approche prometteuse en vue d'optimiser les effets facilitateurs de la tDCS aussi bien sur la performance que l'apprentissage moteur. Les résultats des quelques études ayant intégrées plusieurs séquences de stimulation lors d'une même session montrent la difficulté à déterminer une période inter-stimulation favorable. S'il est bien reconnu l'effet de surcompensation au niveau musculaire, en fonction du temps de repos nécessaire, alors il devrait en être de même pour le conditionnement au niveau du cortex. Un consensus existe actuellement à partir d'hypothèses qui n'ont pas été vérifiées lorsque l'on diminue l'excitabilité au contraire du conditionnement positif ou anodal. Pour autant, les études engagées sur ce thème ont toujours procédé sans que la tDCS soit couplée à la tâche et quand bien même ce serait le cas, alors se poserait la question des perturbations induites par la mesure de TMS.

Nos travaux ont permis de souligner que le couplage apparaissait comme une nécessité pour magnifier les effets de la tDCS alors qu'une phase de conditionnement était un moyen de développer davantage les performances motrices au long cours. Cependant, il ne faut pas limiter à ces deux aspects les moyens d'optimiser les protocoles de tDCS. Il existe aussi un avantage à répéter les séquences de stimulation. Si la répétition de tâches motrices spécifiques est reconnue comme un élément clé dans la réhabilitation post AVC notamment afin que persistent les modifications comportementales attendues, qu'en est-il lorsque la tDCS est surimposée ? À trop vouloir solliciter l'individu avec l'ajout d'une stimulation tDCS anodale lors de l'exécution d'une tâche motrice, on pourrait s'attendre à des mécanismes de protection au niveau des tissus biologiques. La modification de la balance GABA/glutamate liée à une durée de stimulation trop importante conséquence de stimulations répétées peut conduire à une excitotoxicité et provoquer une apoptose neuronale. Pour autant, les résultats des différentes études cliniques sont encourageants, car ils rapportent des améliorations fonctionnelles significatives. D'ailleurs, certaines équipes sollicitent encore davantage les participants en rajoutant la réalité virtuelle reconnue pour accélérer la neuroréhabilitation. Les effets de ces différentes techniques semblent par conséquent cumulatifs. Néanmoins, il s'agira de mieux circonscrire les modifications induites par la tDCS au niveau neurophysiologique avant de pouvoir systématiser et individualiser les protocoles de réhabilitation.

La compréhension imprécise des changements neurophysiologiques spécifiques induits par les champs électriques appliqués au cuir chevelu limite les efforts actuels pour comprendre les mécanismes d'action précis de la tDCS. Il demeure toujours compliqué d'optimiser les protocoles de stimulation. Les paramètres (intensité de courant, durée) et le type de montage (simple ou multiples électrodes) de la tDCS sont couramment appliqués uniformément pour tous les sujets sans prendre en considération les différences anatomiques et physiologiques entre les individus, ce qui peut expliquer en partie la variabilité des réponses à la tDCS. Afin de contourner les limites de la mesure directe du champ électrique induit par tDCS, la modélisation computationnelle du flux de courant entre les électrodes a été utilisée afin de prédire les régions cérébrales impactées par le courant induit par la tDCS. Bien que des approches de modélisation aient été appliquées avec satisfaction pour connaître la quantité de courant induite et ainsi définir le montage optimal, les estimations de la distribution de courant dans les tissus avec application de tDCS restent actuellement théoriques et attendent une validation expérimentale. Il apparaît essentiel d'identifier des corrélats neurophysiologiques de la répartition spatiale du champ électrique à partir du

courant appliqué au cuir chevelu. Dans ce contexte, les méthodes de neuroimagerie peuvent être utilisées pour fournir des informations sur les effets des champs électriques de la tDCS sur les tissus cérébraux. La variation du débit sanguin régional pendant la stimulation tDCS est une façon d'identifier les effets des champs électriques de la tDCS sur les tissus cérébraux actifs. Dans ce contexte, nos travaux ^[2-3] ont permis de montrer en exploitant la combinaison des techniques fNIRS-tDCS (montage 4x1HD) des différences significatives entre les hémisphères stimulé et non stimulé, mais aussi entre des régions de l'hémisphère stimulé. La distribution spatiale de courant par tDCS plus contrainte avec un type de montage dit focal, pourrait permettre de déterminer individuellement des plages d'intensité de courant optimale, ainsi qu'une durée de stimulation adaptée dans des environnements naturels pour améliorer les performances motrices et aussi cognitives. D'autres métriques provenant des techniques de neuroimagerie doivent être développées pour pouvoir guider individuellement les paramètres d'application tDCS.

Les indications fournies par la NIRS permettent d'appréhender les variations hémodynamiques qui ne renseignent que partiellement et indirectement sur les mécanismes sous-jacents à l'usage de la tDCS qui impacte tout autant l'activité neuronale que l'activité hémodynamique extra-corticale. Dès lors combiner les techniques de neuroimagerie apparaît comme incontournable, d'ailleurs il existe de plus en plus d'études combinant NIRS et électroencéphalographie. Pour autant, les méthodes d'analyses posent encore bien des questions. Une collaboration ^[4] a permis d'intégrer le filtre de Kalman pour rendre compte en direct des évolutions liées aux effets de la tDCS. Pour autant, au-delà du caractère autorégressif du modèle relatif aux transformations mathématiques liées à la non-stationnarité des signaux cérébraux, les explications restent basées sur des hypothèses. Malgré tout, la combinaison de ces deux techniques de neuroimagerie permettra d'examiner la robustesse de celles-ci étant donné que les variations d'oxygénation et de volume sanguin reflètent un autre aspect de l'activité neuronale.

[2] **Besson P.**, Vergotte G, Muthalib M, Perrey S. Test-retest reliability of transcranial direct current stimulation-induced modulation of resting-state sensorimotor cortex oxygenation time course. *Brain Stimul* 2017;10. doi:10.1016/j.brs.2017.01.186.

[3] Muthalib M, **Besson P.**, Rothwell J, Perrey S. Focal Hemodynamic Responses in the Stimulated Hemisphere During High-Definition Transcranial Direct Current Stimulation. *Neuromodulation Technol Neural Interface* 2017. doi:10.1111/ner.12632.

[4] Sood M, **Besson P.**, Muthalib M, Jindal U, Perrey S, Dutta A, et al. NIRS-EEG joint imaging during transcranial direct current stimulation: online parameter estimation with an autoregressive model. *J Neurosci Methods* 2016. doi:10.1016/j.jneumeth.2016.09.008.

Enfin, la variabilité inter individuelle est un frein pour faire la preuve de concept que la tDCS est un outil fiable. Les preuves actuelles ne permettent pas de faire une recommandation de niveau A (efficacité définie) pour quelconques applications médicales. Gageons que les améliorations directement visées par la tDCS seraient plus prégnantes lors du couplage tâche motrice-tDCS, mais cela nécessite comme indiqué par la Fédération internationale de neurophysiologie clinique des études avec un nombre de participants assez élevé (i.e., au moins 25 sujets ayant reçu un traitement actif et autant ayant reçu un traitement sham) et surtout avec comme souligné en amont l'obligation d'avoir des sessions répétées.

Les applications possibles de ces travaux de thèse sont relativement nombreuses. Le transfert vers des applications cliniques, notamment la neuro-réhabilitation semble assez évident, alors que les applications sportives, plus particulièrement dans l'aide à la performance restent confidentielles. L'intérêt de nos résultats dans l'objectif d'optimiser les effets de la stimulation cérébrale est de préconiser le couplage tâche motrice-stimulation cérébrale, et aussi de proposer préalablement à tout apprentissage une réduction de l'activité cérébrale. Ce « warm down » qui paraît contre-intuitif pour nombres de praticiens est au contraire un atout supplémentaire pour prolonger les effets de la rééducation ou de l'entraînement.

Le terme de stimulation cérébrale est sciemment utilisé, car en sortant du laboratoire pour s'inscrire dans la complexité inhérente à la vie médicale, sportive ou courante, d'autres techniques pourraient se révéler plus efficaces. En effet, les situations plus écologiques engendrent davantage de bruit soulignant une attention toute particulière à l'usage de la stimulation transcranienne de bruit aléatoire (tRNS) qui mérite d'être investiguée. L'intérêt porté au ciblage fonctionnel avec la tDCS lors de cette thèse prend encore plus de sens et pourrait être davantage bénéfique. L'ajout de bruit au niveau du cortex moteur renforcerait encore davantage le réseau activé lors de la tâche et ainsi permettrait une réorganisation plus efficace et persistante de ce réseau.

