The role of somatosensory feedback for brain-machine interfaces applications

Thèse N° 7083

Présentée le 12 avril 2019

à la Faculté des sciences et techniques de l'ingénieur
Chaire Fondation Defitech en interface de cerveau-machine
Programme doctoral en neurosciences

pour l'obtention du grade de Docteur ès Sciences

par

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2019

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Acknowledgements

I would like to dedicate this thesis to my father who provided me a great support and motivation during four long years. Without him I would not be able to conduct my research. I also would like to dedicate my work to Fábio, for his daily-life support and active participation to this thesis.

Today I am very proud to deliver this thesis that was an enriching life experience.

Firstly, I would like to express my sincere gratitude to my advisor Prof. Millán for the continuous support of my Ph.D study and related research, for his patience, motivation, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis.

Besides my advisor, I would like to thank the rest of my thesis committee: Prof. Cohen, Prof. Murray, and Dr. Bassolino, for their insightful comments and encouragement, but also for the hard question which incented me to widen my research from various perspectives.

My sincere thanks also go to Pr. Thiran, Pr. Guggisberg and Pr. Hummel, who provided me feedback and support about my thesis and my ideas. Without they precious support it would not be possible to conduct my research.

I thank my fellow labmates for the stimulating discussions, coffee breaks, great parties and for all the fun we have had in the last four years. Also, I thank my all my friends from EPFL and everyone who participated to my experiences. Many thanks!

Last but not the least, I would like to thank my family: My parents, my brother, my sister and Fábio's family for supporting me spiritually throughout writing this thesis and my life in general.

Abstract

Brain-machine interfaces (BMI) based on motor imagery (MI) have emerged as a promising approach to enhance motor skills and restore motor functions. However, the efficacy and efficiency of BMI systems remain limited. The current lack of usability can be explained by the fact that significant efforts have been dedicated to improve decoding efficiency and accuracy, but BMI studies have generally ignored the user-training component of BMI operation. It has been suggested that somatosensory feedback would be more suitable than standard visual feedback to train subjects to control a BMI. In this thesis, a novel feedback modality has been explored to improve BMI usability, namely sensory-threshold neuromuscular electrical stimulation (St-NMES). St-NMES delivers transcutaneous electrical stimulation that depolarizes sensory and motor axons without eliciting any muscular contraction. In order to assess the effect of this new feedback modality on BMI skill learning this thesis is composed of four experiments. In a first experiment, the effect of St-NMES on MI performance was investigated. Twelve healthy subjects participated in a cross-over design experiment comparing St-NMES with visual feedback. Offline analyses showed that St-NMES not only enhanced MI brain patterns, but also improved classification accuracy. Importantly, St-NMES alone did not induce detectable artefacts. In a second experiment, physiological impact of online BMI training on corticospinal tract (CST) plasticity was studied according to the feedback modality –either St-NMES or visual feedback. Ten healthy participants were enrolled in a cross-over design experiment testing both BMI systems. Results showed that BMI based on St-NMES significantly enhanced CST excitability compared to BMI based on visual feedback. Moreover, BMI system based on St-NMES was significantly more robust and accurate over days. A third experiment further explored the parallelism between BMI learning based on St-NMES feedback and natural motor learning, putting particular attention on the underlying physiology of the process. Apart from analyzing the evolution of BMI performance, we also examined changes in CST excitability and modulation of intracortical inhibition in the early learning phase (after one BMI session) as well as later learning stage (after 2 weeks training). Ten healthy participants were trained to control a BMI based on St-NMES feedback. Results showed that subjects improved their BMI control with practice, what might be explained by the adaptation of the central nervous system over time. Finally, the last experiment explored the feasibility of BMI-St-NMES for upper limb rehabilitation after stroke. A chronic stroke patient with a severe motor disability was trained with BMI-St-NMES over 3 weeks. After training, upper-limb motor function improved, reaching clinical relevance. Based on our previous observations, we believe that BMI-St-NMES training enhanced CST projections leading to motor recovery.

As a conclusion, this thesis showcases that a contingent activation of central nervous system with somatosensory stimulation through BMI-St-NMES is a promising solution to enhance BMI control and to induce cortico and corticospinal changes. This new BMI modality could become a future opportunity for several fields of research including mental training assistive scenarios as well as motor rehabilitation of patients with lesions within central nervous system.

Keywords

Brain-machine interfaces, somatosensory feedback, electroencephalography, sensory threshold neuromuscular electrical stimulation, transcranial magnetic stimulation, brain-machine interfaces skills, motor rehabilitation.

Résumé

Les interfaces cerveau-machine (ICM) basées sur l'imagerie motrice (IM) sont une nouvelle approche pour améliorer et restaurer les fonctions motrices. Cependant, l'efficacité de ces systèmes reste limitée. Les difficultés d'utilisation des ICM peuvent être expliquées par le fait que les études en ICM ont généralement négligé les aspects liés à l'entrainement du sujet. Il a été suggéré qu'un feedback somatosensoriel serait plus approprié qu'un feedback visuel pour entrainer un sujet à contrôler une ICM. Dans cette thèse, un nouveau feedback basé sur la stimulation électrique neuromusculaire au seuil sensoriel (appelé St-NMES) a été développé. La St-NMES délivre un courant électrique transcutané qui dépolarise les axones sensoriels et moteurs sans induire de contraction musculaire. Dans le but de comprendre l'effet de la St-NMES sur l'apprentissage du control d'une ICM, cette thèse se compose de quatre expériences. Dans la première expérience, l'effet de la St-NMES sur les performances d'IM a été investiguée. Douze sujets ont participé à l'expérience en cross-over, comparant l'utilisation de la St-NMES comme feedback par rapport à un feedback visuel. Les analyses offlines ont montré que la St-NMES non seulement augmentait l'activation cérébrale pendant l'IM mais améliorait également les performances de l'ICM. Une deuxième expérience a été mise en place pour étudier l'impact d'un entrainement avec une ICM selon la modalité du feedback (St-NMES ou visuelle) sur la plasticité corticospinale. Dix sujets ont été recruté pour cette expérience en cross-over pour tester les deux ICM. Les résultats ont montré que l'ICM basée sur la St-NMES était non seulement plus efficace mais améliorait également l'excitabilité de la voie corticospinale en comparaison à une ICM utilisant un feedback visuel. Une troisième expérience a exploré plus en détails le parallèle entre apprendre à contrôler une ICM et un simple apprentissage moteur. En plus d'analyser l'évolution des performances de l'ICM, nous avons aussi étudié les changements de l'excitabilité de la voie corticospinale ainsi que la modulation de l'inhibition intra-cortical dans la phase précoce d'apprentissage (après une séance d'ICM) et dans une phase d'apprentissage plus tardive (deux semaines après entrainement). Dix participants ont été entrainés à contrôler une ICM basée sur la St-NMES. Les résultats ont montré une modification de la plasticité cérébrale et une amélioration des capacités de contrôle de l'ICM avec l'entraînement. Finalement, une dernière expérience a été faite pour explorer la possibilité d'utiliser cette nouvelle ICM basé sur la St-NMES pour la rééducation motrice du membre supérieur après un accident vasculaire cérébral (AVC). Une patiente présentant une atteinte sévère de la motricité, a également testé le protocole d'ICM-St-NMES pendant trois semaines. Après entrainement, la fonction motrice du membre supérieur a été améliorée (avec un gain atteignant le seuil de pertinence clinique).

En conclusion, cette thèse démontre que l'activation contingente entre le système nerveux central et la stimulation somatosensorielle grâce à l'ICM basée sur la St-NMES est une solution prometteuse pour promouvoir l'acquisition de compétences nécessaires au contrôle d'une ICM et induire une plasticité cérébrale. Cette nouvelle ICM pourrait devenir un atout pour différents secteurs de recherche notamment la rééducation motrice de patients avec une lésion du système nerveux central.

Mots clefs :

Interface cerveau-machine, feedback somatosensoriel, électroencéphalographie, stimulation électrique neuromusculaire au seuil sensoriel, stimulation magnétique transcrânienne, rééducation motrice.

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Chapter 1 Introduction

Consolidation and acquisition of motor skills is a major concern for a wide range of fields such as sport, daily life activities and motor rehabilitation. Skill acquisition has been defined as a set of processes by which movements are executed more quickly and accurately with practice [1]. The training involves repetitions of movements with a correlated activation between central nervous system, peripheral nervous system and muscles. In the case of rehabilitation, there is no motor intervention that showed a superiority in improvement of motor skills [2,3].That is the reason why, new technologies have emerged to enhance motor skills, such as robotics, non-invasive brain stimulation, virtual reality, neurofeedback. These practices are based on the current knowledge of the central nervous system and the plastic properties of the brain. Among them, brain-machine interfaces appeared to be a promising strategy to improve motor skills, especially in the case of severely impaired patients.

1.1 Brain machine interfaces (BMI)

« A BMI is a communication system in which messages or commands that an individual sends to the external world do not pass through the brain's normal output pathways of peripheral nerves and muscles. » Jonathan R. Wolpaw

A brain-machine interface (BMI) is a system which records the brain activity and extracts the characteristics of a specific mental state. It involves invasive or non-invasive recordings, but in this thesis we will focus exclusively on non-invasive BMI. The recorded signal of interest is translated into a command for an external device and this without requiring any body movement. Thus, patients with impaired motor function can use a BMI, since the system will directly "connect" patients' brain intention with their environment. A BMI is often composed of 6 steps:

1) Measurement of brain activity. Depending on the application, the recording technique needs to target a high temporal resolution (EEG, MEG) or high spatial resolution (fMRI).

2) Preprocessing. The signal of interest is filtered to obtain a better signal/noise ratio.

3) Features extraction. Values that characterize the signal of interest are extracted.

4) Classification. For each mental state defined by the extracted features, a class is attributed.

5) Translation into a command. Each class is linked to a command for an external device (moving a cursor, driving a robot, etc...).

6) Feedback. Subject receives a feedback of his/her performance. In most BMI, the feedback modality is visual, but it can be also auditive or proprioceptive.

The most common BMI, also used in this thesis, is a BMI based on electroencephalography recordings (EEG). EEG is the measurement of electrical activity of large neuronal populations thanks to electrodes placed over the scalp. The spatial resolution is limited from several millimeters to one centimeter. However, it allows a high temporal resolution (in the range of millisecond) that is crucial to observe time-locked brain activation. Thus, BMI based on EEG can record in real-time brain patterns linked to a specific mental task. Four different types of brain signals are standardly used with BMI-EEG:

- Steady State Visual Evoked Response (SSVERs) appearing over primary visual cortex after visual stimuli with a defined frequency. In this case, different visual stimuli are flickering at specific frequencies on a screen. The subject can select one of the objects by fixating it. After a frequency analysis of the SSVERs, it is possible to assess the object of interest [4–6].
- Event Related Potentials (ERPs) is a short duration electrical signal produced by the brain in response to an external stimulus. ERPs response can be used to create binary BMI commands [7,8] or to develop a BMI for communication [9,10]. As example, P300 is a well-known ERP used for BMI. It represents a positive fluctuation approximatively 300 ms after the appearance of the target of interest among stimuli that are not the target. The appearance of a P300 into the EEG signal is a marker of subject's choice.
- Slow cortical potentials (SCPs) belong to the family of event-related potentials, although it is generated endogenously and does not require any external stimulation. SCPs are slow rhythms in the brain usually below 1 Hz and they appear in a latency range of < 0.5s up to several seconds from the eliciting event. SCPs have been reported as markers for movement planification and anticipation [11,12]. SCPs have been used to control a spelling device for paralyzed patients [13].
- Sensorimotor rhythm (SMR) is a physiological spontaneous brain oscillation recorded over motor cortical regions. It is defined by a frequency of [8 12] Hz (μ band) and [13 30] Hz (β band). The amplitude of the signal reflects the activation of the motor regions and it can be voluntary modulated with motor execution or motor imagery. Relevant features of these SMRs are the so-called event related desynchronization (ERD), characterized by a decrease SMR amplitude due to a desynchronization of the local neuronal activity, and event related synchronization (ERS), an increase in amplitude of the recorded signal due to a local

synchronization of the neuronal activity [14]. For BMI based on the modulation of SMR, the user imagines movements of different body parts (usually, arm/hands and feet).

For motor skills improvement, three BMI strategies can be applied according to the context: motor function substitution, motor function restoration or motor function improvement. For the first context, the motor function is completely missing, and BMIs aim to substitute it. In this case, all types of EEG signals can be used to create an assistive BMI device. Pfurtscheller et al. [15] for example, developed a BMI to substitute the grasping function of a tetraplegic patient. After 5 months training, the patient could grasp again by controlling a functional electrical stimulation through a BMI. Other researchers combined the BMI to robotic orthosis that executes the lost function [16,17]. BMI can also be used to improve daily life independency: to restore communication, for example in the case of locked-in patients that lost the ability to interact with their environment [18], to control devices like a wheelchair with the voluntary brain activation [19,20], the cursor of a computer [21], or a video game [22]. For the two other contexts, motor restoration and motor function improvement, BMI based on SMR modulation are mostly used. The main goal in this case is to improve or restore (in severe cases) a specific motor skill, through the direct training of brain motor regions. During the BMI training, users can learn how to actively modulate their cortical motor areas. This type of BMI have the potential to promote motor recovery after stroke [23–25], and might facilitate motor skills (through MI practice) [26–29]. For this thesis, the main objective was to develop a BMI to enhance activation of motor cortical areas and potentially restore motor skills. Thus, this thesis will discuss about BMI based on SMR modulation. More specifically, these BMI are based on motor imagery.

1.2 BMI based on motor imagery

Motor imagery (MI) is defined as a specific mental imagination of a body action without any corresponding motor output. More precisely, the subject has to re-think and re-feel a movement without any motor execution. During MI, a modulation of SMR is recorded over brain motor regions. These modulations are similar to the ones observed during motor execution but with smaller amplitudes [30]. Indeed, it has been showed that during MI, there is a decrease amplitude (ERD) in μ and β frequency band in the contralateral cortex compared to a resting state [14]. Interestingly, ERD patterns are specific to the limb of interest [31,32]. Thus, it is possible with a BMI to target a specific limb function according to ERD-ERS patterns. Moreover, in the context of motor rehabilitation, there is a strong correlation between the ability to perform large ERD and motor

recovery of stroke patients [24,30]. BMI based on MI are a promising tool to enhance the activation of impaired motor regions, and promote motor recovery [23–25,33–36].

Although everybody, including people with motor impairments, should elicit ERD patterns during MI, this is not always the case [37,38]. It has been proposed that the inability to elicit accurate ERD patterns (namely, chaotic imagery as defined by Sharma et al. [39]) could be sustained by an inefficient strategy such as visual imagery. Indeed, MI strategies can be divided into kinesthetic motor imagery and visual motor imagery. Although related, visual imagery and kinesthetic imagery are two distinguishable cognitive processes [40,41]. Kinesthetic imagery imposes subjects to re-feel a movement and focus their attention on kinesthetic sensation of the limb. This specific internal imagery activates a large fronto-parietal network and recruits in addition subcortical and cerebellar regions, similarly to motor execution and motor preparation. On the contrary, if the subject is visualizing the movement during MI, it resorts to visual imagery. In this case, sensorimotor networks are not activated, while it predominantly involves occipital regions and superior parietal lobules. It has been largely demonstrated that kinesthetic imagery is the predominant component of MI in order to activate sensorimotor networks [42,43] and modulate corticomotor excitability [44].This is the reason why MI have even been also defined as “a mental event where kinesthetic memory of a prior movement is reactivated giving rise to an experience of re-executing the movement” [45]. In practice it seems artificial to split kinesthetic from visual imagery during MI, nonetheless, it is now agreed that BMI users should be clearly briefed on how to perform kinesthetic imagery [46,47], and focus their attention on the sensation instead of the visualization of the imagined movement. However, despite this new instruction to control BMI, BMI usage remains limited to laboratories, and suffer from poor transferability to daily life training.

1.3 BMI current limitations

BMI based on MI suffer from lack of transferability to daily life training because of important technical and usability challenges [48].

Technical limitations are intrinsically linked to the electrophysiology properties of the EEG signal. Indeed, EEG analysis has to cope with the non-linearity and non-stationarity characteristics of the signal. The non-linearity is explained by the fact that the brain is a highly complex system, that do not rely on simple linear activity. The neuronal activation during MI involve multiple interlinked networks that modulates the neuronal activation within primary sensorimotor regions. The EEG

signal can be, then, represented as a chaotic behavior of neuronal ensembles. Although linear methods can accurately discriminate MI brain patterns from resting state, dynamical methods could be a solution to enhance the decoding of MI. However, the non-stationarity of the EEG signal remains a major concern for BMI field. It can be explained by a continuous change of the signal of interest over time, between and even within a single session. These changes are due to several factors: (i) Changes in the electrodes' placement will naturally induce variability in the recorded signal. (ii) EEG is very sensitive to noise. It includes all unwanted signals caused by environmental noise, subjects' related artifacts like movements, or electrical activity of muscles or eye blinking. It results a decrease of signal to noise ratio that limits BMI decoders. (iii) The mental and emotional involvement during the task can differ over time and have a drastic impact on subjects' performance. (iv) The fatigue, the attention and motivation also massively contribute to EEG signal variability. These limitations, especially the non-stationarity of the EEG signal, results in poor efficacy of BMI decoders. Indeed, BMI present high error rates [49,50] and a large percentage (10 to 30 %) of subjects are considered not capable to control a BMI [51].

Usability challenges are defined by the user acceptance to use BMI [52]. The major limitation is the poor efficiency of BMI training. Indeed, all users need to be trained before being able to control a BMI [27]. They need first a relatively long calibration session [53], necessary to build individualized BMI decoder. The calibration is followed by a long and intense training period with numerous sessions (that can be months [15,22]) before being able to control accurately the BMI. This heavy training is necessary for several reasons. It allows to record data over time so that the BMI decoders can model the natural variability of the target signals. Also, it permits the user to understand the task. Indeed, doing MI is not a straightforward task since it does not imply any physical outcomes. Probably, most novice participants just do not know how to focus their attention on their limb sensation. As explained before, even if they are instructed to adopt a kinesthetic approach, it is not obvious how to feel a movement without any internal or external stimulation. The lack of understanding of BMI instructions is a major limitation to obtain an efficient BMI device.