La complexité inhérente aux tâches écologiques dans un environnement dynamique nécessite aussi d'appréhender plus en profondeur la contribution des stimuli. La planification du mouvement nécessite l'intégration des données provenant des aires somatosensorielles et visuelles. À ce propos, la notion de connectivité définie comme la dépendance statistique entre deux aires cérébrales devra à terme être une grille d'analyse dans nos futurs travaux. D'ailleurs, les liens entre tDCS et charge mentale seront prochainement investigués grâce à

l'obtention du financement du projet ANR MODEX (Modulation et Évaluation de la flexibilité mentale de l'opérateur de systèmes à risques) piloté par l'Institut Supérieur de l'Aéronautique et de l'Espace. Il s'agira d'identifier les réseaux cérébraux de la flexibilité mentale et à proposer de nouvelles modalités d'entraînement dans le domaine de la gestion des systèmes à risques à l'aide par exemple d'intervention multimodale (i.e. tâche cognitivo-motrice couplée à la tDCS).

Conclusion

De l'assistance à la personne au développement de la performance humaine, le « human enhancement » est et restera une préoccupation continue. La stimulation cérébrale apparaît dans cette optique comme une opportunité. L'intérêt suscité par les résultats des premiers travaux a *de facto* conduit à une phase de désillusion. Pour autant l'engouement autour de la tDCS n'a pas ralenti avec la volonté de faire une preuve de concept concernant cette technique. Les travaux menés durant cette thèse ont permis de défendre la notion de couplage entre tâche motrice et tDCS, et ce, à travers une approche originale de par l'utilisation de la spectroscopie dans le proche infrarouge. Derrière l'idée que toute aide exogène doit être accompagnée d'une sollicitation endogène sous peine de voir disparaître la fonction se profile la notion de neuroplasticité. L'hypothèse que le ciblage fonctionnel résultant du couplage tâche motrice-stimulation anodale conduit à une augmentation retardée de l'activation cérébrale par rapport à la dissociation a été vérifiée. Cela suppose une réorganisation accrue des réseaux impliqués pour la réalisation de la même tâche. Pour paraphraser Maupertuis, lorsqu'il arrive quelque changement dans la nature, la quantité d'action employée pour ce changement est toujours la plus petite qu'il soit possible. Cette augmentation laisse de fait à penser que cette augmentation vise à une plus grande efficacité future lors de la réalisation de cette même tâche.

Si la notion de répétition n'est plus discutée pour augmenter les performances motrices, celle de conditionnement reste confidentielle. Pour autant au regard du modèle BCM, réduire l'excitabilité corticale préalablement à l'action serait plus propice à engendrer une meilleure rétention de l'apprentissage. Les résultats obtenus durant la seconde étude ont montré la dominance du priming cathodale sur le priming anodale sans pour autant rapporter de différence significative avec la condition placebo. Il reste par conséquent encore des études à

mener pour ajuster les paramètres de ce conditionnement en vue de magnifier davantage les effets de la tDCS.

L'ensemble des résultats de nos travaux ont permis de clarifier la suprématie du protocole avec couplage comparativement à celui avec dissociation, et aussi l'intérêt de moduler l'excitabilité corticale avant de coupler tâche motrice et tDCS. Bien sûr, d'autres études sont attendues afin de cerner davantage les mécanismes neuroplastiques mis en jeu, notamment en combinant les techniques de neuroimagerie. En outre, d'autres méthodes d'analyse seront à développer afin d'appréhender la connectivité des différentes aires cérébrales impliquées ainsi qu'une échelle temporelle plus large pour expliquer la dynamique des phénomènes suscités.

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9

Appendices

Appendix a) **Neuromodulation devices**

Appendix b) **Near infrared spectroscopy**

Appendix a) Neuromodulation devices

The enthusiasm for neuromodulation intervention remained constant from the past. To the evocation of the notion of neurostimulation, the general public has an enthusiastic depiction. A lot of progress has been done from several decades to improve the technology as evidenced by the advertising brochures represented in Fig. A1. In addition there is a growing interest in NIBS techniques over these last 10 years (Fig. A2).

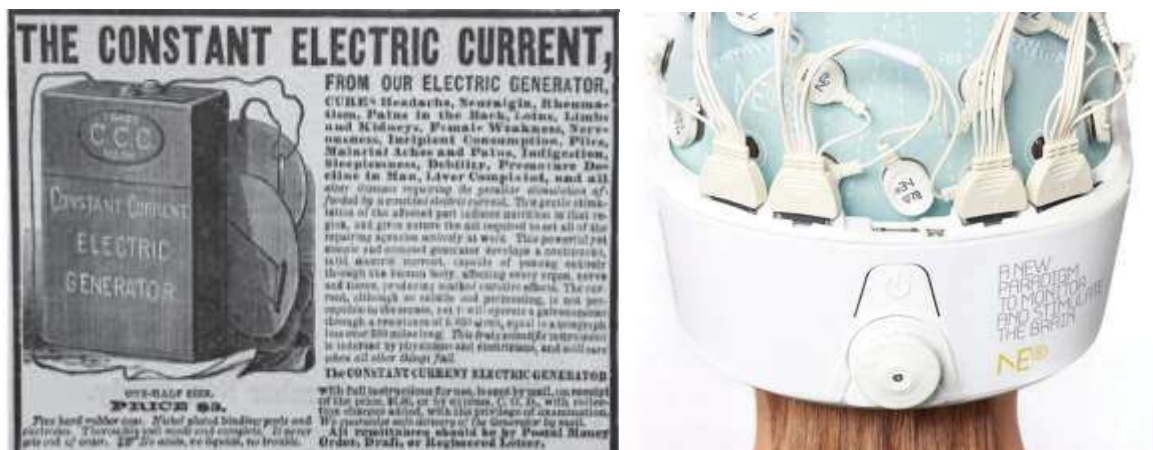


Figure A1 **Evolution of stimulation tools.** On the left side, an advertisement for a model of medical batteries (1881, Frank Leslie's Newspaper, Bakken Ephemera Collection) (Wexler, 2017) and on the right side a cap that allows transcranial electrical stimulation and simultaneous EEG recording (Starstim® R32).

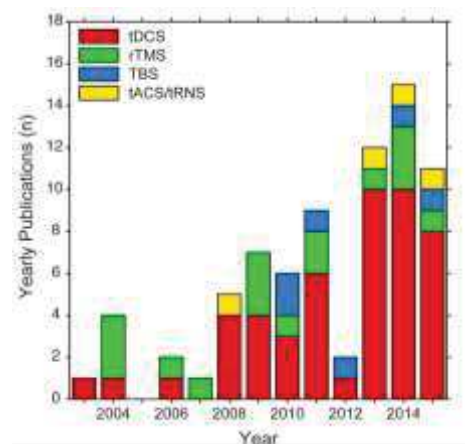


Figure A2 **NIBS publications (2003-2015) related to enhancement of motor learning or memory formation** (Buch et al., 2017). Over years, tDCS showed the greatest increase of publications.

However, a lot of research is still needed to fully understand the underlying mechanisms and real influences and side effects of such electrical stimulation over the brain. Moreover, Stagg (2005) proposed a very nice title in a perspective article: “Stimulation is never quite as simple as it seems”, a wide of stimulation techniques can be used. Within the framework of this thesis, all techniques with invasive features as deep brain stimulation were not considered in this appendix. Only NIBS techniques have been included (and used for some of them). There are two main categories depending if either magnetic or electrical field provides the source of stimulation. Single pulse TMS serves mainly to assess cortical excitability with the evolution of MEP whereas repetitive stimulation aims to induce neuroplasticity. Repetitive TMS (Graef et al., 2016), theta-burst stimulation (Chung et al., 2016), paired associative stimulation (Fratello et al., 2006), quadripulse TMS (Hamada et al., 2007) or controllable pulse shape (Di Lazzaro et al., 2004) are commonly used to this end. But all these techniques are out of our scope, as well as transcranial ultrasound (Tufail et al., 2010) and optical stimulation approaches (Nawashiro et al., 2017).

tES techniques have been declined in 5 categories and are represented chronologically in Fig. A3 (Guleyupoglu et al., 2013):

- 1/ Cranial Electrical Stimulation with ElectroSleep, Cranial Electro-stimulation Therapy, Transcerebral Electrotherapy, and NeuroElectric Therapy;
- 2/ Electro anesthesia with Transcutaneous Cranial Electrical Stimulation and Interferential Stimulation;
- 3/ Electroconvulsive Therapy or Electroshock Therapy with Focal Electrically Administered Seizure Therapy;
- 4/ Direct Current Stimulation with transcranial Direct Current Stimulation (tDCS), Transcranial Micropolarization, transcranial Pulsed Current Stimulation and Galvanic Vestibular Stimulation;
- 5/ Transcranial Alternating Current Stimulation (tACS), transcranial Sinusoidal Direct Current Stimulation, and transcranial Random Noise Stimulation (tRNS).

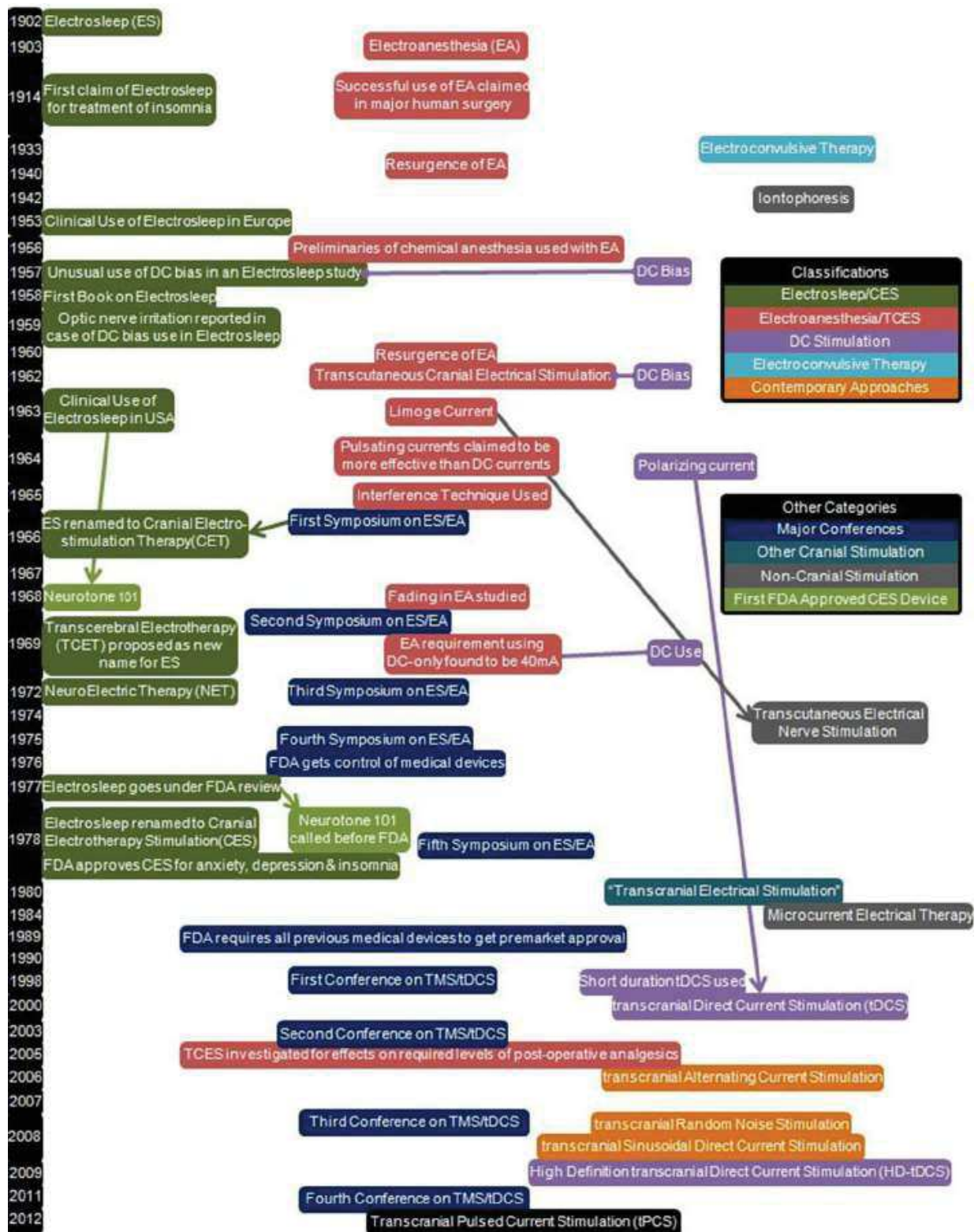


Figure A3 Historical evolution of tES techniques from the beginning of the 20th century (figure 1 in Guleyupoglu et al., 2013).

In the present thesis, we paid a particular attention on the two last categories and more particularly on tDCS, tACS and tRNS.

However, it is important to highlight that these three techniques have not the same interest and scope in the research community and tDCS is still the locomotive with a rate of increase over 10 years in terms of publication; three times superior than tACS and tRNS (Table A1).

Table A1 Evolution of tDCS, tACS and tRNS studies for the last decade.

	2006	2016	Rate of increase
tDCS	35	653	1866%
tACS	16	101	631%
tRNS	11	62	564%

The field of application for tDCS is various (Fig. A4). Interest in ‘Enhancement’ is relatively confidential with only 5% of publications. The major fields are ‘Therapy’ and ‘Investigative’. However, with a very broad vision of the human being, it is possible to combine these 3 domains, because they contribute together to the best being of the individual at short- or long-term, whether healthy or carrying a pathology.

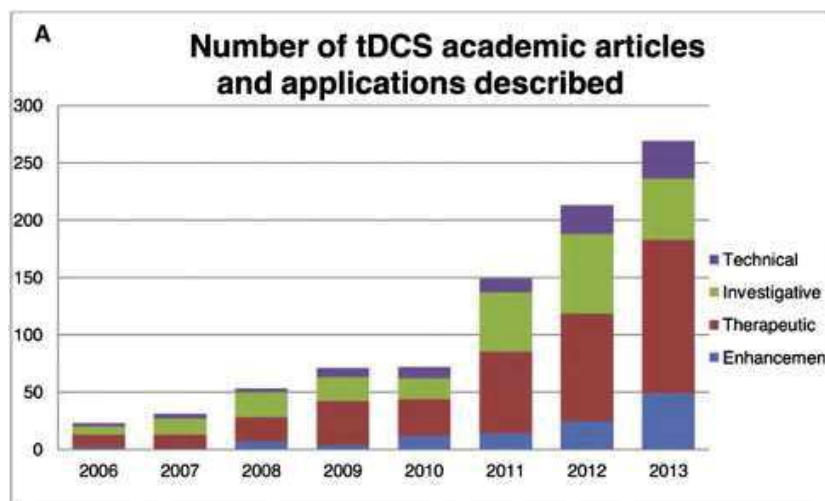


Figure A4 The number of articles and 4 domains of application related to tDCS use (Dubljević et al., 2014)

Whatever the scope of these studies, the results are mostly optimistic for 59.5% compared to the 3.5% being critical; the remaining 37% are more neutral/balanced (Fig. A5). However,

caution should be exercised, since the reproduction of studies is almost never carried out to the dismay of some scientists (see Baker, 2016). Also, it is necessary to have a careful reading of the results by questioning their effect sizes to fully evaluate the results (Zakzanis, 2001).

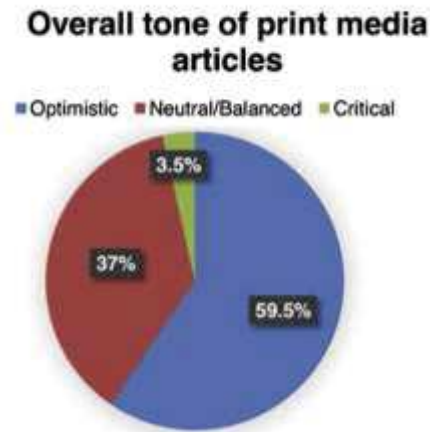


Figure A5 Contribution of the results of the various studies (Dubljević et al., 2014)

Common features

The intensity (1-2 mA) of the current delivered by a battery-driven stimulator is not enough to induce action potential. However, this intensity modulates the spontaneous firing rate and so induces transient changes in corticospinal excitability. A single-pulse TMS elicited muscle response, named MEP, is most commonly used for the assessment of corticospinal neurons activated. NIBS not only alters neuronal activity during the application time (i.e. polarization) but also induces long-lasting alterations depending on the parameters selected. For tDCS, tACS and tRNS techniques the conventional montage is comprised of one active electrode and one return electrode. Note that some variant exists like the HD-tDCS setup as documented previously in this thesis.

A recent study has compared the aforementioned 3 stimulation techniques (table A2) with strictly different waveforms of current delivered (Fig. A6) and reported preliminary findings in their capacity to increase corticospinal excitability (Inukai et al., 2016). The authors used similar stimulation parameters (1 mA, 10 min) with the active electrode (anode) positioned over the left M1 and the reference electrode (cathode) over the contralateral orbit. For tACS, the frequency used was 140 Hz and for tRNS the noise signal contained all frequencies up to half the sampling rate with a maximum at 640 Hz. The results showed an

increase from pre (i.e., baseline condition just before the stimulation) to post stimulation period in MEP amplitudes for the 3 methods but with a larger increase for tRNS that could be considered as the most effective method. Future works with functional targeting are needed to corroborate these first results. Before moving onto the different techniques, it should be noted that the sensations are less regarding tingling and itching for tACS and tRNS as compared to tDCS (Ambrus et al., 2010; Fertonani et al., 2015).