A usable BMI should be defined as a robust signal processing and a well-trained user. A lot of effort and research is provided toward the improvement of signal processing (with better pre-processing and elaborated machine learning algorithms). Unfortunately, we have neglected the user training aspects. We have to re-consider how we are training subjects to control a BMI. Indeed, they need to understand and acquired proper BMI skills. BMI skills include the ability to perform discriminable, stable and accurate MI patterns. Discriminability, stability and accuracy are the three

pillars to improve BMI efficiency: better signal-to-noise ratio, decrease of non-stationarity of the signal, and BMI efficacy: accurate and robust BMI decoder. Moreover, BMI skills encompass also the ability to control and react to the BMI decoder. Regarding this last point, it is not meaningless to make a parallel between BMI skills acquisition and motor skills acquisition. Although there is no motor output when user control a BMI, subjects receive a real-time feedback of the current status of BMI decoding, and they have to adjust their behavior accordingly. Comparatively with motor learning process, with BMI training subjects should improve their performance in terms of accuracy and speed. BMI skills can be compared to a sensorimotor training and in this sense, the feedback used to teach subjects how to control the BMI becomes crucial.

1.4 BMI feedback modality

As discussed by Wolpaw and Wolpaw [54], a brain-machine interface (BMI, or brain-computer interface) is framed on the sensorimotor hypothesis, namely that "the whole function of central nervous system (CNS) is to convert sensory inputs into appropriate motor outputs." Thus, acquiring BMI skills (i.e., learning to modulate brain signals that are translated into new kinds of outputs that are not mediated by the normal pathways of the CNS) should be guided by similar principles to learning any other natural motor behavior. As Wolpaw and Wolpaw noted, "normal CNS outputs … are mastered and maintained by initial and continuing adaptive changes in all the CNS areas involved", areas that extend from the cerebral cortex to the spinal cord.

Adhesion to the sensorimotor hypothesis leads to a number of postulates. First, sensory inputs (i.e., the afferent information to the CNS as result of its efferent commands, or feedback) plays a critical role in BMI –inputs and outputs having to rely on the corresponding natural pathways. In particular, for the case of MI-BMIs, somatosensory feedback should be more effective than standard visual feedback. Second, BMI use should induce plastic changes not only in the cortical area from which it computes the outputs, but also in all other CNS areas that normally adapt to control spinal motoneurons. In particular, we hypothesize that online operation of a BMI based on MI of a limb coupled to somatosensory feedback delivered to that limb should increase corticospinal tract (CST) excitability as measured by motor-evoked potentials (MEP) elicited by single pulse transcranial magnetic stimulation (TMS) of the corresponding muscle. Such an increase in CST excitability is an indicator of positive plastic changes associated to cortico motor outputs in healthy and CNS-injured humans [55,56].

Regarding postulate 1, several studies have underlined the potential advantage of somatosensory feedback for improving performance of EEG-based MI-BMIs; e.g., via robotic devices [17,33,57], vibrotactile stimulation [58–61] or neuromuscular electrical stimulation (NMES) [23,36,62]. For example, Vukelić et al. (2015) [57] demonstrated that a robotic orthosis was more suitable than a visual feedback to entrain motor network with BMI. Reynolds et al. (2015) [62] showed that NMES during MI induced a larger desynchronization of the sensorimotor rhythms compared to motor imagery supported only by visual feedback. Cincotti et al. (2007) [58] have highlighted the fact that vibrotactile feedback was perceived by subjects as more natural feedback for BMI. However, passive somatosensory feedback delivered via these modalities elicits similar brain activation to active MI [63–66], thus risking biasing the BMI output. An alternative source of somatosensory feedback necessitates to be explored. As for postulate 2, different studies have documented plastic changes in the sensorimotor cortical areas used as input for the BMI. However, there is a lack of direct evidence of adaptation in other CNS areas involved in natural motor control. A new somatosensory feedback, supporting CNS plasticity and BMI skills learning needs to be investigated.

1.5 Sensory-threshold neuromuscular electrical stimulation

Neuromuscular electrical stimulation (NMES) is a common tool with a wide range of applications in research and rehabilitation. NMES is a repetitive transcutaneous electrical stimulation that depolarizes lower motor neurons axons until it triggers the contraction of the innervating muscular fibers. In the same way the motor axons are activated by NMES, sensory axons are also depolarized. Volley of depolarization are sent to the central nervous system traveling through the sensory pathways to the somatosensory cortex, at the frequency of the stimulation. Interestingly NMES may induce plastic changes in the nervous system [68–70].

However, as explained before, NMES induces strong ERD and might bias BMI output. Strong somatosensory afferences (e.g., passive movement of the joint of muscular contraction) elicits strong brain activation similar to MI. BMI algorithms are then, not able to dissociate subjects' intentional MI from the evoked brain activation elicited by feedback. As a result, subjects cannot achieve the resting task if, by mistake, the BMI output is MI and triggers somatosensory feedback. Thus, the purpose of this thesis is to investigate the usage of sensory threshold NMES (St-NMES) as a novel somatosensory feedback for BMI. Indeed, NMES can be also used with a sensory threshold stimulation [71,72]. In this way it conveys natural proprioception by depolarizing sensory and motor

nerves without eliciting any muscular contraction related to MI performance. We hypothesize that St-NMES feedback will drastically improve BMI training by (i) improving MI patterns discriminability, accuracy and stability (ii) facilitating the acquisition of BMI skills, and (iii) inducing cortical and subcortical reorganization linked to learning processes. In order to demonstrate the interest of St-NMES as a BMI feedback, this thesis is composed of 4 parts. First of all, we investigated in an offline EEG study the impact of St-NMES on MI performance compared to a standard visual feedback. We also assessed the impact St-NMES on EEG recordings. In the context of BMI control it was important to control that St-NMES does not bias BMI outcomes and by eliciting detectable ERD. Secondly, we compared the usage of St-NMES feedback with a standard visual feedback during online BMI training. We additionally investigated corticospinal tract changes induced by both BMI training based either on St-NMES or visual feedback. Then, different stages of BMI learning and its related cortical and corticospinal changes were explored in a third experiment. Finally, our BMI-St-NMES protocol was tested with a chronic stroke patient suffering from a severe impairment of upper-limb motor function.

Chapter 2 Sensory threshold neuromuscular electrical stimulation fosters motor imagery performance

2.1 Introduction

As previously explained, MI has been defined as "a mental event where kinesthetic memory of a prior movement is reactivated giving rise to an experience of re-executing the movement" [45]. In order to improve the usability of BMI based on MI, it becomes crucial to propose an appropriate training to enhance kinesthetic performance compared to visual imagery [46]. Although it is agreed that users should be clearly briefed on how to perform kinesthetic imagery, MI patterns are not sufficiently reliable and users' performances are still limited. That is the reason why we proposed the usage of a new somatosensory modality, called St-NMES, to foster MI training and subjects' performances. Prior to designing an online feedback for BMI application, it was important to evaluate the feasibility to use St-NMES while performing MI and to study its advantages against standard visual information. We presume that under St-NMES subjects will adopt less chaotic MI strategy and will focus more on kinesthetic sensations. Moreover, since we are using sensory threshold stimulation, we do not expect any contamination of the feedback on the recorded brain patterns. Thus, we hypothesize that St-NMES does not induce detectable ERD patterns and fosters MI performance.

2.2 Material and Method

2.2.1 Experimental paradigm

Twelve healthy subjects (4 females, age 28.8 ±2.69, 2 left-handed) naïve to motor imagery practice, took voluntary part in the experiment. The study was approved by an internal ethical protocol and participants gave their written informed consent before participation. During the whole experiment subjects were seated on a fixed chair in front of a computer screen with hands on the knees, palms

up, to have a relaxed position. EEG signal was recorded at 512 Hz using a gHiAmp system (gTec, Austria) from 60 channels equally distributed over the scalp following the 10/10 International System.

The experiment was composed of two days of recordings during which all subjects were asked to perform motor imagery (MI) of closing their dominant hand with two different guidance during the task: continuous St-NMES or continuous visual guidance (Figure 1). The term guidance is defined as the support a subject is receiving while performing the task. It differs from the term feedback since it is not linked to subjects' performance, but it only assists the task. Tasks, conditions and instructions were the same for both days of recordings, and only differed in the number of executed trials. The instructions were the following: "For MI trials, you have to perform MI of closing the dominant hand while seeing the visual guidance on the screen or while feeling St-NMES. It is one continuous MI, not repetitive MI. In order to perform MI, you should not see your hand closing, but you have to feel it without eliciting any muscular contraction. Try to keep a consistent strategy over trials. During resting trials, you have to stay as calm as possible, you should neither move nor blink, and you should not think about your hand." Thus, the importance of adopting a kinesthetic strategy during MI task was clearly explained to each subject. Importantly, guidance during the resting trials differed for the St-NMES modality and the visual modality, as explained below.

On day 1, subjects were asked to execute 4 runs composed of 15 trials either for MI and rest task, with one guidance modality (St-NMES or visual), then 4 runs with the other guidance modality (visual or St-NMES). The first guidance modality was randomly assigned for each subject as well as the order of trials (MI or rest) of each run. On day 2, only 2 runs were performed per modality. We designed a third condition to control for possible artifacts induced by St-NMES (NMES-control) during which subjects were receiving St-NMES without performing MI. The order of the NMES-control recording was shuffled for each participant. For all 3 conditions (St-NMES, visual, NMES-control) each trial started with the preparation cue (3 s), then a cue indicating the type of trial (MI or rest, 1 s), followed by the task (MI or resting, 4 s) and finished with the appearance of the stop cue (1 s). Inter-trial intervals lasted 3 to 4.5 s.

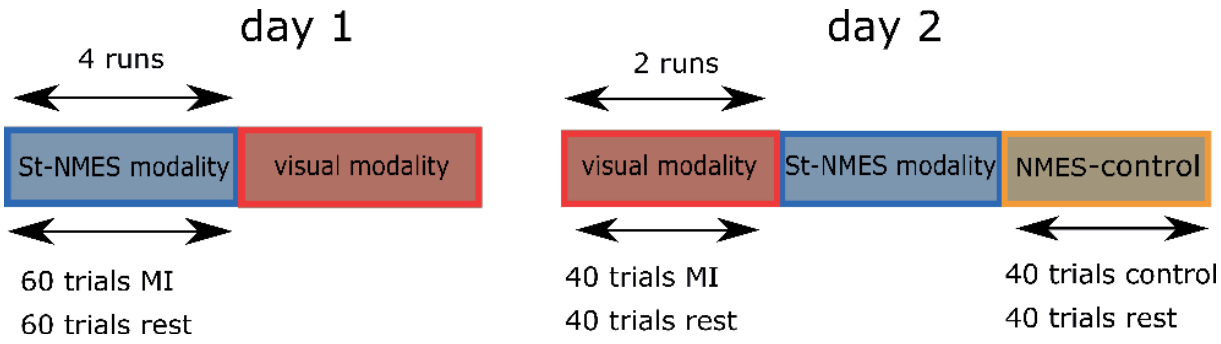

Figure 2:1 Schema of the experimental paradigm

Guidance modality order (St-NMES-visual or visual-St-NMES) is assigned randomly across subjects. During day 1, 4 runs are recorded per modality. During day 2, 2 runs are done per condition. A third condition called NMES-control is randomly run before, between the two guidance trainings or after the training. The NMES-control condition served to evaluate the impact of St-NMES without performing MI compared to rest with no stimulation.

2.2.2 St-NMES modality

NMES electrodes were placed on the *Flexor digitorum superficialis* muscle at the anterior face of the forearm. Sensory-threshold (St-NMES) and motor threshold (Mt-NMES) amplitudes of NMES were evaluated independently for each subject before recordings (on average St-NMES amplitude was 5 ±1 mA and Mt-NMES amplitude was 9 ±1 mA). Sensory-threshold stimulation induced a tingling sensation in the palm and forearm but without eliciting any muscular contraction. Contrarily, Mt-NMES provoked a muscular contraction leading to a passive hand closure. The frequency of stimulation was fixed to 30 Hz for all conditions and subjects. In order to minimize the noise injected by NMES on the EEG signal, we respected the procedure described in the literature [73]: The NMES device was installed on a different surface than the EEG device and an electrode was installed on the ipsilateral biceps to ground the subject. During MI and NMES-control trials, subjects started the MI task right after the appearance of the cue on the screen, when they started feeling St-NMES. Then, during the 4s trials, subjects were performing MI and in parallel they were receiving St-NMES supporting subjects' performances. The trial ended with 1s of Mt-NMES stimulation that closed the hand. No guidance was delivered during resting trials.

2.2.3 Visual modality

Subjects were instructed to perform kinesthetic MI. During MI, subjects received guidance via the visualization of a bar going up (for MI trials) until the bar reached a threshold (represented by a line on the screen) indicating the end of the trial. During resting trials subjects had to stay calm until the bar reached the bottom of the screen.

2.2.4 Preprocessing

EEG was filtered in the frequency band [1-100] Hz (zero-phase Butterworth 4th order) with a 50 Hz notch filter, re-referenced to linked ears, then common-averaged referenced. Noisy channels (detected post-experiment by visual inspection) were manually replaced by the mean of the orthogonal neighboring channels. Trials were concatenated per condition (St-NMES, visual, NMES-control), composed of a baseline from [-3 0] s, a task time window [1 5] s, and a time after the task [5 6] s. These extracted trials were used for all the analyses. Trials with a filtered EEG signal above 100 μV were marked as artifactual and discarded.

2.2.5 Analysis of the sensorimotor modulation

In order to understand the effect of the guidance modality on MI neural correlates, we used data from the second day to compare the 3 conditions (St-NMES, visual, NMES-control). Sensorimotor rhythms modulations (SMR) were computed by extracting the power spectrum for frequency bands 1-45 Hz with 1 Hz resolution for each electrode for all trials. We computed the amplitude spectra of each trial with a sliding window (1 s window with 62.5 ms overlap). The baseline spectrum of each trial was extracted from EEG immediately preceding each event. The spectral transforms of each trial were then normalized by subtracting their respective mean baseline spectra and dividing by this same baseline value in order to compute the corresponding event-related desynchronization (ERD) [14], see Equation 2:1. For left handed subjects (n=2), electrodes were flipped in order to have contralateral electrodes of the dominant hand in the same topographical position. ERDs were finally averaged for each condition. For topographical analysis, ERD data were averaged across time and across μ (8-12 Hz) and β (13-24 Hz) frequency bands. The frequency bands were selected based on what is define in the literature [74]. β band was restricted to 24 Hz in order to avoid the injected noise from St-NMES around 30Hz. The averaged ERD values of each electrode was used to interpolate a topographic map. The obtained topographic maps were compared between pairs of tasks via a cluster permutation approach, which automatically corrects for multiple comparisons [75]. Only significant clusters were considered ($p < 0.05$). Moreover, in order to control

which factor between the task (rest or MI) or the electrical stimulation (stimulation o or stimulation on) had a significant impact on SMR modulations recorded over the sensorimotor cortex (averaged recordings from electrodes Cz, C1 and C3), we performed a repeated measures ANOVA with these two within-subject factors followed by Bonferonni post-hoc test.

$$\mathrm{ERD} = \frac{(\mathrm{signal} - \mathrm{baseline})}{baseline} * 100$$

Equation 2:1 – Event related desynchronization

2.2.6 Connectivity analysis

We also analyzed the impact of the guidance modality at the brain network level. To this end, we performed a connectivity analysis at the voxel level following previous approaches [76]. First, EEG data from MI trials, were re-computed into cortical current density time series at 6239 cortical voxels using standardized Low-Resolution Electromagnetic Tomography [77]. We manually selected 4 regions of interest (ROI) in the contralateral hemisphere BA4: primary motor cortex (mostly recorded by C line channels); BA6: SMA and premotor cortex (FC line channels); BA7: associative somatosensory cortex (CP line channels), and BA18,19: visual cortex, (PO and O lines) [78]. The signal at each cortical ROI consisted of the average activation of voxels belonging to the ROI. Intra-cortical lagged coherence was computed between all possible pairs of the 4 ROIs for each of the following frequency bands of interest: μ (8-12 Hz), β (13-24 Hz). For the sake of simplicity, this analysis was performed only between St-NMES and visual MI tasks. Paired t-statistics were performed for each frequency band, and then corrected using a non-parametric randomization method [79].

2.2.7 Feature extraction and single sample classification

We used power spectral density (PSD) features among all modalities to evaluate the discriminability of the recorded signals. PSD for the 16 channels covering the sensorimotor regions (Fz, FCz-1-3-2-4, Cz-1-3-2-4 and CPz-1-3-2-4) were computed using the Welch method with internal Hanning windows of 500 ms (75% overlap) leading to 49 PSD evaluations per trial. For each condition (St-NMES or visual) features were selected to classify MI, rest and NMES-control trials based on signed squared values of point-biserial correlation coefficients (signed r2). We restricted our feature selection within the bands of interest i.e. 8-24 Hz, to reduce the possibility of selecting

noisy features, and performed classification using a linear discriminant (LDA). Three different analyses were applied :

1. Discriminability (cross-validation on day 1)

   Two classifiers were built according to the guidance condition (St-NMES or visual). To estimate the accuracy of each classifier in order to discriminate MI class from rest class, we computed a 4-fold cross validation, respecting the time structure, based on data recorded on day 1. In order to avoid overfitting, the 5 best features were selected from the training set of each fold.

2. Transferability (train on day 1 and test on day 2)

   In order to have an insight about future online applications, we decided to follow a standard procedure of BMI. To this end, we built classifiers based on data from day 1 (train sets), we manually selected 5 optimal features that were neurophysiologically relevant based on signed squared values of point-biserial correlation coefficients (signed r^2), and finally classifiers were tested with data coming from day 2 (test sets).

3. Artifact evaluation (cross-validation on day 2)

   In order to control if St-NMES induced EEG discriminable patterns, we built all possible pairs of classifiers based on: MI with St-NMES guidance trials; resting trials; NMES-control trials (rest with stimulation). All classifiers were tested with 4-fold cross-validation, respecting the time structure. Since less data were used in the cross-validation, only the best 3 features were selected.

When applicable, classification performances were compared with a non-parametric paired statistical test (Wilcoxon signed-rank test) and Bonferroni corrected. Statistical significance of classification was defined from a binomial cumulative distribution assuming equal priors ($p = 0.5$) and the number of trials available ($n = 80$) leading to a chance level of 0.60. Finally, non-parametric correlations (Spearman correlation) were also computed between discriminability and transferability results. The two correlations were compared, using the cocorr statistical toolbox [80], to assess whether they were significantly different based on the modified Fishers Z procedure [81].

2.2.8 Representative cases

We investigated how the discriminability of MI EEG patterns compared to rest is affected by the guidance modalities (St-NMES, visual). We used all features from μ and β frequency bands for all channels for each condition to fed a then fed them to principal component analysis (PCA). Then

we plotted the first two principal components extracted from 4 pairs of tasks (St-NMES MI vs rest; visual MI vs rest; visual MI vs St-NMES MI; and St-NMES MI vs control), in order to observe the different patterns related to the guidance modality. For sake of simplicity, we selected two representative cases that represent a subject with low performance with visual guidance but high performance with St-NMES and a subject with low performance indepently of the guidance modality.