Table A2. **Summary of the main comparison between tDCS, tACS and tRNS** (adapted from Cohen Kadosh, 2014).

	tDCS	tACS	tRNS
Intensity	1 to 2 mA	0.4 to 1 mA	1 mA
Duration	10 to 20 min	5 to 10 min	10 min
Electrode size	16, 20 or 35 cm ²	16 cm ²	16 cm ²
Neuromodulation classification [§]	tES techniques where DC is sustained for greater than 1 minute with amplitude greater than 0.1 mA and no changes in current significantly (>5%).	tES techniques where biphasic sinusoidal AC current is sustained for greater than 1 minute with amplitude greater than 0.1 mA peak-to-peak.	tES techniques in which AC is sustained for greater than 1 minute with a random and constantly changing amplitude greater than 0.1 mA RMS*.
Side effects	Tingling, itching, redness.	Tingling, itching, redness.	Tingling, itching.
Hemodynamic changes	Increased rCBF at rest (Besson et al. 2017). Increased [HbO ₂] and reduced [HHb] for concurrent tDCS (Muthalib et al. 2016).	Resting state BOLD signal not modulated whereas task related was (Vosskuhl et al. 2016).	Alterations of rCBF without affecting CMRO ₂ during cognitive task (Snowball et al. 2013).
Cortical excitability	Increased cortical Excitability with a-tDCS (Boros et al. 2008) and decreased cortical Excitability with c-tDCS (Ardolino et al. 2005).	No changes (Antal et al. 2008).	Increased corticospinal excitability (Terney et al. 2008); Although other studies do not support this finding (Fertonani et al. 2011).

EEG	Increased slow oscillatory activity (3 Hz).	Increased low alpha (8-12 Hz) and high theta (3-8 Hz) activity (Antal et al. 2008).	No changes.
Neurotransmitters	Increased brain-derived neurotrophic factor (BDNF) (Fritsch et al. 2010) and extra synaptic GABA (Stagg et al. 2011) and decreased interaction of glutamate with its receptor (Fritsch et al. 2010).	No known changes.	Possibly activation of glutamate-mediated synapses (Terney et al. 2008).

* equivalent of DC current

§ <https://neuromodec.com/>

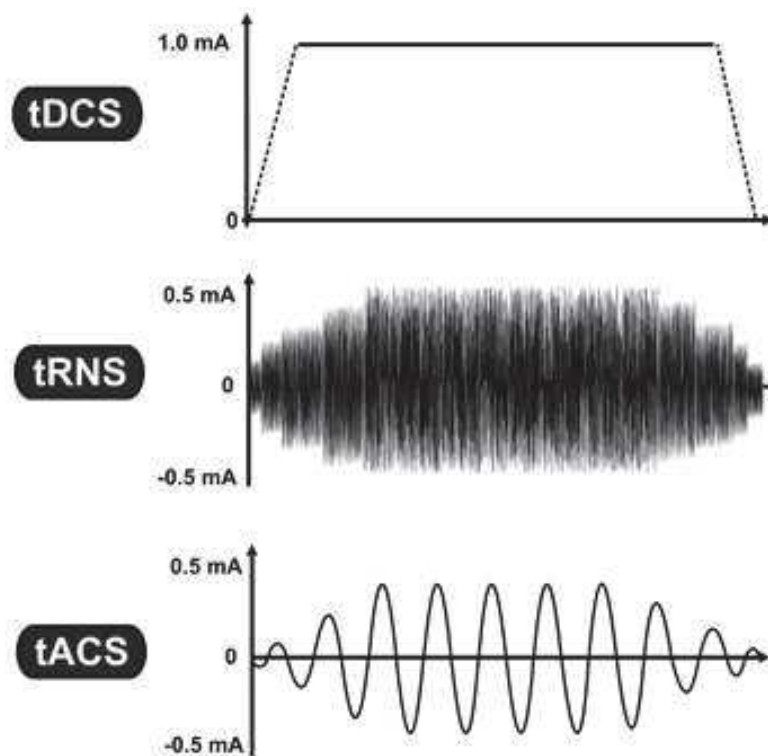


Figure A6 **Current (anodal polarity) waveforms depending on the technique used** (Saiote et al., 2013). tDCS uses constant current whereas tACS and tRNS use oscillatory current (Herrmann et al., 2013)

tDCS

TDCS is the most utilized of the tES techniques. As indicated above, the intensity range is commonly between 1 and 2 mA according to the guidelines and safety recommendations (Antal et al., 2017; Bikson et al., 2016; Charvet et al., 2015; Lefaucheur, 2016; Lefaucheur et al., 2017). In our experimental studies, HD-tDCS setup has been used with a 4x1 montage with electrodes of 8 mm of diameter and a distance of 3 cm between them (Datta et al., 2009). This specific setup based on EEG arrays can be extended to other types of montage (Fig. A7); Based on the MEP changes, 4x1 montage appears to be the most efficient among the different montages tested from 1x1 to 8x1 (Alam et al., 2016).



Figure A7 **Different possibilities of montage for HD-tDCS** (Alam et al., 2016). The first digit represents the number of electrodes return while the second digit represents the number of active electrodes.

However, new types of montage are tested with some encouraging results. In a recent study, Fischer et al. (2017) reported with a so-called multifocal tDCS montage an twice increase in left M1 excitability as compared to traditional tDCS montage. The performance for intensity delivered and focality could be improved by combining HD-tDCS at the scalp level with a transcranial channel as an interface through the skull to the brain as introduced by Wingeier (2007) and used by Seo et al. (2015). Notably the capacity to be more focal with a 4x1 montage has been reported by some studies (Datta et al., 2009; Dmochowski et al., 2011; Muthalib et al., 2017). Furthermore, the focality of the multi electrode montage could impact with greater effects the deeper cerebral layers, particularly corticolimbic network (Ruiz de Lara et al., 2017). Indeed, the high conductivity of the cerebrospinal fluid (CSF) lead to remote tDCS effect (Lang et al., 2005). Even if few studies have compared conventional tDCS to HD-tDCS, the available studies reported for anodal polarity an increase of corticospinal excitability in both amplitude and duration (Kuo et al., 2013) and a better performance for an executive cognitive task (Hogeveen et al., 2016).

tACS

TACS can also alter the subthreshold of the neuronal resting membrane potential (Kuo and Nitsche, 2015). The application of sinusoidal current at a given frequency is assumed to modify the endogenous neural oscillations (Ali et al., 2013; Antal et al., 2008). In higher ranges (1-5 kHz), oscillation interaction is unlikely to occur, but cortical excitability has been suggested (Chaieb et al., 2011). tACS modulates brain oscillations in a frequency-specific manner that can synchronize neuronal network when using the EEG frequency range (0.1-80Hz) (Antal and Herrmann, 2016). tACS applied at a beta frequency (i.e., between 12.5 and 30 Hz) over M1 could increase corticospinal excitability (Feurra et al., 2011) and may also modulate amplitude (Helfrich et al., 2014b), frequency (Fröhlich and McCormick, 2010) or phase/antiphase coherence (Helfrich et al., 2014a) of brain oscillation. The willingness to understand the relations between the brain oscillations and the cognitive functions has allowed the rise of interest in this technique. The application of tACS is interesting in a wide of field which ranges from motor function to lucid dreaming including the study of visual function (Schutter and Hortensius, 2010; Turi et al., 2013; Voss et al., 2014).

The fact to switch the polarity from the anode during the first half of the cycle that becomes the cathode for the second half of the cycle and vice and versa leads to focus on frequency patterns. The range of frequency generally used with tACS (i.e., 0.1 Hz and 80 Hz) includes the EEG frequency range, even if some studies investigated the effects of tACS at 140 Hz and 250 Hz (Moliadze et al., 2010a). The frequency is a crucial parameter as reported by Laczó et al. (2012). As reported in Fig. A8, tACS with high frequencies up to 1, 2 and 5 kHz causes an increase of cortical excitability in M1 during and after 10 minutes of stimulation at 1 mA (Chaieb et al., 2011).

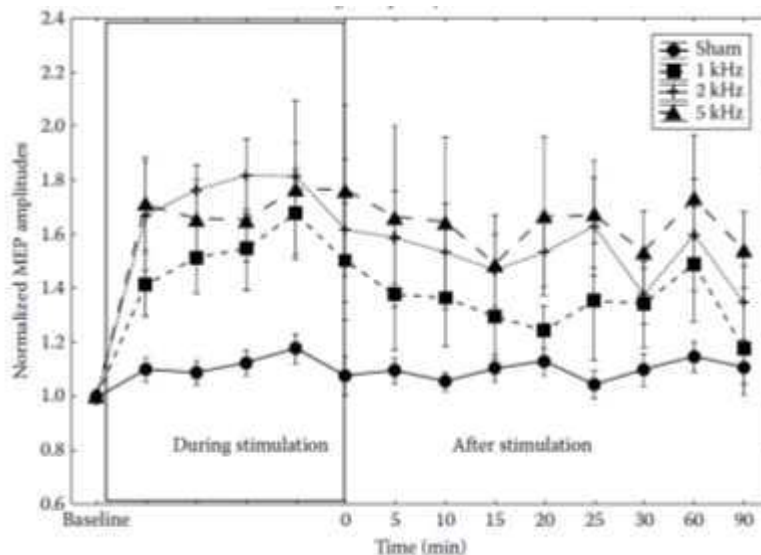


Figure A8 **Time course of cortical excitability of M1 during and after 1, 2 and 5 kHz tACS over M1.** Changes of MEP amplitude is normalized to baseline (Chaieb et al., 2011).