Furthermore, we also asked subjects to subjectively evaluate the two modalities in order to understand which kind of guidance would be more suitable for online experiments. To this end, the NASA TLX questionnaires were filled by all subjects for each guidance modality. This questionnaire evaluates the workload of the task from the following points: mental, physical and temporal demand, the estimated performance, the effort and the frustration.

2.3 Results

2.3.1 MI neural correlates

In order to understand MI neural correlates, we used topographic interpolation of EEG modulation during MI for the three conditions (St-NMES, visual, NMES-control) Figure 2:2. During motor imagery task a clear ERD pattern appeared in the contralateral hemisphere with both guidance modalities in μ and β rhythms (Figure 2:2b). The time-frequency plots (Figure 2:2a) confirmed that the subjects were performing motor imagery in a sustained manner, with larger desynchronization in μ and β bands when using St-NMES. Additionally, it can be seen that Mt-NMES also generates a large desynchronization not related to MI. However, theses ERD were larger with the St-NMES guidance compared to visual and these topographical differences were significant ($p < 0.05$) in the β frequency band (Figure 2c). Interestingly, the stimulation itself, without performing any MI (NMES-control), did not induce any significant desynchronization ($p > 0.05$). MI patterns for visual and St-NMES conditions were also significantly different than the brain patterns induced by the stimulation itself (NMES-control), for both β (Figure 2c) and μ rhythms ($p < 0.05$ for all conditions). However, from the moment the NMES induced a muscular contraction (motor threshold NMES) a significant desynchronization was recorded over the sensorimotor areas for μ and β.

2.3.2 Task-related desynchronization

We investigated which factor between the task (MI or rest) and the electrical stimulation had an impact on ERD over the contralateral primary sensorimotor cortex. The ANOVA analysis Figure

2:3 confirmed that the task factor (MI vs rest) had a significant effect on the desynchronization over the primary sensorimotor cortex for both μ and β bands ($F_{1,11} = 8.20$, $p = 0.015$ and $F_{1,11} = 22.50$, $p = 0.001$ respectively). However, the stimulation factor had a significant effect only on β ($F_{1,11} = 7.12$; $p = 0.022$) band, but not on μ rhythm ($F_{1,11} = 0.05$, $p = 0.823$). The interaction between the two within-subjects' factors (task*stimulation) was only significant for β band ($F_{1,11} = 5.02$, $p = 0.047$), contrary to μ rhythm ($F_{1,11} = 0.14$, $p = 0.713$). Bonferonni post-hoc test for β band highlighted that the desynchronization was significantly larger ($p = 0.008$) with St-NMES guidance (MI task with sensory stimulation) compared to visual guidance (MI task with no sensory stimulation). Importantly, during the resting task the stimulation did not induce significant differences ($p = 0.86$) in the power spectrum of the region of interest.

2.3.3 Connectivity

At the brain network level, significantly higher connectivity ($p < 0.05$) was found in the fronto-parietal network during MI with St-NMES guidance compared to MI with visual guidance. In particular, in β (13-24 Hz) rhythm, the connectivity was significantly higher between BA7 (associative somatosensory cortex, mostly computed from CP line channels) and BA6 (Premotor cortex and SMA, FC line), and between BA4 (primary motor cortex, C line) and BA7 (CP line). Higher connectivity was also found in between BA6 (FC line) and BA7 (CP line) and in β between BA4 (C line) and BA6 (FC line), but these results were not significant ($p > 0.1$). No higher connectivity was found for the visual guidance compared to St-NMES, and no significant differences were found between occipital and fronto-parietal regions.

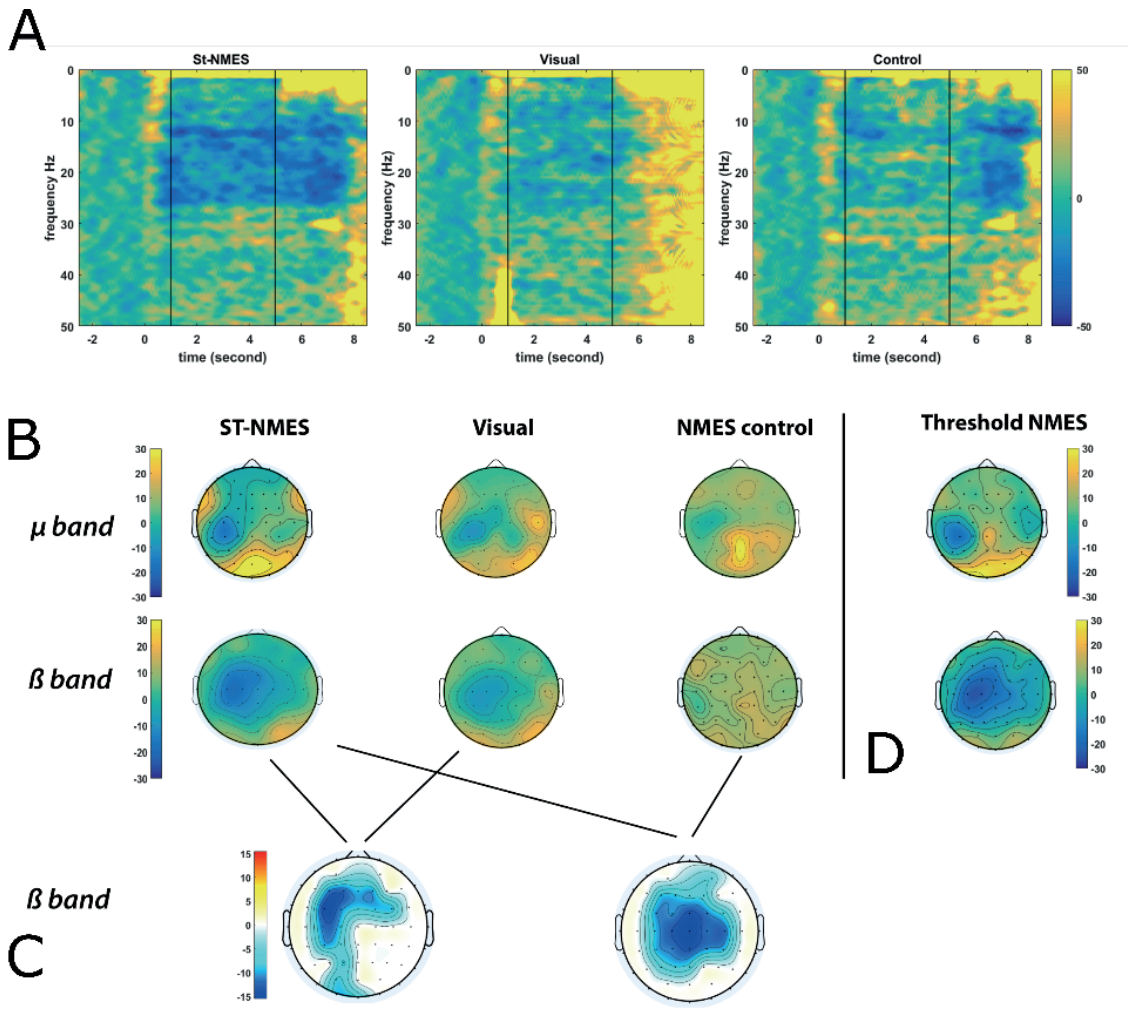

Figure 2:2 Topographical analysis

a) *Time-frequency plot over C3 channel, grand averaged across subjects for the three conditions (St-NMES, Visual, NMES-Control). The period [1 5] s indicates the MI task. The time window before [-3 0] s corresponds to baseline and the period after [5 7] s corresponds to Mt-NMES (St-NMES and Control condition) or end of trial (Visual).*

b) *Topographical analysis of μ (8-12 Hz) (top) and β (16-24Hz) (bottom) rhythms modulations during MI epochs for the three conditions St-NMES, visual and NMES-control.*

c) *Cluster permutation analysis highlighting significant topographical differences between pairs of conditions in β band between St-NMES vs visual (left) and between St-NMES vs NMES-control (right).*

d) *Topographical analysis of μ (top) and β (bottom) rhythms modulations while subjects received motor threshold stimulation (Mt-NMES) that induced muscular contraction. Note that subjects were not performing MI task during Mt-NMES.*

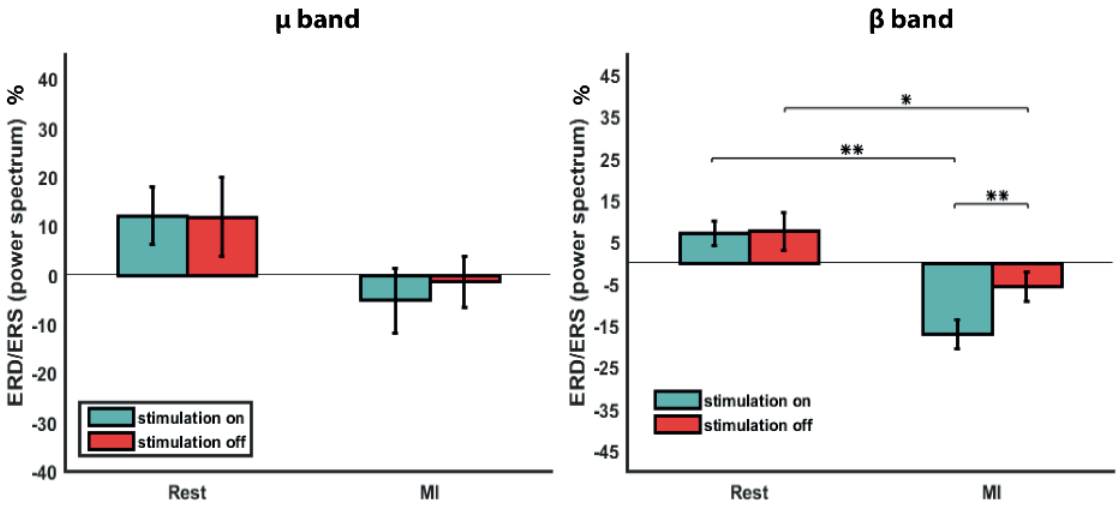

Figure 2:3 ERD over contralateral sensorimotor cortex

Repeated measure ANOVA with 2 within-subjects' factors: task (rest or MI) and stimulation (St-NMES on or St-NMES off) of EEG modulation recorded over the sensorimotor cortex (averaged signal from Cz, C1 and C3). Data are recorded the same day (day 2). Rest with stimulation represents St-NMES control data, Rest without stimulation represents resting task during visual condition, MI with stimulation represents MI trials with St-NMES guidance and MI without stimulation represents MI trials during visual guidance.

** $p < 0.05$, ** $p < 0.01$*

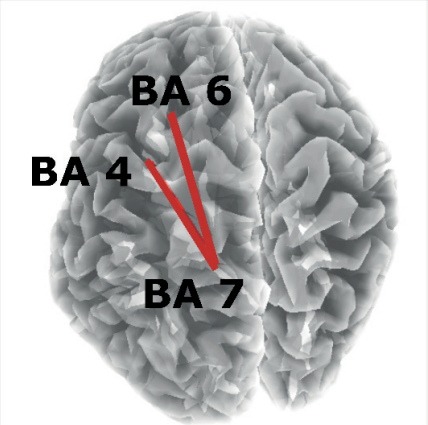

Figure 2:4 Connectivity analysis

Representation of significantly larger functional connectivity (lagged coherence) during MI with St-NMES guidance compared to visual guidance, in β frequency band.

2.3.4 Classification accuracy

In order to evaluate whether St-NMES guidance makes MI EEG patterns more distinguishable, we computed classification accuracy metrics (Figure 2:5). Classification accuracies above chance level (0.60) highlight the ability to significantly detect an MI brain pattern as compared to rest. Discriminability (on day 1) and transferability accuracies (on day 2) are represented on Figure 2:5a. The discriminability was better for St-NMES classifier compared to the visual (St-NMES: 0.73 ±0.13 and visual: 0.68 ±0:07), yet this difference was not significant (p = 0.078). More specifically, 10 subjects over 12 performed better (on average 8%), whereas only 1 subject achieved better classification with visual guidance (St-NMES: 0.53 and visual: 0.66). The remaining subject achieved no significant performance with any condition (accuracy < 0.60). Moreover, transferability results were significantly better for the St-NMES condition compared to visual (St-NMES: 0.72 ±0.13, visual: 0.65 ±0.09, p = 0.014). Knowing that all subjects were naïve to MI, 9 subjects over 12 attained a significant classification (accuracy > 0.60) under St-NMES guidance whereas, only 7 subjects over 12 had a significant classification with the visual condition. Possible discriminable artefacts during St-NMES were controlled in order to understand what is classified during St-NMES guidance (Figure 2:5b). NMES-control represents the situation when subjects were receiving St-NMES without

performing any MI. We found that the stimulation itself did not generate neither discriminable ERD nor discriminable artefacts. Indeed, no significant classification was possible between rest and NMES-control (accuracy = 0.59 ±0.07). Moreover, the two classifiers MI vs rest and MI vs NMES-control were not significantly different (accuracies = 0.75 ±0.13 and 0.74 ±0.13 respectively, p = 0.301). These two classifiers were also significantly different than rest vs NMES-control (p = 0.0049 and p = 0.0122).

Interestingly, subjects' performances across days were more consistent with St-NMES guidance. Indeed, accuracies results were highly correlated with St-NMES guidance (r = 0.92, p < 0.0001), contrary to results with visual guidance (r = 0.56, p = 0.057) (Figure 2:5c). The correlation of St-NMES was significantly better than that obtained with a visual guidance (r = 0.92 vs r = 0.56, p = 0.02, z-score = 2.27, two-tailed modified Fishers Z procedure).

The increase classification performance observed with St-NMES guidance might be explained by the fact that subjects' MI distribution is becoming more discriminable compare to the rest distribution. Moreover, some subjects considered "bad" for MI with visual guidance became "good" with St-NMES. *Figure 2:6* illustrates the case of subject 1 that had low MI performance since its distribution is poorly discriminable from rest distribution. With St-NMES guidance, the discriminability was strongly increased and the variance of MI performance decreased and. Thus, this subject obtained better classification performance. However, for some subject like subject 3 St-NMES did not facilitate MI performance.

We also investigated which kind of feedback would be more convenient for subjects. To this end, subjects answered NASA TLX questionnaire. Results highlighted that the workload of the MI task was significantly lower with St-NMES than visual modality (St-NMES: 9.47 ±2.87, visual: 11.96 ±3.34, p = 0.0015). More specifically, the frustration, the effort and the mental demand, which can affect motor learning and motor performances, were lower. Thus, subjects were more engaged with St-NMES than visual condition. All together these results suggest the benefits of the proposed guidance modality not only from an electrophysiological point of view, but also from a subjective perspective.

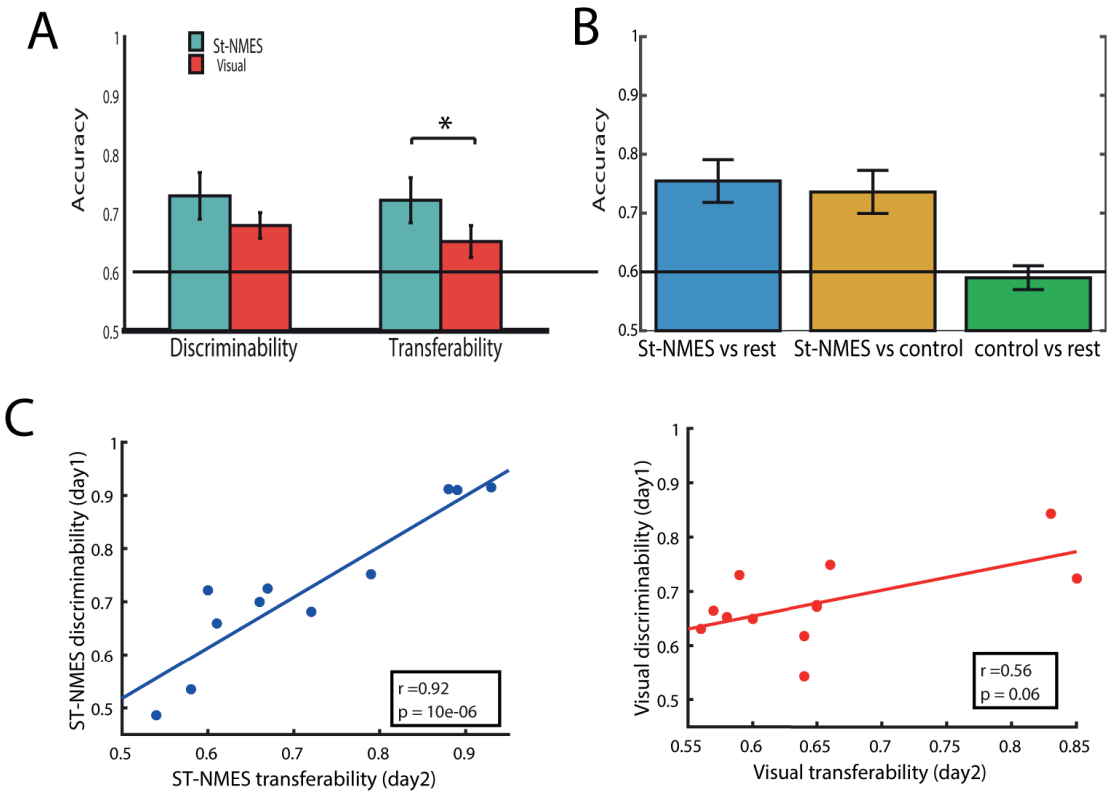

Figure 2:5 Classification accuracy results

a) Left panel represents discriminability results (cross-validation on day1) and right panel represents transferability results (training on day 1 and test on day 2). b) control of artefact discriminability (cross-validations on day 2). The black line represents the chance level estimated at 0.60 with at 95% confidence. c) non-parametric correlation (Spearman correlation) between accuracies from both days (discriminability and transferability results) for St-NMES condition (left panel) and visual condition (right panel).

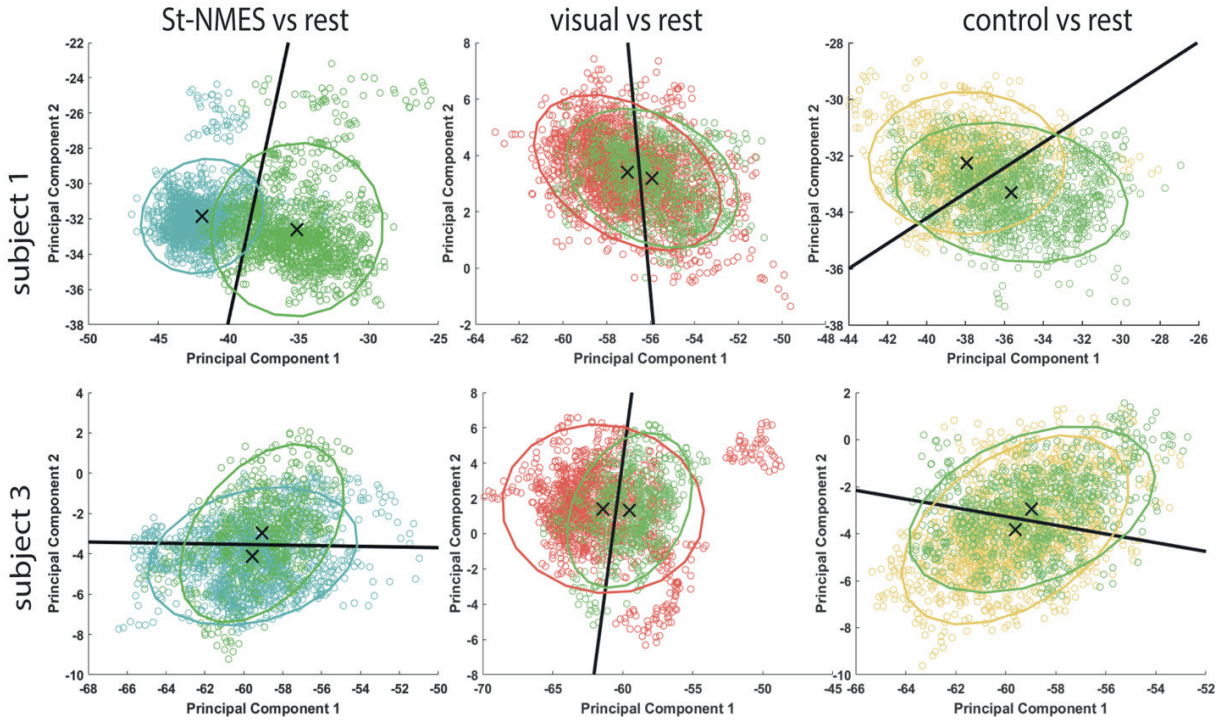

Figure 2:6 PCA analysis, example of 2 representative subjects

PCA analysis between the 4 pairs of tasks St-NMES (blue), visual (red), rest (green) and control (yellow). Representation of the two first principal components of each pairs of tasks. Each dot represents a sample. The ellipsoids represent the covariance matrix of the distriutions and the cross the mean of the distribution. The black line represents the hyperplane computed from an LDA classifier. Subject 1 represents the case of a subject with "bad" MI performance with visual guidance, but "good" MI performance with St-NMES. Subject 3 represents the case of a subject with "bad" MI performance independently of the guidance modality

2.4 Discussion

This study investigated a novel guidance modality for novice subjects during MI based on sensory threshold neuromuscular electrical stimulation (St-NMES) compared to standard visual guidance. We found that St-NMES fostered subjects' performances by enhancing MI neural brain patterns without inducing any bias in the EEG signal.

2.4.1 Enhancement of MI neural correlates

EEG neural correlates of MI production were fostered when the MI guidance was St-NMES compared to visual. Indeed, μ and β rhythms modulations in the contralateral hemisphere were larger with St-NMES. In the case of β frequency band, these results were significantly larger over the fronto-parietal brain regions. This specific enhancement of ERD patterns in the β frequency band could be explained by the hypothesis of Auman et al. (2015) [74], which indicates that oscillations play a crucial role for muscle representations in the brain solicited during MI. This idea is also supported by a recent study showing that oscillations are particularly relevant in the context of corticospinal communication [82]. Importantly, the neural correlates enhancement was linked to an improvement in MI efficiency and not by the stimulation itself. Indeed, the sensory threshold stimulation did not induce detectable brain activation due to the brain treatment of somatosensory afferences. Moreover, MI with St-NMES guidance induced not only larger ERD, but it also enhanced connectivity between fronto-parietal regions similar to those described by fMRI studies. Indeed, fronto-parietal regions such as M1, SMA, PMC in the frontal lobe and inferior parietal lobule, superior parietal lobule and S1, are well described during kinesthetic motor imagery and reflect subjects' MI performances [41–43,45,83]. Furthermore, Hanakawa et al. (2003) [84] demonstrated that activity of the superior precentral sulcus and intraparietal sulcus areas, predominantly on the left hemisphere for right-handed subjects, was associated with more reliable imagery task performance. Along these lines, our results show that subjects were more accurate in the imagery performance with St-NMES. Moreover, it is known that MI has a distinguishable correlate to motor execution which is connectivity between Brodmann's area 7 (superior parietal lobule and intraparietal sulcus) and Brodmann's area 6 (supplementary and pre-supplementary motor areas) [37,42,84,85]. This specific connectivity seemed to be stronger for the St-NMES modality implying that subjects were performing better MI compared to the visual guidance. Due to the limitations of our source localization model, though, results should be taken with caution, and additional analysis using fMRI would be needed in order to confirm these results. However, compared to fMRI studies, no significant ipsilateral activation was detected.

Furthermore, no activity in visual areas was described with the visual guidance condition whereas it is known that visual imagery involves occipital regions and the superior parietal lobules [42]. A possible explanation is that even with visual guidance subjects were able to produce MI and they were not performing visual imagery still, correlates of motor imagery were weaker.

2.4.2 Enhancement of kinesthetic imagery

As already stated in the introduction, it is necessary to enhance kinesthetic experience during MI. Hanakawa et al. (2008) [86] explained that "Motor Imagery likely corresponds to activation of the neural representation of a "potential" movement, which may be triggered by sensory stimuli or retrieved volitionally from motoric memory". That is the reason why athletes or experts, with an efficient memory of the movements, produce more efficient motor imagery of the specific field of expertise [87–89] . On the contrary, for novice users, MI might be mostly triggered by sensory stimuli. Moreover, it is known that motor actions such as motor execution or MI require the knowledge of body representation and body location. Recent evidence has shown that congruent sensory feedback is crucial to properly represent our body [90]. MI performance is linked to the internal body representation [91,92] combined with somesthetic sensations [30]. Indeed, Lorey et al. have shown that proprioceptive information on actual body posture is more relevant for first person perspective imagery [93], which should also be the case for MI. Also, Shenton et al. suggested that proprioceptive in ow may represent the dominant sensory input of body representation [94]. In line with these previous works, our results suggest that, by providing somatosensory input, St-NMES may have helped subjects to trigger motoric memory of a given movement and support better body limb representation, leading to better MI. MI performance may also be enhanced by the attention towards the limb sensations (defined as an internal focus) induced by St-NMES [95]. Thus, St-NMES might be more suitable to encourage subjects to drive efficiently their attentional resources and exploit better motoric memory strategies during MI.

Furthermore, we also assume that St-NMES, by depolarizing motor and sensory nerve, mimics the physiological peripheral MI response. Indeed, Solodkin et al. [42] have shown that kinesthetic MI induces an increase in muscular tone. Several studies confirmed the fact that kinesthetic MI induces an increase of corticospinal tract excitability [44,96]. Recently, Takemi et al. [97] have suggested that this increase could also happen at the spinal cord level measured as an increase of F-wave. Kinesthetic MI "may correspond to activation of the neural correlates of motor representations probably involving sensory threshold activation of the descending motor pathway" [86]. Following this theory, with St-NMES guidance the descending and ascending motor pathways

are both activated below the motor threshold, which might correspond to the physiological activation of the peripheral pathway during MI. As explained in Veldman et al.'s review about sensory electrical stimulation [98], St-NMES activates sensorimotor nerves and sensory volley ascends in the rostral thalamus and project to S1 (BA1,2,3a,3b and 4) and S2 (BA 40 and 43). Due to this activation, St-NMES can induce long-term potentiation in M1 via excitatory glutamatergic synapses. Indeed, it has been shown in several studies that sensory electrical stimulation had the potential to induce brain plasticity in particular the excitability and the organization of the motor cortex [71,99] . Combined to MI, St-NMES probably facilitates the activation of sensorimotor networks and reinforces corticospinal excitability. Thus, St-NMES is a promising tool that, associated to MI, may not only foster brain patterns but also enhance motor learning and recovery by reinforcing peripheral and central pathways activation during MI.

2.4.3 Comparison with other somatosensory guidance/feedback

In this study, we have presented a novel method for providing guidance to induce accurate MI, and compared it to the most common modality (visual) usually provided in the field. Nonetheless, the comparison between St-NMES and other types of kinesthetic feedback, such as a robotic orthosis or vibrotactile feedback, needs to be investigate in the future. Despite it has been demonstrated that a somatosensory feedback is more suitable to perform MI, it remains unclear how such rich feedback could be used without biasing the analysis. As an example, Vukelić et al. (2015) [57] have shown that a robotic orthosis is more suitable than visual feedback to train motor imagery networks, whereas a passive movement of the joint will induce similar activation of motor networks [17,63].

In our experiment we confirmed that when muscular contraction and joint movement are induced by Mt-NMES, a large desynchronization was recorded over sensorimotor areas, similarly to other studies [64]. It worth noticing, that the resting inter-trial interval was sufficiently long, 7 to 8.5 times longer that the Mt-NMES, to prevent any priming effect. Importantly, the control condition also received Mt-NMES and the analysis showed no possible influence of 1s Mt-NMES on results. However, since Mt-NMES has a direct impact on EEG modulation, we may then conclude that the limb should stay at rest during the entire MI task. We may then conclude that the limb should stay at rest during the entire MI task. Nonetheless, vibrotactile stimulation which does not induce any movement, seems to also elicit ERD and bias MI classification. Indeed, Chatterjee et al. (2007) [59] demonstrated that the placement of vibrotactile electrodes induces a significant bias in MI classification accuracy. In our study we did not investigate the possible bias due to different electrodes placements; nevertheless, St-NMES itself did not bias MI classification. Ahn et al. (2014) [61] also

showed that selective attention using vibrotactile stimulation causes a large ERD over the sensorimotor cortex, similarly to motor threshold NMES as revealed in our study. In our case the selective attention to St-NMES did not induce ERD during the NMES-control condition. Further investigation will be needed to shed light on the differences between vibrotactile stimulation and St-NMES. We presume that the main difference between both modalities reside in their mechanisms. Indeed, mechanical vibrations only activated cutaneous afferences, whereas St-NMES directly stimulates sensory and motor nerves which might involve a more complex sensory neural treatment that is less detectable at the cortical level. This hypothesis is in line with an fMRI experiment that also shows that sensory threshold NMES do not significantly induce detectable brain activation [100]. On the contrary, several studies demonstrated significant BOLD activations in the sensorimotor networks during vibrotactile stimulation [65,101,102].

2.4.4 Implication for brain-machine interfacing

The improvement of MI neural correlates thanks to St-NMES enhanced the possibility to classify more accurately MI with EEG. These results could possibly have a positive impact on brain-machine interfaces (BMI) based on MI. Thanks to BMI systems, subjects can receive in real-time a feedback on their ability to generate the expected brain pattern. Interestingly, subjects' MI performances have been correlated to motor skills level in healthy subjects [27,88,89]. Even if EEG-based BMI are very promising, they are still limited by the poor reliability and stability of decoders [49,103]. Our results suggest that St-NMES could be interesting to be used as a feedback during BMI-based MI training. We showed that classification accuracy was higher and a large majority of subjects obtained better classification accuracy under St-NMES guidance (10 over 12 subjects). More importantly, subjects' performances were more stable over time contrary to standard BMI with visual guidance approaches. Nonetheless, two subjects did not improve their performances with St-NMES. These two subjects were right-handed subjects similarly to 8 other subjects. Our study does not allow us to assess any hand-related differences in MI ability. To the best of our knowledge, we do not know any prior work showing differences between left- and right-handed MI performers. Further online studies involving a larger cohort of subjects, able-bodied and with motor disabilities, will be needed to understand the advantages and limitations of the proposed approach.

Chapter 3 Sensory threshold neuromuscular electrical stimulation promotes the acquisition of BMI skills

3.1 Introduction

We previously explored the use of sensory-threshold NMES (St-NMES) in an offline BMI study. Our results showed that St-NMES alone did not elicit brain patterns significantly different from resting. Furthermore, during MI, St-NMES induced significantly larger activity over sensorimotor areas and significantly increased connectivity within the fronto-parietal cortical network as compared to visual feedback. The objective of this new study is to investigate the usability of St-NMES as a real-time feedback and its effect on BMI performance compared to a visual feedback. As previously suggested, learning to control a BMI system might be compared to a natural motor learning although no motor output is required. Thus, in this experiment we also investigated the underlying mechanisms linked to BMI learning. According to motor learning theories, acquiring the skills to control a BMI should induce plastic changes at cortical and subcortical levels. We hypothesized that BMI based on St-NMES will facilitate the acquisition of BMI skills and will induce an increase corticospinal tract (CST) excitability, as measured by motor-evoked potentials (MEP) elicited by single pulse transcranial magnetic stimulation (TMS) of the corresponding muscle. Such an increase in CST excitability would be an indicator of positive plastic changes associated to cortico-motor outputs in healthy and CNS-injured humans [55,56].

3.2 Material and Methods

In this experiment, we investigated the impact of the feedback modality on subjects and system learning, comparing St-NMES to a visual feedback, during a BMI training. Twenty healthy subjects (10 female, age: 25.6 ±2.9, from 22 to 31 years old) right handed and naive to MI and BMI, took part in the experiment. Ten of these subjects (including 5 female) were enrolled in a cross-over BMI experiment and ten other subjects (gender and aged-matched) were recruited in a control St-

NMES experiment. Every subject provided written informed consent. The experimental procedure was approved by the Cantonal Ethical Committee of Geneva (Ethics approval number: PB_2017_00295).

3.2.1 Cross-over BMI experiment

Subjects in the cross-over design BMI experiment performed both BMI protocols based on St-NMES or visual feedback (Figure 3:1). The first BMI modality (St-NMES or visual) was pseudo-randomly assigned to each subject, balancing the conditions. For both BMI systems, subjects received similar instructions and they were asked to perform the same MI task. Instructions were the following: "you are requested to perform continuous MI of wrist and finger extension of the dominant hand while looking at visual feedback on the screen or while receiving St-NMES feedback. In order to perform MI, you should not visualize your hand, but you need to feel it without making any muscular contraction. Try to keep a consistent strategy over trials". Each BMI protocol was composed of three consecutive days (Figure 3:1): an offline calibration session (day 0) followed by two days of closed-loop BMI training (days 1 and 2). Before and after each recording of days 1 and 2, MEP peak-to-peak amplitude as well as the resting motor threshold (RMT) of the primary motor cortex, were recorded with transcranial magnetic stimulation (TMS). Between the first and second BMI training protocols a break of 10 to 14 days was respected in order to limit a possible learning effect being transferred from one feedback modality to the other.

3.2.1.1 Offline calibration (day 0)

Subjects were seated on a fixed chair in front of a computer screen with arms on a folded towel with approximately 15 degree of wrist flexion. During the whole BMI experiment, EEG was recorded at a sampling frequency of 512 Hz with 16 active surface electrodes placed over the sensorimotor cortex i.e., on positions Fz, FC3, FC1, FCz, FC2, FC4, C3, C1, Cz, C2, C4, CP3, CP1, CPz, CP2 and CP4 of the 10/20 system (reference: right mastoid; ground: AFz; gtec gUSBamp, Guger Technologies OG, Graz, Austria). Both BMI protocols, with St-NMES or visual feedback, were based on the same BMI system except for the feedback modality. Raw EEG was filtered in the frequency band [1-45] Hz (Butterworth 4th order). Noisy channels (detected post-experiment by visual inspection) were manually replaced by the mean of the orthogonal neighbouring channels. Each of the EEG channel was spatially filtered with a Laplacian derivation, whereby the weighted sum of the voltages of orthogonal neighbouring channels is subtracted from that channel. Trials with a filtered EEG signal above 100 μV were marked as artefactual and discarded. Then, trials were

concatenated per condition (MI or rest trials). As a final pre-processing step, we computed the power spectrum density (PSD) of each spatially-filtered EEG channel for the frequency bands [8 26] Hz with 2 Hz resolution. We have restricted our analysis to μ and β bands, with an upper limit of 26 Hz in order to avoid eventual noise from St-NMES around 30 Hz.

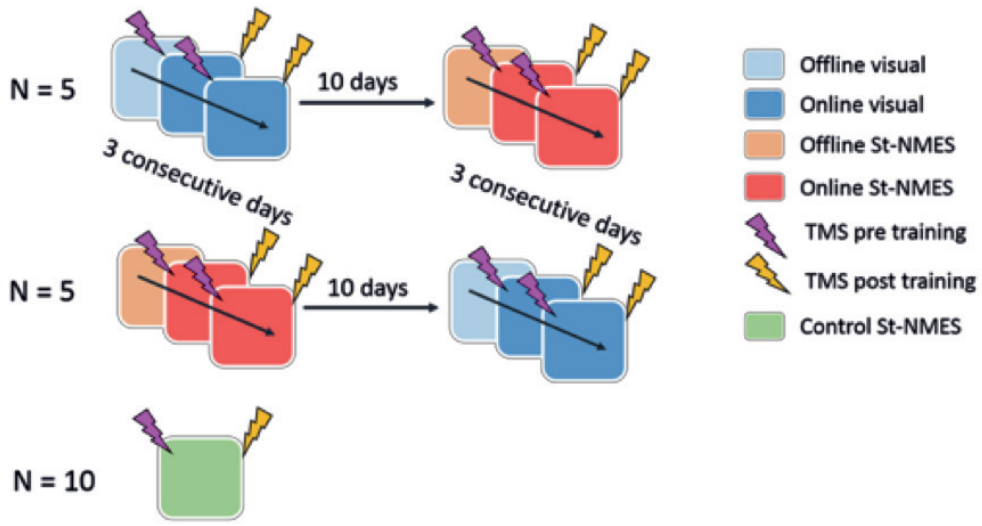

Figure 3:1 Experimental protocol

Ten healthy subjects were enrolled in the cross-over design BMI experiment. Five subjects started with BMI with visual feedback (blue squares) and 5 subjects with BMI-St-NMES (red squares). Each BMI training block was composed of three consecutive days. Day 0 was an offline calibration recording. Day 1 and day 2 were closed-loop BMI training. Before and after each BMI training session, we recorded MEP-peak-to-peak amplitude as well as the resting motor threshold of the extensor carpi longus radialis with TMS (TMS-pre and TMS-post). A break of, at least, 10 days was respected before starting the other feedback modality. Ten other subjects (aged and gender-matched) participated to the control St-NMES experiment (green square), during which we tested the impact of St-NMES alone on CST excitability.