Neuroplastic effects have been showed from high frequency (up to 140 Hz) (Moliadze et al., 2010a, 2012). In addition to the TMS measures, EGG and EMG methods were also used to explain the effects of tACS, more particularly for studying the coherence between oscillatory patterns. The effects of tACS are related to the intensity of the stimulation. Low intensity (0.4 mA) leads to a decrease of motor cortical excitability whereas higher intensity (1 mA) has opposite effects. Lower intensity seems to expose more inhibitory networks than excitatory (Moliadze et al., 2012).

In connection with the topic of this thesis, the timing of application is also important with motor task (Joundi et al., 2012). The effects of tACS are depending on the state of the brain. Like tDCS, different types of montage with more than two electrodes are possible. This is primordial regarding the STDP for anti-phase or in-phase stimulation (Fig. A9) (Vossen et al., 2015). Improvement or worsening of plasticity depends on the phase pattern of tACS (Polanía et al., 2012).

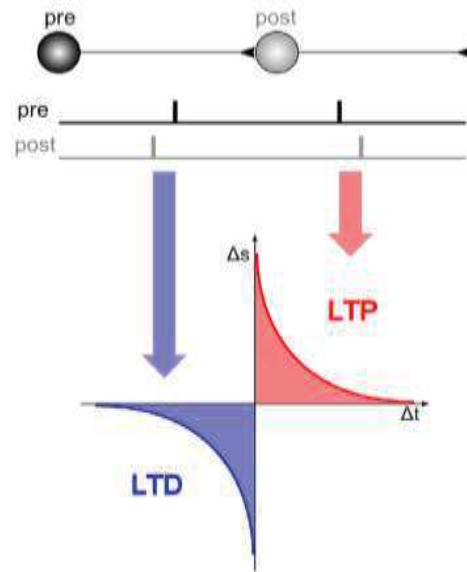


Figure A9 **Spike timing dependent plasticity**: synaptic weights are increased if a post-synaptic potential follows a pre-synaptic spike (LTP). They are decreased if a post-synaptic potential occurs prior to a pre-synaptic spike (LTD) (Zaehle et al., 2010)

The extra parameter, that is frequency in tACS as compared to tDCS leads to a more difficult understanding of physiological mechanisms related to tACS. Similarly to tDCS, tACS studies have described possible remote effects (Ozen et al., 2010; Polanía et al., 2011, 2012; Strüber et al., 2014).

tRNS

tRNS was derived from tACS with the intensity and the frequency of the current varying in a randomized manner. The willingness to desynchronize cortical rhythms in order to restore pathological disorders was the first reason of its development (Terney et al., 2008). The frequencies applied are either the full spectrum (0.1 to 640 Hz) or the high frequency stimulation (101 to 640 Hz). They may follow a Gaussian or bell-shaped curve with zero mean and a variance, for which 99% of all generated current levels are between ± 1 mA. High frequencies are used regarding their capacity to functionally alter excitability of M1 in comparison to low frequency. As reported in Fig. A10, tRNS has an analogous effect to that of atDCS on MEP changes over time; namely, 10 min of tRNS at 1 mA over M1 can have excitatory effect up to 1.5 hour (Terney et al., 2008).

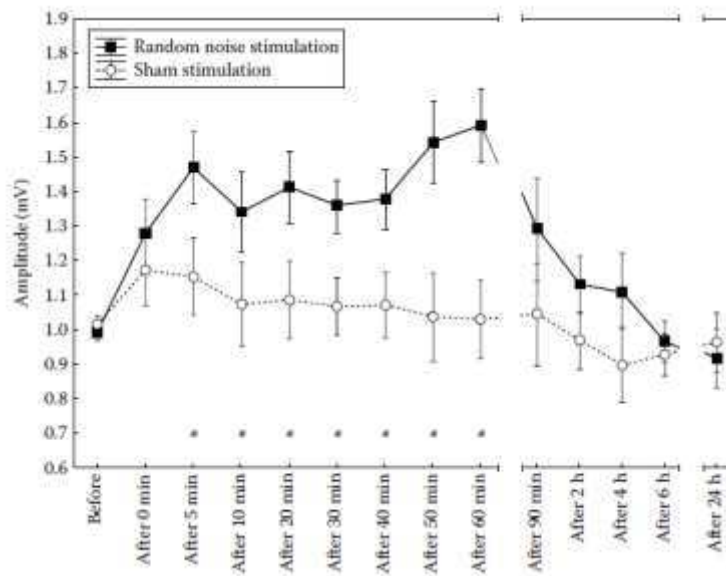


Figure A10 **Time course of tRNS on cortical excitability of M1.** Parameters of stimulation are 10 min random noise (RN) stimulation over M1 at 1 mA compared to sham stimulation (Terney et al., 2008).

tRNS can improve performance of motor learning task (Terney et al., 2008) or visual perceptual learning task (Fertonani et al., 2011). It is expected that adding external noise with tRNS might impact the endogenous noise represented by the signal-to-noise ratio in the central nervous system that could exceed the existing subthreshold activities and so sensitizes sensory processing (Miniussi et al., 2013a; Moss et al., 2004). This extra noise might induce the synchronization of neuronal firing rate and so reduce the amount of endogenous noise (Miniussi et al., 2013a).

Conclusion

The differences between tDCS, tACS and tRNS techniques offer a large spectrum of uses. By covering a broad range of stimulation frequencies, these techniques could be efficient to alter cortical excitability and in turn cognition and motor production with more or less after-effects. The expanding access to these stimulation techniques should ultimately improve functions in everyday life of patients. However, several limitations do apply regarding the variability of the responses to these stimulation techniques. For a regular use in neurorehabilitation, individualization is the next target to achieve. Some studies (Antal et al., 2011b; Lang et al., 2005; Nitsche, 2011; Notturmo et al., 2014; Roche et al., 2011) have reported remote effects of these stimulation techniques. This indicates the rather poor focality of the electrical

stimulation (particularly of tDCS) while highlighting the difficulty to explain those effects. This problem may be on the way to being resolved by combining neurostimulation and neuroimaging techniques (Muthalib et al., 2017). This limitation will probably be solved in the near future principally due to technical improvements as well as the use of new materials especially concerning the electrodes of stimulation that should remove many barriers. Development of stimulation protocols as supported in this thesis remains for the moment another key point. This consideration is shared by all researchers as evidenced by this sentence of Paulus: “The challenge in the future will be to refine and optimize techniques for distinct brain areas, diseases, genetic predispositions, cortical geometry and many more aspects” (Miniussi et al., 2013b). Among other possibilities, concurrent tDCS protocol is a promising way.

Appendix b) Near infrared spectroscopy (NIRS)

In the biological domain of living organisms, the NIRS was first presented by Jobsis (Jobsis, 1977). It was in 1977 that he described in *Science*, the first device for monitoring cerebral oxygenation, relating the intensity of light emitted by lasers or LEDs and that recovered after passing through the brain tissue. It is thus possible to evaluate the variations in hemodynamics and local blood oxygenation of a surface brain area in order to infer its neuronal activity in a non-invasive and non-traumatic manner (Villringer and Chance, 1997).

The first commercial NIRS instrumentation arrived on the market 12 years later with a single channel (Ferrari and Quaresima, 2012). Over the last years, technological evolution has made substantial progress in NIRS technique (Fig. B1). A special issue has been devoted to NIRS in *Neuroimage* "Celebrating 20 Years of Functional Near Infrared Spectroscopy (fNIRS)" (January 2014).