Raw EEG was filtered in the frequency band [1-45] Hz (Butterworth 4th order). Noisy channels (detected post-experiment by visual inspection) were manually replaced by the mean of the orthogonal neighbouring channels. Each of the EEG channel was spatially filtered with a Laplacian derivation, whereby the weighted sum of the voltages of orthogonal neighbouring channels is subtracted from that channel. Trials with a filtered EEG signal above 100 μV were marked as artefactual and discarded. Then, trials were concatenated per condition (MI or rest trials). As a final

pre-processing step, we computed the power spectrum density (PSD) of each spatially-filtered EEG channel for the frequency bands [8 26] Hz with 2 Hz resolution. We have restricted our analysis to μ and β bands, with an upper limit of 26 Hz in order to avoid eventual noise from St-NMES around 30 Hz (see below). PSDs were computed every 62.5 ms, using the Welch method with an internal Hanning windows of 500 ms (75% overlap), and the obtained data were log-transformed. The five most relevant features, one channel associated with one frequency bin, (e.g. channel C3 at [10 12] Hz) were manually selected. Finally, a BMI decoder was trained to discriminate MI neural correlates from the resting condition using these features (EEG sample).

3.2.1.2 Online closed-loop BMI training (day 1 and day 2)

In day 1 and day 2, subjects were asked to perform 4 runs of 15 trials of MI and 5 trials of rest. For each trial, subjects received real-time feedback about their performance –i.e., probability that they were performing MI or resting. This probability was computed by integrating the outputs of the decoder to EEG samples (extracted from the raw EEG as in the calibration session) in order to better estimate the confidence of the subject's intention. More details on BMI decoder training and operation can be found in [104]. The BMI response was "MI" when the integrated probability reached a certain confidence threshold. In order to keep the same motivation and involvement across the BMI training, the decision threshold was manually adjusted (from 60% to 85%) to obtain an average of 70% of success for both BMI feedback modalities (St-NMES or visual), as done in [23]. If needed, the decision threshold was adjusted after each run depending on performance. Each trial started with a fixation cross (3 s), then a cue indicating the type of trial (MI or resting, 1 s), followed by the task (MI or resting, up to 7 s). Inter-trial periods lasted from 4 to 6 s. MI trials were considered as a success when the subject managed to reach the decision threshold in less than 7 s. In resting trials, designed to probe that the BMI decoder was not biased by feedback (especially, St-NMES), subjects had not to reach the decision threshold during 7 s.

3.2.1.3 St-NMES feedback

Two pairs of NMES oval electrodes (4 x 6.4 cm) for neurostimulation were placed on the posterior part of the forearm (*Figure 3:2*). Sensory-threshold amplitudes of NMES were evaluated independently for each pair of NMES channels and each individual subject before recordings (on average St-NMES amplitude was 4 ±1 mA). Sensory-threshold stimulation is the minimal intensity necessary to induced a light tingling sensation in the arm for the proximal channel and in the hand and fingers for the distal channels. We verified that no muscular contraction was elicited by visual and tactile inspections. The frequency of stimulation was fixed to 30 Hz. In order to minimize the noise injected by NMES on the EEG signal, we respected the procedure described in the literature

[105]: The NMES device was installed on a different surface than the EEG device and an electrode was placed on the ipsilateral biceps to ground the subject. During online trials, subjects started the MI task right after the appearance of the cue on the screen. Then, during a maximum of 7 s, when the decoder confidence that the subject was performing MI increased, St-NMES was delivered on the two proximal channels. On the contrary, if the confidence decreased, no St-NMES was provided. Moreover, once the decoder confidence was approaching the decision threshold, the subject received St-NMES on the proximal and distal channels. Thus, at every time point subjects were informed about the dynamics of their BMI performance. The success of the trial was indicated on the screen (similarly to the visual condition). For the resting trials, feedback was identical; i.e. subjects received stimulation when the system classified subjects' performance as MI.

3.2.1.4 Visual feedback

Subjects received similar instructions except that the feedback provided was visual. During trials, a bar was moving up when the decoder confidence was increasing, and down when it was decreasing (*Figure 3:2*). The trials ended when the bar reached the decision threshold (represented by a line on the screen). During the resting trials the visual feedback was the same, and the purpose was to keep the bar low, avoiding it to reach the decision threshold during 7 seconds.

3.2.1.5 Transcranial magnetic stimulation (TMS)

Subjects were seated on a chair with the arms pronated and relaxed on a table. They were instructed to keep their eyes opened, and to stay relaxed. Surface electromyography (EMG) was recorded from their extensor carpi radiali (ECR). The signal was amplified (gain 500) and online filtered (Noraxon DTS Receiver, sampling rate 3kHz, high-pass filter/sensor-based analog Sallen-Key 10 Hz, low-pass filter: 1000 Hz digital FIR 128th order Butterworth 1kHz). A Magstim 200 stimulator TMS

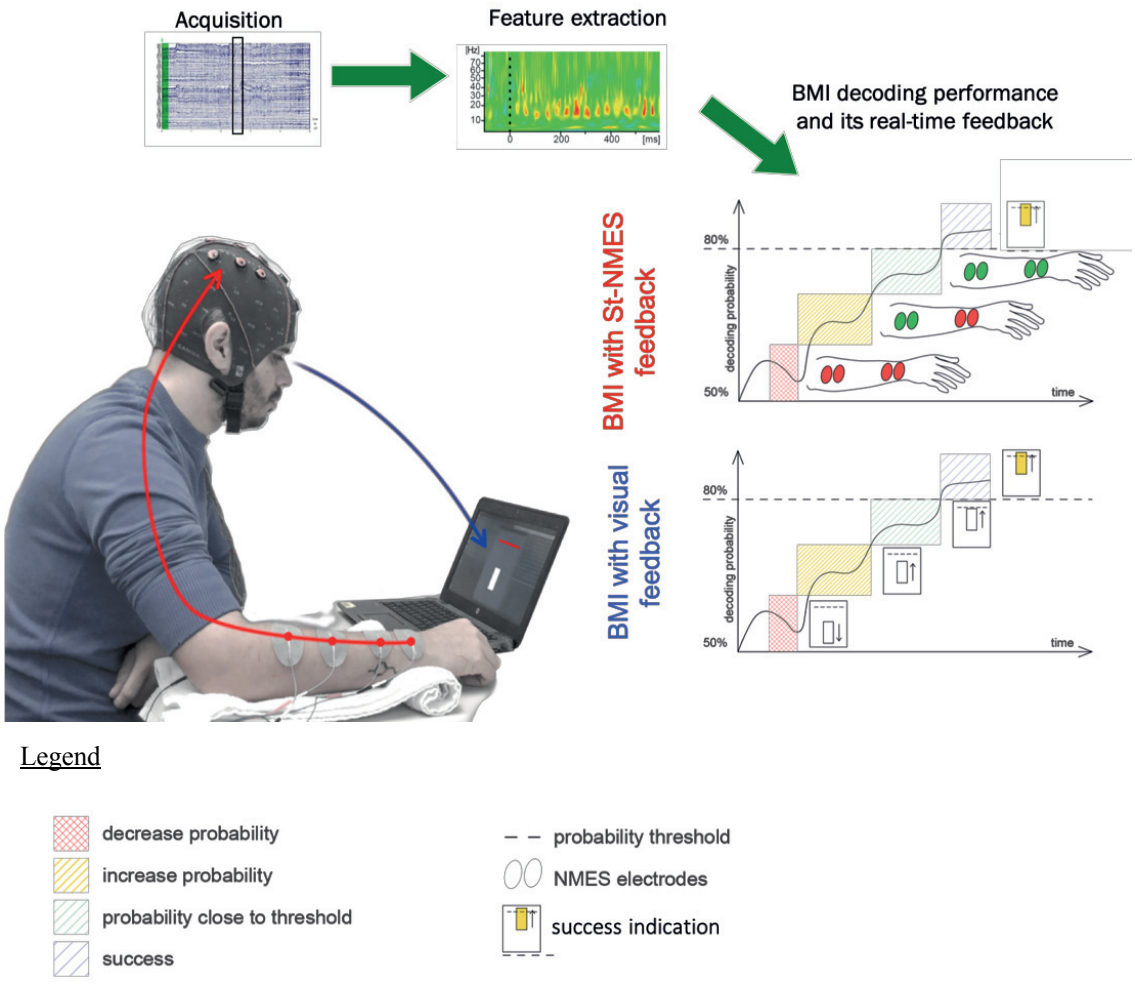

Figure 3:2 Illustration of the BMI training experiment

Ten healthy subjects were enrolled in the cross-over design BMI experiment. Five subjects started with BMI with visual feedback (blue squares) and 5 subjects with BMI-St-NMES (red squares). Each BMI training block was composed of three consecutive days. Day 0 was an offline calibration recording. Day 1 and day 2 were closed-loop BMI training. Before and after each BMI training session, we recorded MEP-peak-to-peak amplitude as well as the resting motor threshold of the extensor carpi longus radialis with TMS (TMS-pre and TMS-post). A break of, at least, 10 days was respected before starting the other feedback modality. Ten other subjects (aged and gender-matched) participated to the control St-NMES experiment (green square), during which we tested the impact of St-NMES alone on CST excitability.

system was used to deliver single-pulses with a monophasic current waveform. A figure-of-eight-shaped coil (double 70 mm alpha coil) was used, and the center of the coil was placed over the motor hand area, with an angle of 45 degrees relative to the midsagittal line. The first TMS recording (day 1 before closed-loop BMI session) was used to define the optimal position (motor hot spot). By slightly moving the coil over the left M1 area until we selected the spot with the highest and most stable MEPs response from the ECR for a fixed intensity of stimulation. The exact position of the coil and of the EMG electrodes were marked with a felt pen and preserved for the four recordings (day 1 pre and post, day 2 pre and post). Then, we defined the stimulus intensity S1 used to evoke MEPs in the range of approximately 0.8 to 1 mV peak-to-peak amplitude. This stimulation intensity and the hot spot were identical for the four recordings (day 1 pre-post and day 2 pre-post). We also measured resting motor threshold (RMT) defined as the lowest stimulus intensity to evoke at least five out of ten MEPs responses (with peak-to-peak amplitude of 0.05 mV) [106]. Finally, 25 MEPs of the ECR were recorded at the defined stimulation intensity S1. The inter-stimulus-intervals were randomized in-between (7 s ± 2 s).

3.2.2 Control St-NMES experiment

Ten subjects (gender and aged-matched) were enrolled in the control experiment (Figure 3:1). We investigated if St-NMES alone had an impact on modulation of CST excitability. Thus, we performed similar TMS recordings before and after an St-NMES session. MEP peak-to-peak amplitude as well as RMT were recorded. The St-NMES session was composed of 4 runs of 15 trials (similar to the number of MI trials) of 7 s. We decided to set the time to 7 s because it is the maximum length of one BMI-St-NMES trials. During these trials, subjects had to relax and not to move. Each trial was the same than an MI trial. After the cue subjects received first 4 s St-NMES at the proximal channel and then 2 s St-NMES on both channels, proximal and distal.

3.2.3 Data analysis

One subject was excluded from all EEG data analysis because EEG data were corrupted by artefacts for the first day of St-NMES online training.

3.2.3.1 Motor-evoked potentials (MEP) and resting motor threshold (RMT)

An increase CST excitability has been reported in literature as a marker of MI learning [107]. MEP amplitude is a common measure of CST excitability [108]. That is why we recorded MEP peak-

to-peak amplitude with TMS before and after every BMI training was analysed offline. MEP were visually inspected and trials with muscular pre-activation were discarded. We extracted MEP peak-to-peak amplitude of each trial, and trials were averaged for each of the 4 recordings (day 1 pre-post, day 2 pre-post). Results for each recording were, then, averaged across subjects. Importantly, for the 4 consecutives TMS recordings (in day 1 and 2), the hot spot, EMG electrodes placement and stimulation intensity S1 were kept identical. We compared the effect of BMI training on CST excitability by comparing MEP peak-to-peak amplitude. Similarly, we also compared the effect of BMI training on the recorded RMT.

3.2.3.2 Event-related desynchronization

The contingency between neural correlates of motor imagery (as detected by the BMI) and success delivery has been showed to be important in order to induce brain plasticity [23]. A prominent component of these sensorimotor rhythms is the ERD, which we computed using the last second of each successful MI trial (when the desynchronization of the contralateral sensorimotor cortex has to be strong) and the last second of preceding inter-trial period (considered as our baseline) [14] (see Equation 2:1). ERD analysis was limited to the electrodes FC3, C3 and CP3 since they are located over the contralateral sensorimotor cortex. For each subject, ERDs in the μ (8-12 Hz) and β (14-26 Hz) bands were averaged across trials. Before averaging, we discarded trials contaminated by artifacts by computing the z-score of the power spectrum in the μ and β bands for each electrode of interest. A trial was discarded if a MI window or its corresponding baseline had a z-score above 3 for μ or β.

3.2.3.3 BMI success rate

We controlled that subjects' BMI success rate was on average 70% for both feedback modalities so that the motivation and involvement during the MI task were similar. The number of success trials (i.e., number of times the decision threshold was reached), was divided by the total number of trials. Moreover, in order to probe that the decoder was not biased, especially during St-NMES feedback, we also computed the success rate of rest trials.

3.2.3.4 Decoding accuracy

EEG processing was similar to the one described in paragraph offline calibration 3.1.1.2. In addition to computing subjects' BMI performance at the trial level, designed to be constant, we also report BMI decoding accuracies at the single EEG sample level that is not affected by the value of the decision threshold.

3.2.3.5 BMI speed

We compared whether the speed of command delivery during closed-loop sessions (time for

the BMI to reach the decision threshold) was different between feedback modalities. For this a-posteriori analysis we computed the time needed for every subject and trial to reach different decisions ranging from 50% to 100%. For trials that ended with a cumulative probability below the decision threshold, the time was set to 7 s (maximal duration of a trial).

3.2.3.6 Stability of MI features

To investigate the stability of MI features, we analysed how the distribution of the selected features on day 1 and 2 diverged from the original distribution from day 0. Feature stability was computed as the Kullback-Leibler divergence between the features' distribution from day 0 and the distribution of each run (4 runs per day).

3.2.4 Statistical analysis

For all analyses, we defined the significance level to 0.05. A Kolmogorov-Smirnov test did not reject the null hypothesis of normal population distribution for MEP data, RMT data nor for ERD data (evaluate independently for each day each condition). For MEP and RMT data sets we performed a repeated-measure ANOVA with three within-subject factors; namely feedback (St-NMES or visual), time (pre or post training with the online BMI), and day (day 1 or day 2). For ERD data we performed a two within-subjects repeated-measure ANOVA between feedback x days independently for the three channels FC3, C3 and CP3. The ANOVA analyses were followed by post-hoc paired-wise comparison analyses with a two-tailed paired t-test, Bonferroni corrected. For decoding accuracy data Kolmogorov-Smirnov test indicated that the decoding accuracy data, only the St-NMES on day did not follow a normal distribution ($D(9) = 0.29$, $p = 0.031$). We performed a repeated ANOVA analysis with two within-subjects factors; namely feedback and day. The amount of delivery success as well as the amount of resting trials success among conditions were compared with a Wilcoxon signed-rank two-tailed paired test. To analyze stability of MI correlates over runs, we compared Kullback-Leiber distance between MI distributions from day 0 to days 1 and 2 with non-parametric Wilcoxon signed-rank two-tailed paired tests, and we applied FDR correction for multiple comparisons.

3.3 Results

3.3.1 Cortico-spinal tract excitability

We investigated if the feedback modality (feedback factor: St-NMES or visual) could influence CST excitability after BMI training (time factor: pre, post), and if it induced an effect across days (day factor: day 1, day 2) (Figure 3:3). The ANOVA analysis showed no interaction among feedback x time x days factors ($F(1,9) < 0.01$, $p = 0.64$). The time factor had significant effect ($p < 0.01$) and we could notice a trend for the feedback effect ($p = 0.08$). No significant effect was found for the day factor ($p = 0.40$). However, there was a significant interaction between feedback x time ($F(1,9) = 6.73$, $p = 0.03$). Post-hoc analyses, Bonferroni corrected, revealed that St-NMES modality significantly increased MEP peak-to-peak amplitude after BMI training (St-NMES pre = 1.09±0.52 mV, St-NMES post = 1.45±0.52 mV, two-tailed paired t-test $p < 0.01$), contrary to the visual feedback (Visual pre: 0.94±0.28 mV, Visual post: 1.05±0.29 mV, two-tailed paired t-test $p = 0.14$). No significant difference between feedback modalities were found pre-intervention (two-tailed paired t-test $p = 0.34$), but they were significantly different after the intervention (two-tailed paired t-test $p = 0.03$). No significant interaction between factors feedback x time x days was found for RMT ($F(1,9)$ 0 8.64, $p = 0.089$) and no interaction was found between feedback x time ($F(1,9) = 2.74$, $p = 0.13$.

Figure 3:4a illustrates the intra-subject variability of CST modulation over days. Using BMI-St-NMES, 80% of subjects increased CST excitability for both days after training, whereas only 30% of subjects did with the visual feedback. Figure 3:5 shows the statistical analysis for each individual subject, comparing MEP trials recorded before and after a BMI session based either on St-NMES feedback or visual feedback. The comparison was performed with a non-parametric Wilcoxon paired test (two-tailed). Results showed that 8 subjects obtained a significant increase in MEP peak-to-peak amplitude after one of the BMI - St-NMES session whereas only 3 subjects showed a significant increase in MEP after one of the BMI-visual session.

The control condition was used to examine the impact of St-NMES alone (without MI) on CST excitability. Subjects received the maximum amount of stimulation that a subject could have received in the BMI- St-NMES group. St-NMES alone had no significant effect on MEP-peak-to-peak amplitude (Control pre = 0.98±0.40 mV, Control post = 1.04±0.45 mV, two-tailed paired t-test $p = 0.95$) (Figure 3:3) The MEP peak-to-peak difference between post and pre-stimulation was on average 0.06±0.2 mV (see Figure 3:4b).

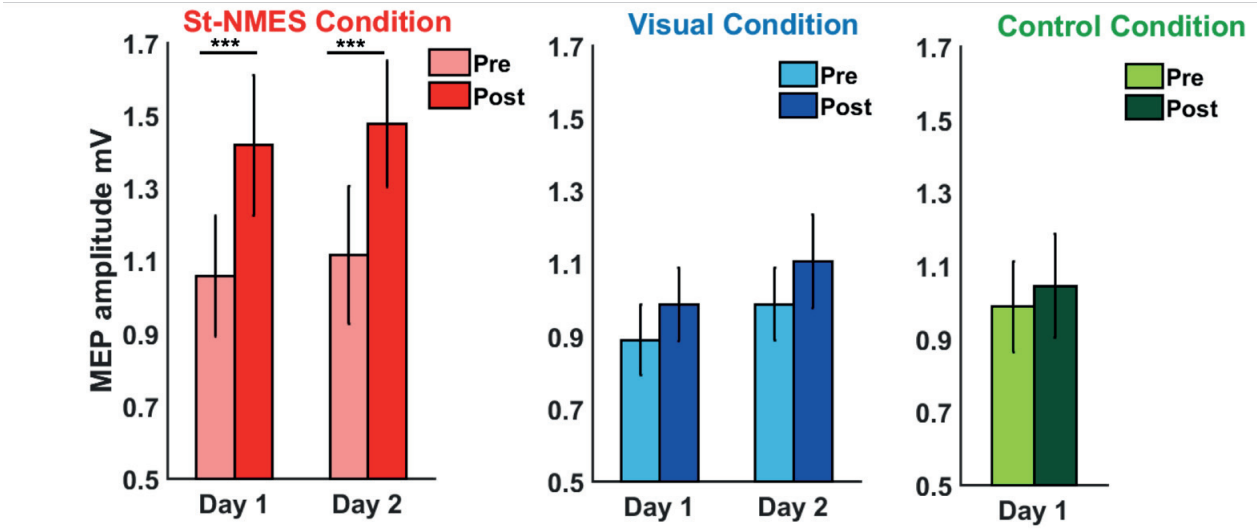

Figure 3:3 MEP peak-to-peak amplitude.

*The figure shows the average MEP peak-to-peak amplitude with its standard error of the mean, averaged across subjects for each of the TMS recordings. From the left to right panel, it shows the MEP amplitude recorded pre and post BMI intervention for St-NMES feedback day 1 and day 2, for BMI with visual feedback, and finally for the St-NMES condition (that consists of only St-NMES stimulation without MI). A paired-wise comparison, Bonferroni corrected was applied. *** indicates $p < 0.01$.*

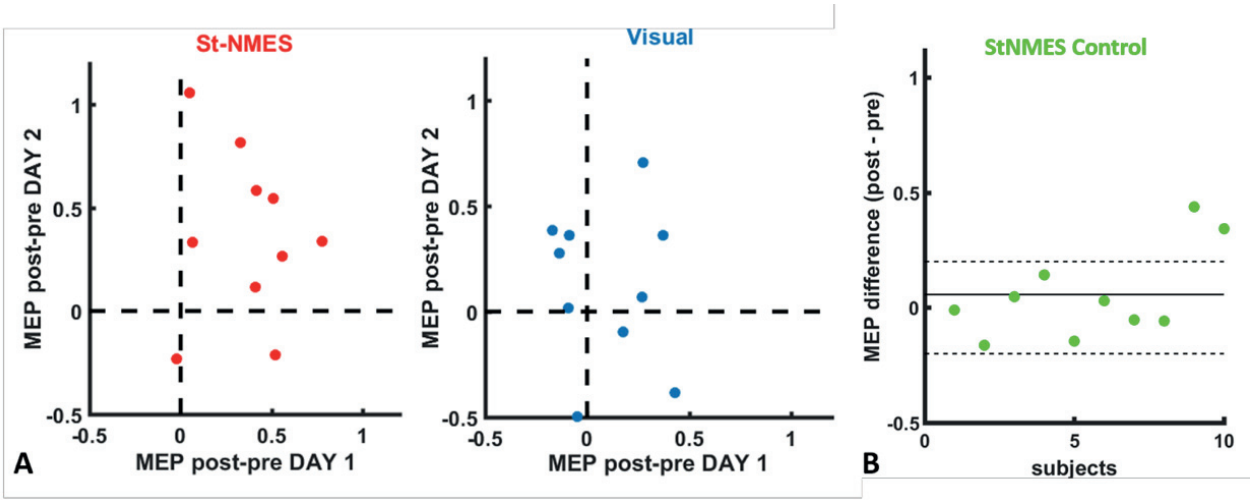

Figure 3:4 Modulation of CST excitability per subject.

A) Difference between post and pre-BMI interventions for both online BMI days. It reflects the stability of MEP peak-to-peak results across two days. The square on the top-right highlights subjects that increased their CST excitability after each day of BMI training. For St-NMES feedback, 8 subjects out of 10 had an increase of MEP amplitude both days. With a visual feedback, only three subjects out of ten obtained a consistent increase of MEP amplitude. B) Difference between post and pre-St-NMES stimulation session. No MI was performed. The black line indicates the mean difference (0.06 mV) and the dashed lines the standard deviation.

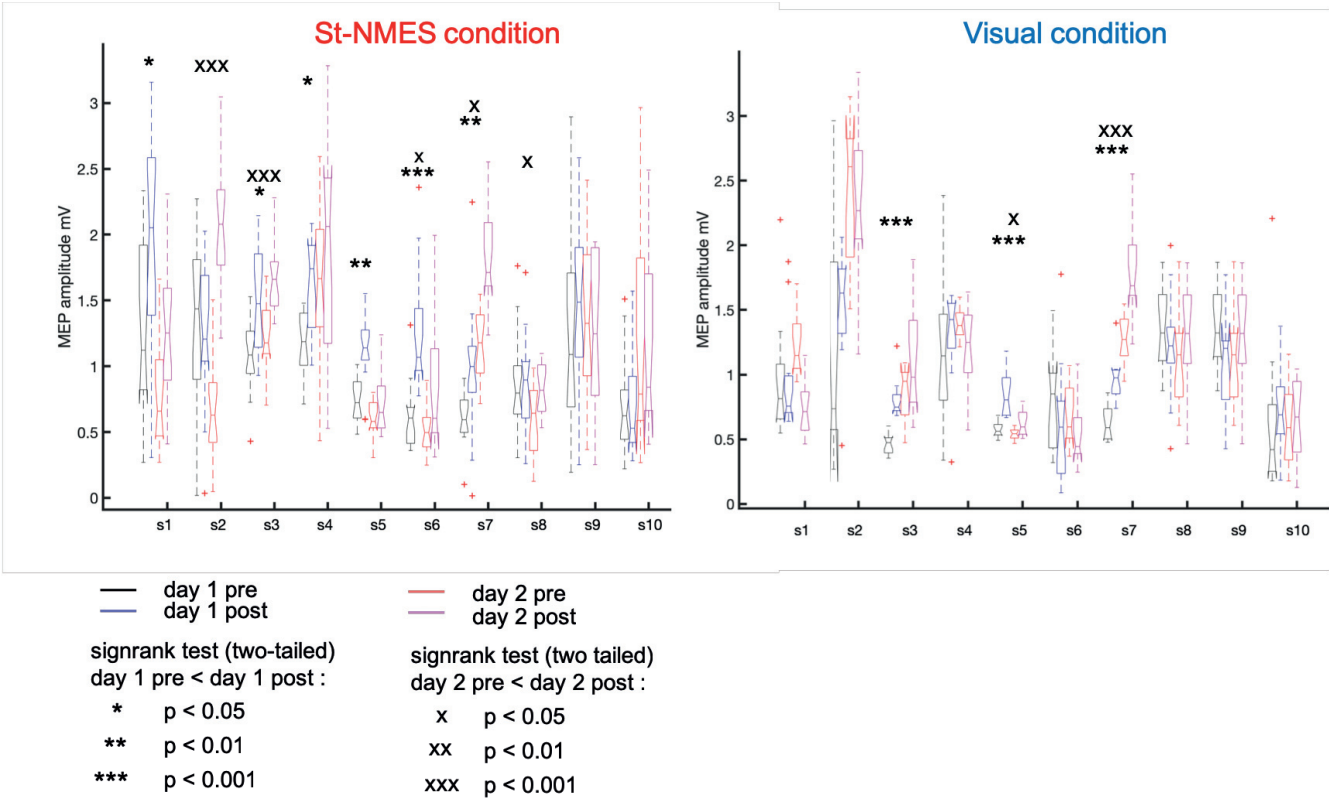

Figure 3:5 Modulation of CST excitability per subject, statistical analysis

Each boxplot represents the distribution of 15 MEP peak-to-peak amplitude recorded before (pre) or after a BMI session either with St-NMES feedback (left panel) or visual feedback (right panel) for each individual subject. ***Black*** *boxplots represent MEP recorded over* ***day 1 before*** *the BMI session,* ***blue*** *boxplots: MEP over* ***day 1 after*** *BMI session,* ***red****: MEP over* ***day 2 before*** *BMI session****, magenta****: MEP* ***over day 2 after*** *BMI session. For each subject we compared the difference in MEP amplitude for both days. The paired-wise comparison was performed with a non-parametric Wilcoxon paired-test (two-tailed). On the figure,* ***** *represent a significant MEP* ***increase*** *after BMI during* ***day 1*** *and* ***x*** *represent a significant MEP* ***increas****e after BMI during* ***day 2.***

3.3.2 Event-related desynchronization

We wanted to compare the impact of feedback modality on the ability to desynchronize the contralateral sensorimotor rhythm. Figure 6 shows the strength of ERD recorded over the contralateral sensorimotor network. No significant differences could be observed for the μ band ($p >$ 0.1, paired-ttest two tailed not corrected). However, in the β band, subjects exhibited a significantly stronger ERD over C3 and CP3 channels. An ANOVA analysis showed a significant effect of the feedback modality (C3, $p = 0.05$ and CP3, $p = 0.024$), with larger ERD for St-NMES compared to visual feedback modality. Moreover, the ANOVA analysis revealed a significant interaction day × feedback ($F(1,8) = 7.06$, $p = 0.029$) for the ERD recorded over CP3. The paired-wise comparison, followed by a Bonferroni correction, showed that on day 2 the ERD were significantly larger with St-NMES compared to visual feedback (St-NMES: -: -44.03±4.5, Visual: -30.56±6.62, $p = 0.01$). Moreover, for the visual feedback, ERD were significantly smaller on day 2 (day 1: -37.53±4.8, day 2: -30.56±6.62; $p = 0.04$); whereas for St-NMES, ERDs tend to be larger the second day but the difference was not significant (day 1: -37.88±5.30, day 2: -44.03±4.5; $p = 0.06$). There was no significant interaction for C3 ($F(1,8) <1.73$ $p = 0.22$) nor for FC3 ($F(1,8) < 0.001$ $p = 0.99$).

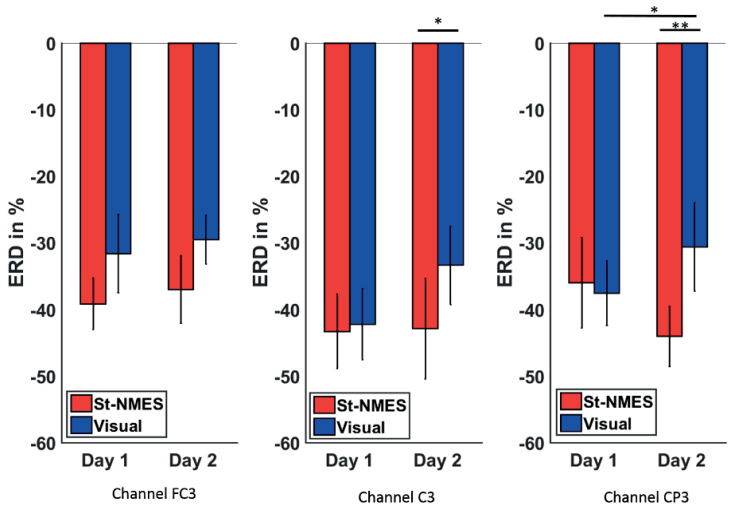

Figure 3:6 Event related desynchronization ERD in β band (14-26 Hz)

*ERD for channels FC3 C3 and CP3, for both days and each feedback (red St-NMES, blue visual). The bar plot indicates the mean and the error of the mean. Statistical analyses were based on a Bonferroni-corrected two-tailed paired t-test. * $p < 0.05$; ** $p < 0.01$.*

3.3.3 BMI performance

We also investigated if the feedback modality also had an effect on BMI performance (Figure 3:7). In both conditions, and as per our experimental design where we adjusted the decision threshold of the BMI for every subject and session, subjects reached a similar amount of success during online MI trials (Figure 3:7a) St-NMES 73.3% ±9.9; visual 74.1% ±16.4, (Wilcoxon signrank two-tailed test, $p = 0.92$). The amount of success for resting trials was neither significantly different among groups: St-NMES 66.0% ±21.9; Visual: 68.6% ±23.8, (Wilcoxon signrank two-tailed test, $p = 0.85$). This indicates that the BMI based on St-NMES was not biased by somatosensory feedback, as subjects were able not to deliver commands during the resting trials even if they were eventually receiving St-NMES.

We also compared BMI decoding accuracies at the single sample level, which is not affected by the value of the decision threshold that was manipulated to achieve a constant level of BMI performance. The single sample accuracy was on average significantly better for St-NMES feedback compared to visual feedback (on Figure 3:7b). A repeated measure ANOVA revealed a significant effect of the feedback factor: St-NMES: 0.89±0.09, Visual: 0.80±0.12, $p = 0.04$. There was no significant interaction between feedback x day $F(1,8) = 0.16$, $p = 0.70$). Nevertheless, we can notice that St-NMES had a positive influence on BMI decoding accuracy (Figure 3:7c). Although in day 1 there was no significant difference (St-NMES: 0.88±0.11, Visual: 0.80±0.17; two-tailed paired t-test $p = 0.28$), for day 2 St-NMES had a significantly better classification accuracy (St-NMES: 0.91±0.11, Visual: 0.80±0.11, two-tailed paired t-test $p = 0.004$).

As for any motor skill, apart from better accuracy, another indication that St-NMES feedback better supports BMI learning is the speed at which commands were delivered. Figure 3:8reports BMI speed during closed-loop sessions for both feedback modalities for different decision thresholds (DT). On average across all subjects and trials (Figure 3:8a), BMI based on St-NMES seemed to be faster than when the BMI was coupled to visual feedback on both days for DTs up to 70%. In particular, subjects did significantly better on day 2 for St-NMES at DT 0.6 (signrank Wilcoxon two tailed test, FDR correction, $p = 0.039$), and there was a positive trend for DTs 0.5, 0.55 and 0.65 (signrank Wilcoxon two tailed test, FDR correction, $p = 0.058$ for all three DTs). For higher decision thresholds BMI speed was similar for both feedback modalities. It is worth noting that the actual DTs set during the closed-loop sessions were, on average, always below 75% (St-NMES day 1: 0.74±0.07; St-NMES day 2: 0.72±0.07; Visual day 1: 0.70±0.08; Visual day 2: 0.71±0.05; no statistical differences, Wilcoxon signrank two-tailed test). Moreover, as illustrated in Figure 7b right panel, a higher percentage of subjects reached decision thresholds in between 60% and 75% at least once (60% was

the lowest threshold actually used during the closed-loop sessions) with St-NMES, while only for 80% more subjects did it with visual feedback. At the single subject level (Figure 3:8 b), and combining results for the two days, 5 subjects out of 9 were faster with St-NMES, while only 1 did with visual feedback, the remaining 3 achieving similar BMI speed.

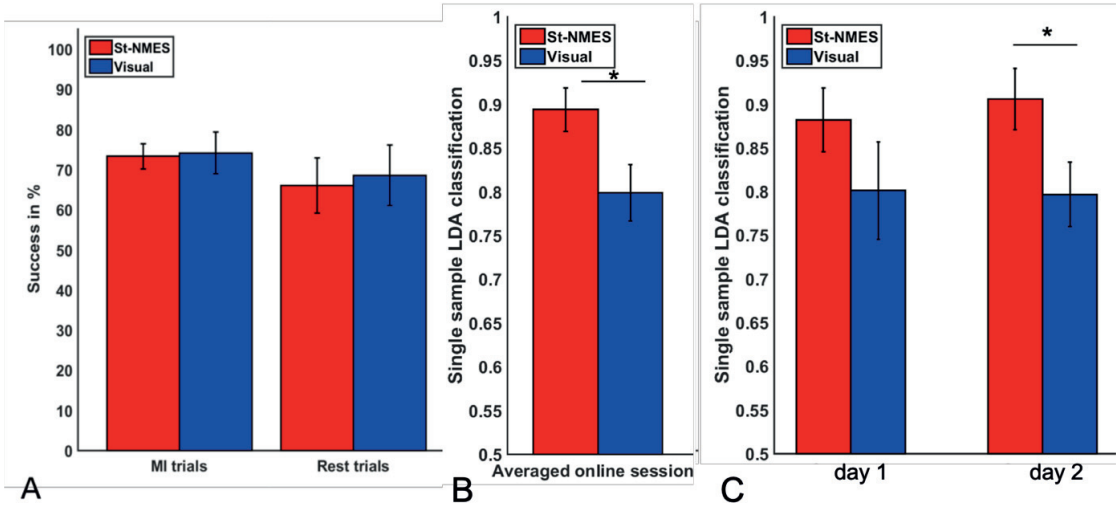

Figure 3:7 BMI decoding accuracy

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***A:** Percentage of success for online MI trials and resting trials for both feedback conditions, St-NMES (red) and visual (blue). No significant difference in success was reported suggesting first that subjects' involvement and motivation should be similar and second that the BMI system was not bias by St-NMES feedback since subjects managed to perform resting trials. **B:** Single sample accuracy of BMI based on St-NMES feedback (red) or visual feedback (blue) for both online days. **C:** St-NMES significantly enhanced BMI accuracy on the second day. Statistical analyses were based on a two-tailed paired t-test. * $p < 0.05$.*