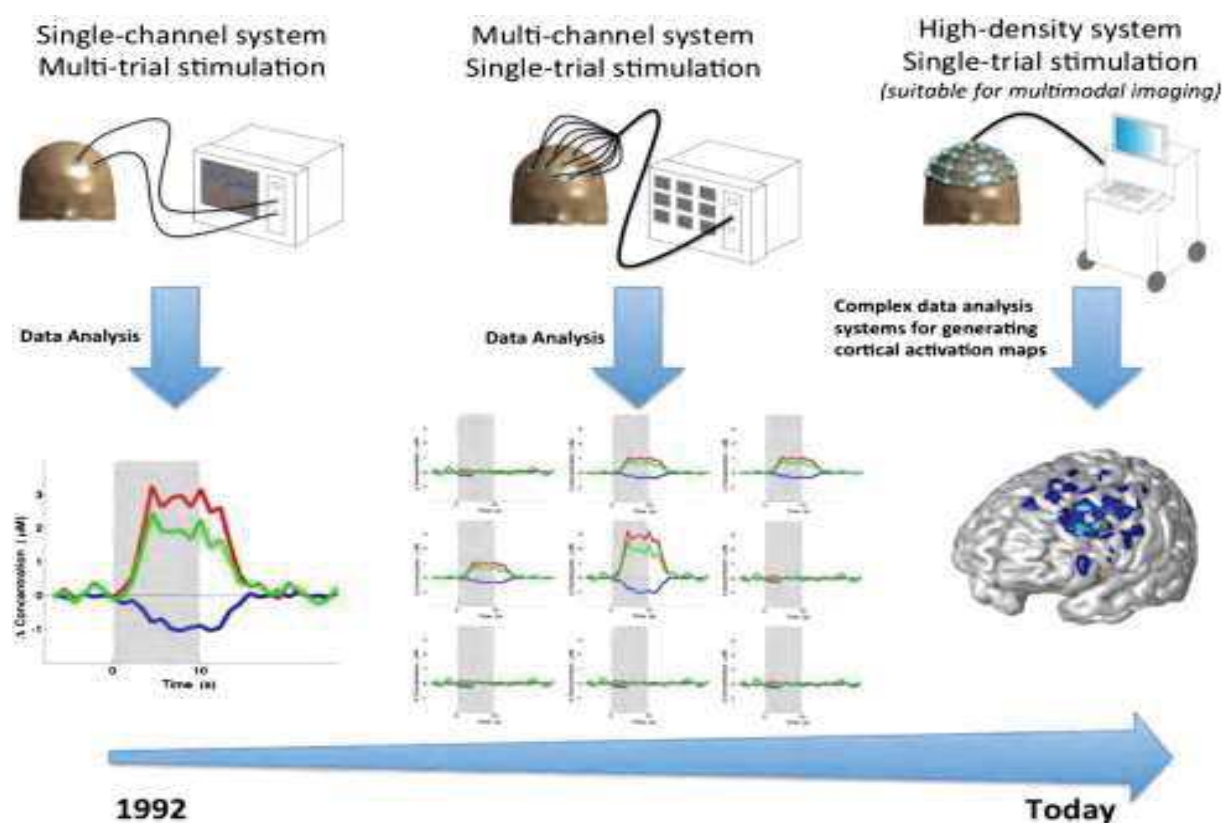


Figure B1 **Evolution of the development of fNIRS instrumentation.** From 1992 with a single-channel system (with low temporal resolution and low sensitivity) until today with high-density systems (Ferrari & Quaresima, 2012).

The NIRS has other advantages beyond being non-invasive: a quality signal-to-noise ratio where the instrumental noise, physiological artefacts can be taken into account by the modified beer-Lambert law (MBLL) (Huppert et al., 2009). The possibility to use such NIRS instrumentation in ecological condition due its capacity to be either portable or wearable. Also, the speed of data acquisition with a large range of sampling frequency allows a variety of use. Finally, the fact of being able to cohabit with the electrical and magnetic systems is beneficial when working with tES.

The major disadvantage, as other techniques such as fMRI and PET, is that neuronal activity is based on hemodynamic changes by regional increases in glucose and oxygen demand. Nevertheless, NIRS has gained maturity and is a relatively used technique in several scientific fields (sensorimotor, cognitive, visual, social) with various paradigms. As we can read in the literature review of Leff et coll. NIRS measurements have been applied successfully during various motor tasks (finger tapping, finger bending, finger opposition, handgrip, pinching, pointing, peeling, walking, running, pedaling, rowing).

The principle of NIRS is to measure the amount of light absorbed by human tissue, but also the amount of light scattered, reflected and ultimately transmitted (Fig. B2).

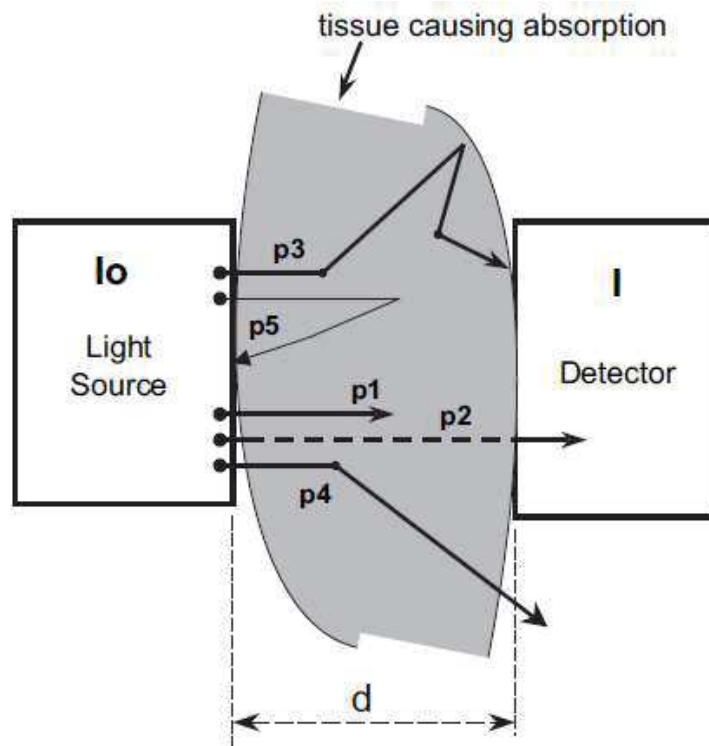


Figure B2 **Propagation of light in contact with biological tissues.** The paths that can be taken by the photons of light in interaction with a biological medium are various: photons can be attenuated in biological tissues by the absorption effect (p_1). Photons can pass through biological tissues through the effect of transmission (p_2). Photons can propagate in different directions within the biological tissues by the dispersion effect (p_3 and p_4). The tissues can be returned from the biological tissues by the reflection effect (p_5) (Maikala, 2010).

The propagation of light is governed by physical laws. The Beer-Lambert or Beer-Lambert-Bouguer law establishes proportionality between the concentration of a chemical element in solution, the absorption coefficient of solution and the length of the path traveled by light in this solution. The different modes of light propagation in biological tissues due to their heterogeneity (present, at the cerebral level) led to the rewriting of this law named modified Beer-Lambert. This makes it possible to correct the dispersion, the photon loss and the long travel time by these photons. Thus, NIRS is primarily based on the modified Beer-Lambert law in which the changes in the concentration of light absorbing components are assumed to be proportional to the changes in light absorbance divided by both the mean optical pathlength and the extinction coefficients of the chromophores in tissue. The mean optical pathlength is a measure of the average distance that light travels between the source and detector through the scattering and absorbing tissue.

In view of these elements, the near-infrared spectrum (Fig. B3), due to its low retention in biological tissues, was used for cerebral NIRS to measure changes in hemoglobin concentration [Hb], whether it is oxygenated (O_2Hb) or reduced (HHb). The preferred optical window will be between 700 nm and 900 nm. Above, water absorbs the photons of infrared light and on the other side, it is the hemoglobin which represents a coefficient of extinction too high. Within this window, it is possible to calculate the concentration variation of the hemoglobin chromophore, relative to the isosbestic point, that is to say, the wavelength at which the total absorbance of the hemoglobin, a chromophore remains constant regardless of the state in which it is located. It is then possible to obtain a measure related to the total volume of hemoglobin since the absorption at this wavelength is independent of the oxygenated or reduced state in which the hemoglobin is located (Pouratian et al., 2003). Hemoglobin, when not bonded to oxygen, will absorb more light in the near infrared in the 700-800 nm range, whereas when it is saturated with oxygen it absorbs more light for 800-900 nm (Matcher et al., 1995). The best practice as suggested by Orihuela-Espina et al. (2010) is to use a first wavelength close to 830 nm and the second wavelength between 660 and 770 nm.