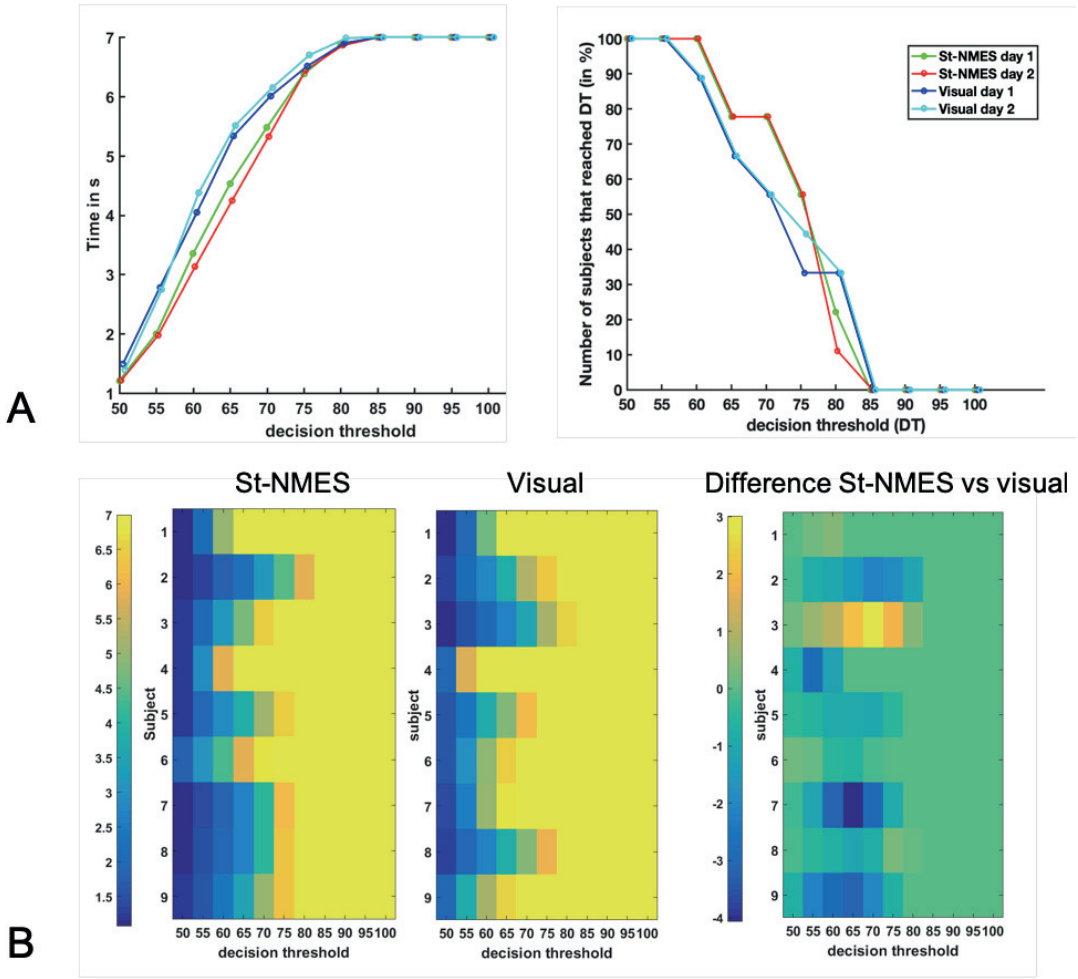

Figure 3:8 BMI speed decoding

*BMI speed during closed-loop sessions for both feedback modalities, measured as the time needed by the BMI to reach the decision threshold. **A:** Average BMI speed across all subjects and trials, for each feedback modality and day, for different decision thresholds ranging from 50% to 100% (left) and percentage of subjects who successfully reached the decision thresholds (DT). For trials that ended with a cumulative probability below the decision threshold, the time was set to 7 s (maximal duration of a trial). **B:** Single subject analysis for St-NMES and visual feedback, both days together. The right panel shows the speed difference between the two modalities per subject. Yellow highlights faster performance for visual feedback compared to St-NMES, blue faster for St-NMES compared to visual, and green equal BMI speed for the two feedback modalities.*

On the physiological side, acquisition of BMI skills can be ascribed to a key property of the brain features that subjects have to learn to modulate, namely stability. Features stability is the ability to reproduce accurately a similar brain activation over runs and over days. Features instability (fluctuations of brain patterns associated to mental commands) is a major limitation of current BMI systems. *Figure 3:9* reports the stability of MI features used to control the BMI. The Kullback-Leiber divergence was computed between MI features on day 0 (calibration day) and during online BMI training runs (day 1 and day 2). Run-wise averages were larger for visual compared to St-NMES feedback, indicating that MI features were more stable for St-NMES. Significant differences were found for runs 5-6-7, corresponding to runs from day 2 (signrank Wilcoxon two tailed test, FDR correction, run 5: St-NMES: 1.20, Visual: 2.17 $p = 0.03$; run 6: St-NMES: 1.25, Visual: 2.11 $p = 0.02$; run 7: St-NMES: 1.10, Visual: 1.95 $p = 0.02$).

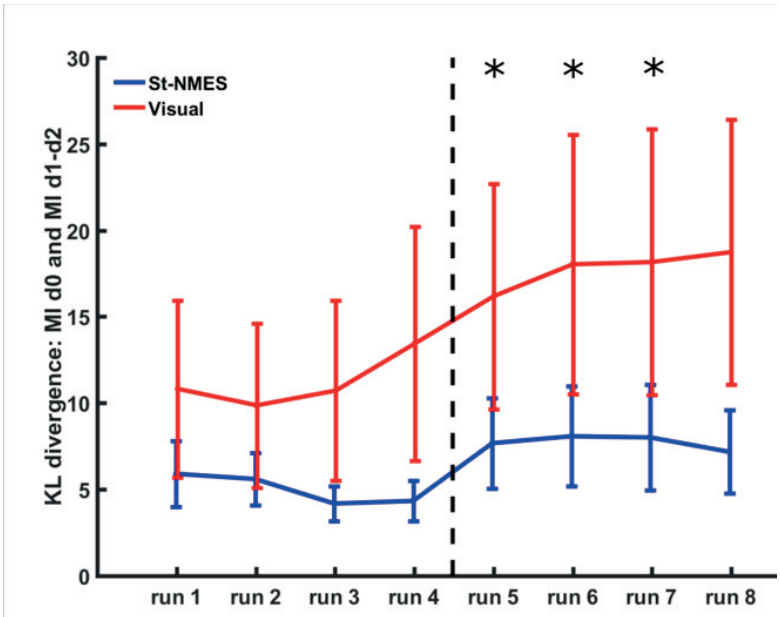

Figure 3:9 Features stability.

Stability of MI features across days (dashed line sperate the two days) measured with Kullback-Leiber divergence between MI features selected from day 0 and the MI features executed on day 1 and day 2., for both feedback modalities St-NMES (red) and visual (blue). Statistical analyses were based on paired Wilcoxon test, Bonferroni corrected ($p < 0.05$).*

3.4 Discussion

In this study we investigated the effect of BMI feedback modality on the acquisition of BMI skills. We compared our new feedback St-NMES with a commonly used visual feedback during online BMI training. Results showed that St-NMES facilitates BMI learning through two different aspects, as postulated by the BMI sensorimotor hypothesis. First, BMI performance and stability were significantly enhanced with St-NMES feedback compared to visual feedback. Second, subjects' CST excitability and cortical ERD increased only after BMI with St-NMES, highlighting a BMI learning process supported by plastic changes across CNS areas that normally adapt to support natural motor control.

3.4.1 CST excitability as a marker of MI-BMI learning

Ruffino et al. [107] propose a neural adaptation model of MI practice involving cortical and subcortical adaptation over three different stages of learning: initial phase, (proper) learning phase and automatic phase. They propose that, at the cortical level, both cortical representation and cortical excitability should increase during the learning phase then would decrease in the automatic phase. In our experiment, which corresponds to the learning phase of Ruffino et al.'s model, we observed a significant increase of cortical ERD (implying a desynchronization of a larger area) and CST excitability only after a BMI based on St-NMES training suggesting that subjects were able to better learn how to perform MI and control the BMI with somatosensory feedback as compared to a standard feedback.

In the literature, it has been showed that MI activates CST projection [86]. Indeed, several studies showed an increase MEP peak-to-peak amplitude during MI [96,105,109,110]. However, to the best of our knowledge, only Bonassi et al. [111] was able to show a post-training effect of MI combined to auditory cues. All other studies only reported an effect during MI, but they did not observe any post training effect [112–114]. In our experiment, BMI coupled to visual feedback did not induce a significant enhancement of CST excitability. A simple MI training or MI-BMI training based on visual feedback is probably not enough to promote immediate plastic changes of the CST that support MI-BMI skill acquisition. Only by combining BMI with St-NMES we could induce a significant post-training effect.

On the other side, it is known that prolonged sensory stimulation (at least 1.5 hours) can induced persistent changes in excitability of CST projection and cortical reorganization [115,116]. For

example, St-NMES has been successfully used for rehabilitation of dysphagia after stroke [99]. More recently, St-NMES was also used in the context of upper limb rehabilitation. Tu-Chan et al. [117]. have recently shown with 8 chronic brain injured subjects that a 2 hours session of St-NMES over the medial, ulnar and radial nerves was associated with significant improvements of motor performance in upper limb motor function (ARAT score) as well as in finger fractionation. Similarly, Klaiput et al. [118] found an increase strength in pinch after 2 hours stimulation of the median and ulnar nerves, for subacute stroke patients. Using peripheral nerve stimulation (PNS, series of brief electrical pulses), Celnik et al [119] illustrated that synchronous PNS on the median and ulnar nerves at 1 Hz for 2 hours, but not asynchronous PNS (alternative stimulation of each single nerve every 15 min), induced an increase CST excitability in chronic stroke patients. On healthy subjects, Golaszewski et al. [72] showed that St-NMES of the whole hand during 30 min elicited increases in motor cortical excitability lasting at least 1 h. Still, the mechanisms of St-NMES on brain plasticity remain unclear and results inconsistent [120]. In our study, St-NMES itself did not induce a significant modulation of CST projections. It is important to point out that in our case the amount of sensory stimulation was considerably shorter (60 trials of 7 s stimulation; i.e., 7 min) compared with previous studies [115–119] (1.5-2 hours session stimulation) and more focal than in [72], suggesting that longer periods might be required to induce effects. On the other hand, with our BMI-St-NMES intervention, only a session of 45 minutes (including the setup and less than 7 min of effective focal stimulation) was enough to induce a significant modulation of CST projections. Thus, it seems that contingent delivery of St-NMES upon BMI decoding of MI is key for fast elicitation of brain plasticity.

Our results indicate that closing the sensory-motor loop with BMI-St-NMES induces plastic changes across CNS areas and, thus, facilitates BMI learning. Nevertheless, in our study the effect of BMI St-NMES on CST excitability was limited in time. Indeed, we could only observe a post-training effect, and no pre-BMI training difference was detected over the two days. This absence of carry-over effect on MEP amplitudes suggests that subjects were still in the learning phase and they had not yet acquired completely the MI-BMI skill (according to the learning model of Ruffino et al. [107].

3.4.2 BMI performance and stability

Learning to control a BMI system reliably remains a major challenge in the field. Although many studies report improvement of subject's BMI accuracy, this is not necessarily a marker of BMI skill acquisition [121]. A more appropriate indicator of such a learning process is the stability of the brain features fed to the BMI decoder that subjects have to learn to modulate. Only a few studies have

reported feature stability although during offline BCI usage [67]. The present study confirms that St-NMES feedback fosters stability of BMI features, especially on the second day. Furthermore, all our subjects were naïve to MI-BMI and, yet, they were all able to control their BMI system with higher performances with St-NMES feedback as compared to visual feedback. However, the design of our experiment does not allow to corroborate whether feature stability will persist with a longer training.

Several studies already showed that somatosensory feedback enhanced BMI features and BMI performance [17,57–59,62]. However, none of them probed that somatosensory feedback does not bias BMI decoding. Indeed, strong somatosensory afferences (e.g., passive movement of the joint of muscular contraction) elicits strong brain activation similar to MI. BMI algorithms are then, not able to dissociate subjects' intentional MI from the evoked brain activation elicited by feedback. As a result, subjects cannot achieve the resting task if, by mistake, the BMI output is MI and triggers somatosensory feedback. To the best of our knowledge, our study is the first one demonstrating a full control of a BMI system coupled with somatosensory feedback. Although subjects' performance for resting trials was lower than for MI trials, this performance was similar between feedback modalities.

As a conclusion, St-NMES is a promising feedback for BMI applications since it enhanced BMI learning. However, the training duration was short in time. A longer training would be interesting to investigate different stages of BMI learning and the associated physiological changes.

Chapter 4 Sensory threshold neuromuscular electrical stimulation supports different stages of BMI skills learning.

4.1 Introduction

In the previous experiment we showed that a short BMI-St-NMES training enhanced BMI learning and increased CST excitability. In this chapter we further explore the parallelism between BMI learning based on St-NMES feedback and natural motor learning, putting particular attention on the underlying physiology of the process. Acquiring a new skill is mostly based on repetitive training and requires different stages of learning and neural adaptation. Motor learning is characterized by three consecutives phases: (i) an early learning during which improvement in performance occurs within the initial session, (ii) a later phase during which the performance continues to be improved but the task required less cognitive resources, and (iii) a retention phase during which the task can be executed after long delays without further practice. BMI learning can be assimilated to a motor learning skill since it activates a similar central and peripheral motor network and it requires motoric memory of movements.

In this new experiment, we investigated the effect of an intensive BMI training based on St-NMES feedback on BMI learning. Apart from analyzing the evolution of BMI performance, we also examined changes in CNS and more specifically CST excitability and modulation of intracortical inhibition (SICI) in the early learning phase (after one BMI session) as well as later learning stage (after 2 weeks training). Moreover, we tested subjects' retention ability to control a BMI after 3 weeks of break. Based on our previous results and according to Ruffino et al.'s neural adaptation model of MI learning skills [107], we expected an increase of CST excitability and a decrease SICI during an early learning stage; then, a decrease CST excitability as well no modulation of SICI with performance stabilization during the later learning phase. Finally, we predicted that our subjects would still be able to control the BMI system after three weeks of break.

4.2 Material and Methods

In this experiment, we investigated subjects' ability to control a BMI and CNS adaptation during an intensive BMI-St-NMES training. Ten healthy subjects (5 female, age: 26 ± 2 years old) right handed and naive to MI and BMI, took part in the experiment. Every subject provided written informed consent. The experimental procedure was approved by the Cantonal Ethical Committee of Geneva (Ethics approval number: PB_2017_00295).

4.2.1 Experimental design

The BMI-St-NMES training consisted in 10 different days of recordings:

- Day 1, BMI calibration: During the first day subjects were asked to performed MI of wrist and fingers extension or a resting task similarly to the calibration session of the previous experiment (cf 3.2.1.1 offline calibration).
- Day 2, baseline or early learning stage: During the baseline recording we assessed the impact of the first BMI-St-NMES online sessions on CNS plasticity, similarly to our previous experiment (cf Chapter 3). TMS recordings were performed before and after the BMI-St-NMES training to evaluate CST excitability and intracortical inhibition.
- Days 3 to 8, BMI-St-NMES training: Subjects were trained to control the BMI-St-NMES three times a week during two consecutive weeks. The training consisted in performing MI of right-hand extension or a resting task.
- Day 9, post-training or later learning stage: the effect BMI-St-NMES session on CNS adaptation was recorded with similar TMS protocols than baseline (day 2).
- Day 10, follow-up or retention stage: after a break of approximately 15 days without any practice (minimum 8 days maximum 30 days), subjects were evaluated on their ability to control the BMI-St-NMES and the associated CNS adaptation. TMS protocols were similar to baseline and post-training evaluations (day 2 and day 9).

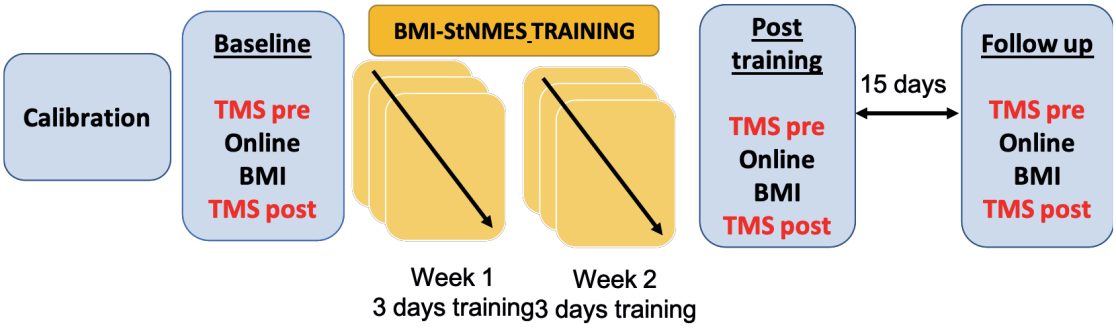

Figure 4:1 Illustration of the experimental design

The study is composed of 10 days of recording. Day 1 is the calibration day during which we calibrate our BMI system to discriminate MI neural correlates from resting state EEG. Day 2 is the baseline. The baseline is composed of TMS recordings before and after the 1st closed-loop BMI training, to access CST excitability and short intracortical inhibition within M1. Days 3 to 8 are closed-loop BMI training sessions during which subjects are trained to control the BMI system. Day 9 is the post-training evaluation with similar evaluations than during baseline. Day 10 is the follow-up, in which we tested the retention of BMI skills. Evaluations were similar to baseline and post-training.

4.2.2 Data acquisition

4.2.2.1 EEG recordings

During EEG recordings, subjects were seated on a fixed chair in front of a computer screen with arms on a folded towel with approximately 15 degree of wrist flexion. During the whole experiment, EEG was recorded at a sampling frequency of 512 Hz with 16 active surface electrodes placed over the sensorimotor cortex i.e., on positions Fz, FC3, FC1, FCz, FC2, FC4, C3, C1, Cz, C2, C4, CP3, CP1, CPz, CP2 and CP4 of the 10/20 system (reference: right mastoid; ground: AFz; gtec gUSBamp, Guger Technologies OG, Graz, Austria).

EEG recordings were composed of four different acquisitions: (i) BMI calibration (ii) offline recordings (iii) online BMI-St-NMES during baseline, post-training and follow-up (iv) intensive online BMI-St-NMES training:

i. Calibration (day 1): The calibration was similar to the previous experiment (cf 3.2.1.1 offline calibration). Subjects were asked to perform 4 runs of 15 MI trials supported by St-NMES

guidance and 15 resting trials, in a randomized order. The data were analyzed offline to build an individual BMI classifier.

ii. Offline recordings (day 2, day 9 and day 10): During baseline, post-training and follow-up recordings, the ability to perform discriminant MI patterns compared to rest was evaluated without any external support (without St-NMES or real-time feedback). Similarly to calibration, subjects were asked to perform 4 runs of 15 MI trials and 15 resting trials without any kind of feedback. Data were storage for further offline analyses.

iii. Online BMI-St-NMES (day 2, day 9 and day 10): Subjects were asked to control a BMI-St-NMES. The session was composed of 4 runs of 15 trials of MI. They received in real-time a St-NMES feedback (see 3.2.1.3) about their actual performance, and a successful trial was rewarded by a muscular contraction elicited by NMES.

iv. Intensive online BMI St-NMES training (days 3 to 8): Three times a week, during two weeks, subjects were trained to control the BMI-St-NMES. Each day of training was composed of 4 runs of 15 MI trials and 5 resting trials presented in a randomized order. The protocol was comparable to online recordings from the previous experiment (see 3.2.1.2 for more details). During MI trials subjects were ask to perform MI in order to reach the decision threshold. When the trial was a success they received motor threshold NMES (Mt-NMES). During resting trials subjects were instructed to control the BMI in order to not reach the decision threshold and avoid receiving Mt-NMES. The decision threshold was manually adjusted before each run to control the level of difficulty of MI task. The idea was to keep the task engaging and not too boring or too demanding.