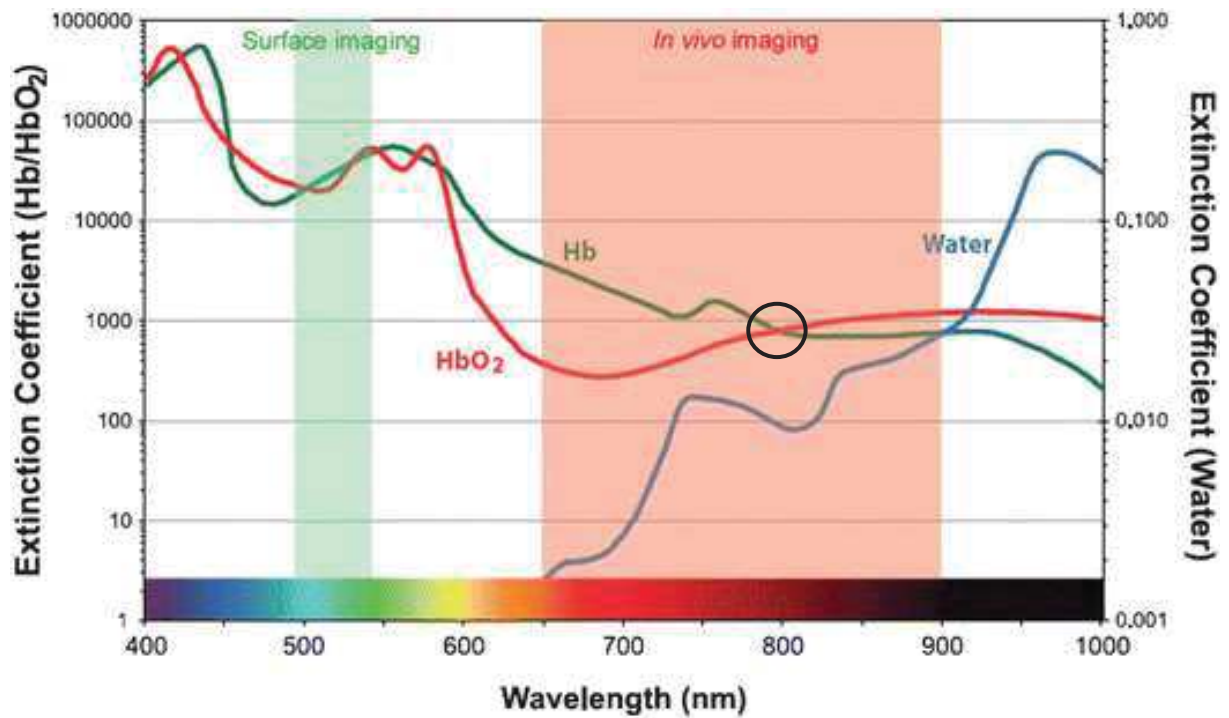


Figure B3 **Spectrum of light absorption and isosbestic point in the NIRS optical window.** The knowledge of the absorption coefficients allows to approximate the concentration of the chromophore. The circle represents one of the isosbestic points (Ma and Su, 2010).

The light is emitted by a transmitter (source), crosses the inhomogeneous multilayers (ie scalp, cranial bone, cerebrospinal fluid) to reach the cerebral cortex and then be collected a few centimeters away for a receiving optode (detector) (Fig. B4). The intensity and power of the NIR lasers are limited so as not to cause burns to the skin (Strangman et al., 2002). The path traveled by the photons is thus often modeled in the form of a banana or a half-moon. Nevertheless, it appears that the photons are mainly reflected at the output of the transmitter, which would create an accumulation in this zone (Strangman et al., 2002).

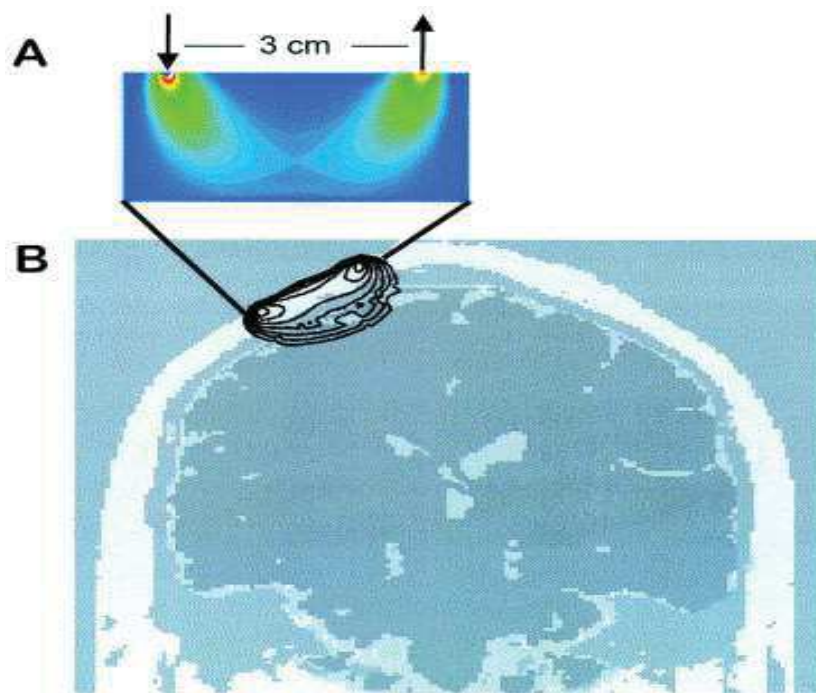


Figure B4 **Path of light through the biological tissues of the head.** (A) Regarding the NIRS, the arrows indicate the source (left) and the detector (right). Colors indicate the number of photons detected. Red and yellow indicate the greatest number (and therefore the highest sensitivities) while blue and purple indicate the progressively weaker sensitivities. (B) The similar pathway deduced via MRI (Strangman et al., 2002).

The inter-optode distance will determine the depth of the photon path, the penetration of the photons being proportional to the distance between the point of entry and the point leaving the light (Gervain et al., 2011). The distance recommended by several studies for the cerebral region is 4 cm (± 1 cm) (Orihuela-Espina et al., 2010). The greater the inter-optode spacing, the greater the illumination, and the more negligible the extra-cortical haemodynamic contributions. To differentiate cortical and extracortical contributions, several technologies (Fig. B5) have been developed.

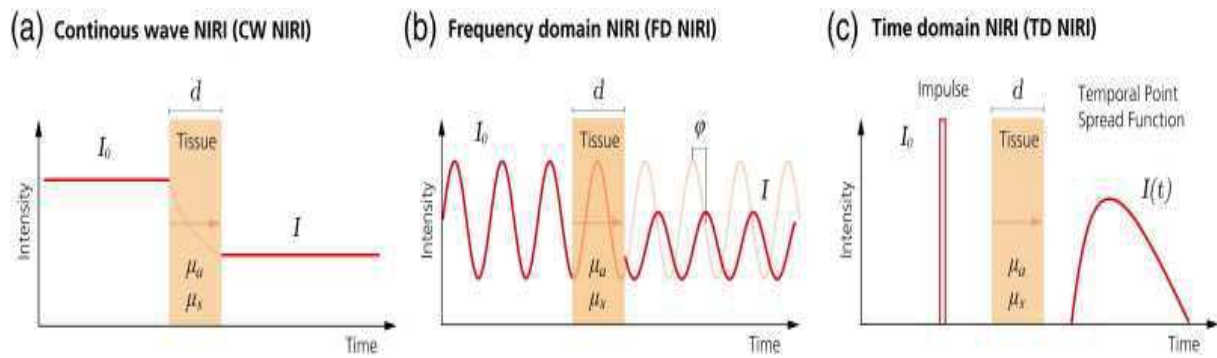


Figure B5 **The different types of measurement in NIRS.** The NIRS with continuous wave (CW, a) uses a continuous and constant intensity which makes it possible to measure the overall attenuation of light. The frequency-resolved (FD, b) NIRS modulates the emitted light intensity and then measures the intensity of the detected light as well as the phase shift, which corresponds to the time of flight. In c) the NIRS is time-resolved (TD) with a short pulse of light to measure the temporal profile of the transmitted light (Scholkmann et al., 2014).

The system at our disposal was a continuous wave of type OxyMon MkIII, Artinis, Netherlands, which allowed us to connect up to 16 channels. This type of system is very widespread because of the simplicity of its use with regard to other systems, but also the very good signal-to-noise ratio, its portability and finally its cost. The limits of this type of NIRS are that the measure only provides relative information on concentration variations, and in fact, does not dissociate the absorption and diffusion effects or estimate the optical differential pathlength factor (DPF) depending on the optical characteristics of tissue; DPF multiplied by the physical distance between the source and detector positions gives the mean pathlength of light.

NIRS is, therefore, a privileged instrument of neuroimaging in order to indirectly measure brain activity. The main variables of interest to be captured by the continuous wave NIRS are the relative concentration variations of oxyhemoglobin $\Delta [O_2Hb]$ and deoxyhemoglobin $\Delta [HHb]$ expressed in μM (micromole). Cortical activation is characterized by an increase in $\Delta [O_2Hb]$ with a concomitant decrease in $\Delta [HHb]$ and can be called fNIRS response. This activation pattern indicates an increase in neuronal activity (Perrey, 2008, Fig. B6).

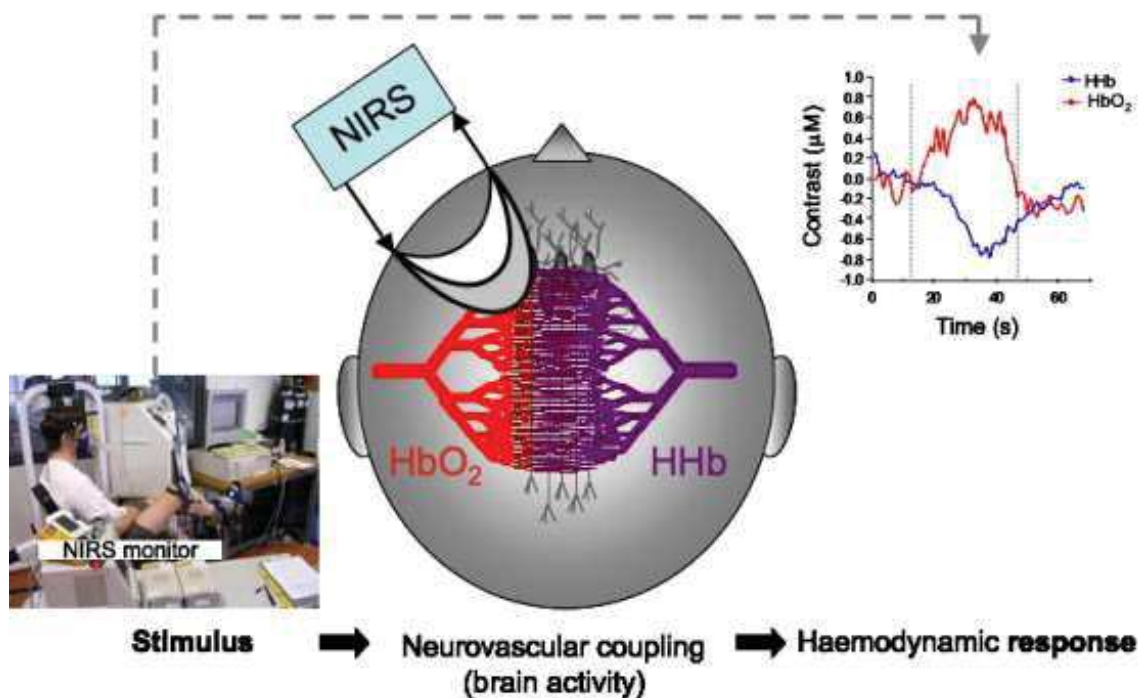


Figure B6 **Typical NIRS response**. During a stimulus, NIRS captures the cerebral hemodynamic changes that will characterize cortical activation (Perrey, 2008).

In order to explain the shape of these activation patterns, we must understand the notion of neurovascular coupling, i.e. the interactions between electrical neuronal activity, cerebral blood circulation and substrate consumption by tissues of the brain (Wolf et al., 2002). Any electrical signal from the neurons generates a localized energy expenditure, which can only be filled by a vascular increase since the brain does not have its own energy reserves. Neurovascular coupling is the sudden and continuous mechanism in which regional neuronal activity leads to hemodynamic changes reflected by an excessive increase in local blood flow (Fox et al., 1988; Logothetis et al., 2001; Mukamel et al., 2005). Neurovascular coupling is, therefore, the temporal sequence that follows the stimulation, from the electrical response of the neurons (very fast, on the order of a millisecond) to the delayed hemodynamic response (on the order of a few seconds) (Mandrick et al., 2013a). The hemodynamic response is a function of (i) blood oxygenation, (ii) blood flow and volume, (iii) neurophysiological processes of the neurovascular unit, and (iv) metabolic activity in oxygen and glucose (see Scholkmann et al., 2014). This adjustment of cerebral blood flow to neuronal activity is related to metabolic activity. The later involves chemical signals, as well as certain cells such as pericytes and astrocytes which will allow local vasodilation. This adjustment is often excessive, and this phenomenon is called hyperemia (Fig B7).

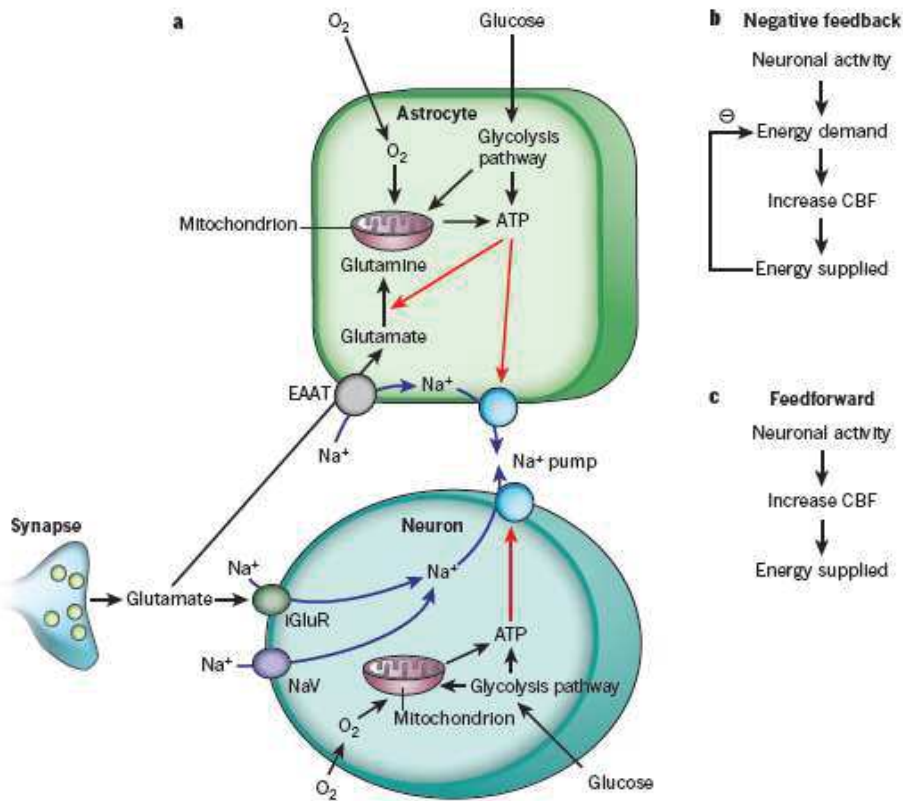


Figure B7 **The supply of energy, use and regulation of blood circulation in the brain.** a. ATP is generated from glycolysis and mitochondrial oxidative phosphorylation in neurons and glial cells; b. Negative feedback control for vascular energy supply, in which a decrease in energy level induces an increase in cerebral blood flow (CBF); c. Regulation anticipation hypothesis for the vascular energy supply (Attwell et al., 2010).

For a temporal reading of the relationships between the pattern of the typical activation pattern in fNIRS and the different steps involved in the hemodynamic response, see Mandrick's thesis (2013).

Variables from NIRS response

The NIRS has the particularity of capturing information about the dichotomous aspect of hemoglobin, that is to say, the variations of oxyhemoglobin and deoxyhemoglobin. There are three ways of presenting the results with the presence of the two states of hemoglobin, or one of the two. An increase in O₂Hb is relevant to defining cortical activation (Obrig and Villringer, 2003), however, this may reflect changes due to perturbations and extracerebral

factors. The tDCS, as such, is a factor favorable to this increase. A decrease in HHb also appears to reveal cerebral activation. However, Hoshi et al. (2001) showed that HHb changes would reflect changes in the venous compartment primarily and not changes induced by regional CBF elevation. This type of response with this typical pattern for the motor region is not necessarily valid for all brain areas (Zimeo Morais et al., 2017).

According to the protocol and wishes, there are several indicators used to characterize NIRS-related data:

- The peak of the oxy- and/or deoxyhemoglobin response, i.e. the maximum value found during the stimulation period compared to the starting value considered as the reference or baseline. And the time taken to reach the peak values (time to nadir, TTN) (Leff et al., 2011).
- The amplitude alone of the oxy- and/or deoxyhemoglobin response, i.e. the averaged value over the whole period of activation or for a given period of seconds at which the average is subtracted over a short period of rest (10-20 s).
- The slope index of the oxy- and deoxyhemoglobin response, i.e. the calculation of the coefficient of the slope of the linear regression applied to oxy- and deoxyhemoglobin responses during the entire stimulation or on a defined temporal portion (Mandrick et al., 2013b).
- The maximum likelihood estimate between the oxy- and deoxyhemoglobin response measured and their equivalents modeled a priori according to the "general linear model" (GLM). This statistical modeling is a mean of (re) parameterizing the signals so that they have a canonical form based on the "hemodynamic response function" (Kamrani, 2012).
- The area under the curve (AUC) of the oxy- and deoxyhemoglobin response, using the calculation of the integral of each temporal piece of curve. Gagnon et al. (2012) use the area under the curve closest to the maximum and minimum magnitudes for oxy- and deoxyhemoglobin.
- The saturation of oxygenated hemoglobin (StO₂) or the tissue oxygenation index (TOI) formulated by the ratio between oxyhemoglobin on the sum of oxy- and deoxyhemoglobin.

On the other hand, it is possible to take as variables of interest the following parameters:

- The difference between the oxyhemoglobin and deoxyhemoglobin amplitude usually denoted Hbdiff gives an approximation of the oxygenation variations of the blood at constant

hematocrit level.

- The sum between the amplitude of oxyhemoglobin and deoxyhemoglobin values usually denoted Hbtot, gives an approximation of the local variations of blood volume with constant hematocrit level.

Finally, amplitude values whatever the method can be transformed with the Z-score. The Z-score which is the difference between the mean value of the amplitude of the oxy- or deoxyhemoglobin response during the task minus the previous period, all divided by the standard deviation of the oxy- or deoxyhemoglobin response. By dividing by the standard deviation in the rest period, this allows normalizing the value of the amplitude. For example, the Z-score for the oxyhemoglobin response provides a normalized value calculated as: $z\text{-O}_2\text{Hb} = (\text{O}_2\text{Hb task} - \text{meanO}_2\text{Hb pre-task}) / \text{SD} (\text{O}_2\text{Hb}) \text{ pre-task}$.