4.2.2.2 BMI-St-NMES setting

Similarly to the previous BMI-St-NMES experiment (see 3.2.1), features that contain the most discriminable information between MI neuronal correlates or resting task have been manually selected during the offline calibration session. An individual classifier was trained with data recorded during day 1, and each classifier had been preserved the whole experiment. No re-calibration was run during the whole protocol. Only for 2 subjects, their classifiers had to be trained a second time after the first online training (on day 3) due to a poor performance during day 1 (calibration day).

4.2.2.3 St-NMES feedback

The St-NMES feedback provided during closed-loop BMI sessions (from day 2 to day 10) and the St-NMES parameters were comparable to the feedback used in the previous experiment (see 3.2.1.3 and *Figure 3:2*.). Two St-NMES channels were placed on the forearm (channel 1 at the proximal location and channel 2 at distal location) to deliver sensory threshold sensation according

to the BMI output probabilities. The way to provide St-NMES feedback was slightly different from the previous experiment. We decided to reward subjects when they had sufficient brain activation related to MI performance. Thus, the St-NMES was delivered when the BMI system output was in favor of the MI class compared to rest, subject received St-NMES on the distal channel (channel 1). When the probability got closed to the decision threshold (see 3.2.1.2 for more explanation) subject received St-NMES at channel 1 and channel 2. When the decision threshold was reached, subject received Mt-NMES eliciting a muscular contraction with a wrist and fingers extension. However, if the probabilities were in favor of a resting task no St-NMES was delivered neither at channel 1 nor channel 2. The St-NMES and Mt-NMES amplitudes were adjusted for each subject before each BMI session (on average St-NMES amplitude was 4 ±1 mA and Mt-NMES amplitude was 10 ±1 mA).

4.2.2.4 TMS recordings

The TMS settings and parameters were similar to our previous experiment (see 3.2.1.6). Subjects were seated on a chair with the arms pronated and relaxed on a table. They were instructed to keep their eyes opened, and to stay relaxed. Surface electromyography (EMG) was recorded from their extensor carpi radiali (ECR), first dorsal interosseous (FDI) and abductor digiti quinti (ADM). The ECR was defined as the main muscle of interest and TMS was calibrated according to EMG of ECR muscle. The hot spot was defined as the best coil location that induces the largest and the most stable MEP of the target muscle (ECR muscle). For the three days with TMS recordings (baseline, post-training and follow-up) the hot spot and EMG electrode locations were defined at the beginning of the pre-recording, marked with a pen, and used for all TMS recordings within the same day (for pre and post recordings). The resting motor threshold (RMT), in respect to the target muscle, was defined as the lowest stimulus intensity to evoke at least five out of ten MEPs responses (with peak-to-peak amplitude of 0.05 mV) [60], was measured before and after the BMI session.

Corticospinal excitability was assessed by TMS recruitment curves (RC), during baseline, post-training and follow-up, before and immediately after a BMI-St-NMES session. TMS RCs represent the mean of MEP peal-to-peak amplitudes values for different level of TMS stimulator output. TMS stimulator outputs were defined for each individual as a percentage of their initial RMT (*RMTinit*) measured during the baseline before the BMI session. MEP were elicited at stimulus intensities of RMTinit and 110% - 120% -130% - 140% -150% and 160% of RMTinit. The same intensities defined on RMTinit were used for the three days baseline, post-training and follow-up. For the three first subjects we did not recorded the intensities of 150% RMTinit and 160% RMTinit. For each amplitude, 15 MEPs were recorded over three blocks containing 5 trials of each amplitude in a randomized order. The inter-stimulus-intervals within one block were randomized in-between 7 s ±

2 s.

Paired-pulses TMS were also used to assess changes in short-interval intracortical inhibition (SICI) during baseline, post-training and follow-up. SICI paired-pulse paradigm uses a subthreshold conditioning stimulus delivered 1 to 6 ms before a supra-threshold test stimulus [122] delivered through the same coil. From this interaction results an inhibition of MEP amplitude. In our experiment, we defined the conditioning stimulus (CS) intensity as 80% of subject's RMT. The test stimulus (TS) intensity was selected as the TMS stimulator output intensity able to evoked MEPs peak-to-peak amplitude in the range approximately 0.8 1 mV ± 0.2mV. The inter-stimulus interval was fixed to 3ms. In order to understand possible changes in cortical inhibition due to BMI-St-NMES training, SICI paradigm was performed when subjects were at rest and during a MI task:

(i) SICI during rest: Subjects were asked to keep eyes opened and to relax. A total of 30 MEPs was recorded including 15 conditioned MEPs (with CS-TS) and 15 non-conditioned MEPs (with TS). The order between conditioned and non-conditioned pulses was randomized, and the inter-stimulus-interval was randomized in-between 7 s ± 2 s.

(ii) SICI during MI: The SICI parameters were the same than the previous SICI protocol run during rest. Subjects were asked to perform the same MI than during BMI recordings, but without St-NMES nor BMI set-up. On the screen placed in front of them subjects saw the following instructions: a fixation cross during 1s, then a ball appeared on the screen and after 1s started to move on the left until it reached a bar. The ball displacement lasted 4s. Subjects were instructed to perform MI while the ball was moving on the screen and relax when the ball reached the bar. Each trial was followed by an inter-trial break of 4 s ± 2 s. We recorded over two blocks equally distributed: 24 non-conditioned MEP and 24 conditioned MEP.

4.2.3 Data analysis

4.2.3.1 Recruitment Curve analysis

Each trial was visually inspected, and trials containing a pre-activation on ECR, FDI or ADM muscles were discarded. Then, for all EMG channel we computed the detrended EMG signal. For each amplitude, MEP peak-to-peak amplitudes were averaged. Then, we averaged the obtained MEP peak-to-peak amplitudes across subjects for each amplitude (from the 1 to 7) for each day and each pre or post recording. For the sake of simplicity, we reported only MEP recorded for the ECR muscle since the TMS protocols were exclusively tuned for this muscle.

4.2.3.2 Short interval intracortical inhibition

For SICI during rest, each trial was visually inspected, and trials containing a pre-activation on ECR, FDI or ADM muscles was discarded. Then, for all EMG channel we computed the detrended EMG signal. During rest as well as during MI task, MEP amplitude of each condition was averaged for each subject. The degree of inhibition was computed using Equation 4:1 where NC is the average of non-conditioned MEP amplitude after test stimulus pulses, and C average conditioned MEP amplitude. The degree of inhibition is represented by the % of inhibition. Only results regarding the ECR muscles are presented.

$$SICI\% = 100 - (\left(\frac{C}{NC}\right) * 100)$$

Equation 4:1 – Short interval intracortical inhibition

4.2.3.3 Event-related desynchronization

We assessed the ability to elicit ERD during MI trials at the beginning or later in the process of BMI learning. We computed ERD in β frequency band for FC, C and CP lines, similarly to the previous experiment (see 3.2.3.2). We compared ERD during baseline, post-training and follow-up for the offline (without any feedback) and online recordings (with BMI-St-NMES).

4.2.3.4 Decoding accuracy

EEG processing was similar to the one described in paragraph offline calibration (cf 3.2.1.1 offline calibration). We extracted log(PSD) for the 16 channels covering the sensorimotor regions, and we evaluated the discriminability of the recorded signals. For online trials performed each day (baseline, post-training and follow-up) we extracted the selected features of interest and we performed a single-sample classification using a linear discriminant (LDA).

4.2.3.5 BMI speed

We evaluated the speed of command delivery over days. For this a-posteriori analysis we computed the time needed for every subject and trial to reach different decisions ranging from 50% to 100%. For trials that ended with a cumulative probability below the decision threshold, the time was set to 7 s (maximal duration of a trial).

4.2.3.6 MI discriminability

For each day of assessment (baseline, post-training and follow-up) we measured how MI patterns were discriminable from rest. In particular, we computed the Fisher score between MI and

rest distributions (from the selected features) as a measurement of how the two distributions (MI and rest) were distinguishable.

4.2.4 Statistical analysis

For all analyses we defined the significance level to 0.05. Kolmogorov-Smirnov test was performed to evaluated the normality of the data. For MEP recorded with TMS-RC protocol, all the recorded variables (including: days (baseline, post-training, follow-up); time (pre, post) and amplitude (from 0 to 7)) did not reject the null hypothesis of normal population distribution. Except for three variables: baseline pre at amplitude 0 ($D(10) = 0.3$, $p = 0.008$), post-training post at amplitude 4 ($D(10) = 0.28$, $p = 0.025$) and follow-up post at amplitude 2 ($D(10) = 0.37$, $p = 0.001$) did not follow a normal distribution. However, we decided to perform an ANOVA analysis since it has been described that ANOVA is robust to violations of normality [123]. A repeated-measure ANOVA with two within-subject factors; namely time (pre or post training with online BMI), amplitude (from amplitude 1 to 7) for each day (baseline, post-training and follow-up) was performed.

For MEP recorded during TMS-SICI protocols during rest and during MI, the Kolmogorov-Smirnov test did not reject the null hypothesis of normal population distribution. A repeated-measure ANOVA with two within subjects' factor day (baseline, post-training and follow-up) and time (pre or post online BMI). Sphericity of data was tested with Mauchly's test of sphericity. In the case of data that were not rated equally, we applied a Greenhouse-Geisser correction. The ANOVA analyses were followed by post-hoc paired-wise comparison analyses with a paired two tailed t-test, Bonferroni corrected.

For ERD recorded online the Kolmogorov-Smirnov test did not reject the null hypothesis of normal population distribution. However, for ERD recorded offline, two variables did not follow a normal distribution: ERD recorded with FC and C electrodes during baseline ($D(10) = 0.35$, $p = 0.001$ and $D(10) = 0.34$, $p = 0.003$). As previously explained, although two variables were not normally distributed we performed a repeated-measure ANOVA with two within-subjects' factors day and feedback, for each of the three groups of EEG channels (FC3-FC1, C3-C1and CP3-CP1). The ANOVA analyses were followed by post-hoc paired-wise comparison analyses with a paired two tailed t-test. For BMI performance analyses including percentage of success, decoding accuracy, discriminability of MI patterns, we performed non-parametric paired-wised comparison (two-tailed Wilcoxon signrank test).

4.3 Results

4.3.1 Corticospinal excitability

We investigated the effect of an intensive BMI training on CST excitability. CST excitability was assessed with a recruitment curve protocol. For different intensities of TMS stimulator we recorded MEP peak-to-peak amplitude before and after an online BMI-St-NMES session, at different stages of learning (baseline, post-training and follow-up). The ANOVA analysis showed a significant interaction between time x amplitudes for baseline ($F(2.8, 25.9) = 5{,}75$, $p = 0.004$ Greenhouse-Geisser corrected). No significant interaction was found neither for post-training ($F(2.33,21.02) = 1.86$, $p = 0.18$ Greenhouse-Geisser corrected) nor follow-up $F(2.34, 18.76) = 2.77$, $p = 0.082$ Greenhouse-Geisser corrected). The amplitude had a significant effect for each day (baseline $p < 0.001$, post-training $p < 0.001$, follow-up $p = 0.003$, Greenhouse-Geisser corrected). The time factor (pre, post training) had a significant effect only for baseline ($p = 0.004$), highlighting significantly larger MEP peak-to-peak amplitude after the 1st online BMI. Time had no significant effect neither for post-training ($p = 0.18$) nor follow-up ($p = 0.37$). CST excitability was significantly enhanced after the first online BMI session; however, after BMI training the CST excitability was not modulated after an online BMI session.

Figure 4:3 shows MEP peak-to-peak amplitudes recorded only for a stimulator intensity of 120% RMT for each individual subject. A non-parametric Wilcoxon paired test (two-tailed) compared the MEP recorded before and after the BMI session for the three days of assessment (baseline, post-training and follow-up). Results showed that 5 subjects significantly increase their MEP amplitude after the first online BMI session (baseline). After two weeks of BMI training (post-training), only one subject had a significant increase of MEP amplitude. For the follow-up, three subjects significantly increased their MEP amplitude.

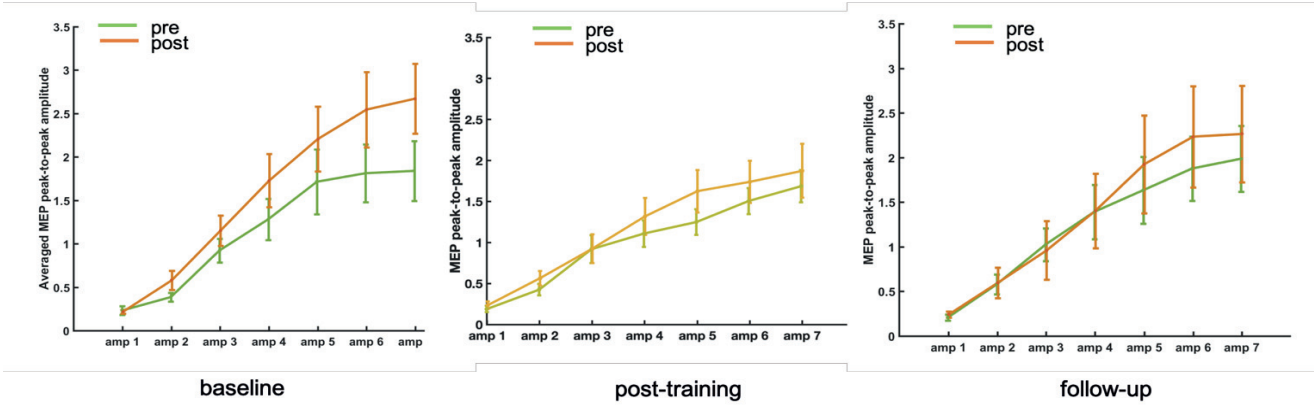

Figure 4:2 Recruitment curve analysis

From right to left panel, recruitment curve pre and post BMI training, for the early stage of learning (baseline) later stage of learning (post-training) and retention two weeks without training (follow-up). The averaged MEP peak-to-peak amplitude of the ECR are reported for each TMS amplitude. For each subject the amplitudes were defined as 100% to 160% (with incrementation of 10%) of the RMT recorded during baseline pre. For each subject the individualized amplitudes were the same across days. As a result, during baseline, we can observe an increase CST excitability compared to post-training and follow-up.

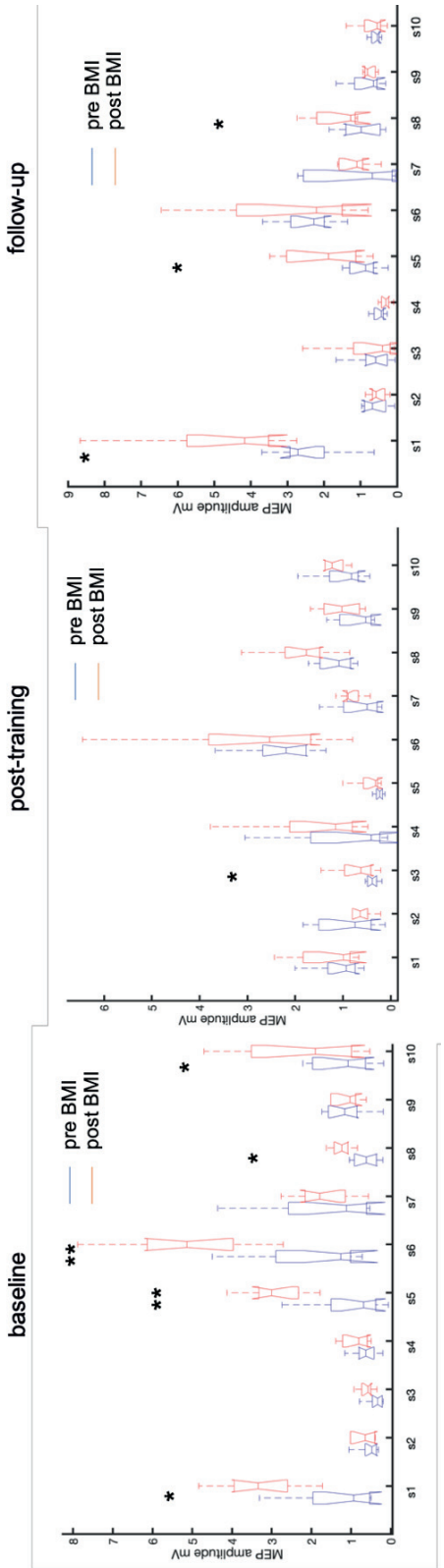

Figure 4:3 MEP amplitude at 120% RMT

*Each boxplot represents 10 MEP trials recorded at 120% RMT. We compared per subject the MEP amplitude before (blue) and after (red) a BMI session at the baseline, post-training and follow-up. The paired-wise comparison was performed with a non-parametric Wilcoxon paired test (two-tailed). * highlight a significant increase in MEP $p < 0.05$ and ** $p < 0.01$*

4.3.2 Cortical inhibition during rest

The level of inhibition within primary motor cortex (M1) can be assessed with a standard SICI protocol. Figure 4:4 presents the amount of inhibition in percentage within M1 during rest, comparing before and after an online BMI session during baseline, post-training and follow-up. The ANOVA analysis showed a significant effect of time (p = 0.019) but no significant effect of day (p = 0.075). The interaction time x day was significant ($F(1,9)$ =5.93 , p = 0.010 Greenhouse-Geisser correction). Paired-wise comparison (2-tailed paired ttest Bonferroni corrected) comparing pre and post for each day, showed significantly less inhibition after an online BMI session during baseline only ($t(9)$ = 3.05 p = 0.042). No difference was recorded neither for post-training ($t(9)$ = 1.24, p = 0.93) nor follow-up ($t(9)$ = 1.05, p = 0.96).

4.3.3 Cortical inhibition during MI

A decrease inhibition during MI is a marker of good MI performance. Figure 4:5 shows the comparison of SICI during MI before and after an online BMI-St-NMES session for baseline, post-training and follow-up. A paired-wise comparison between pre and post training, for each day, did not reveal any significant difference during baseline and follow-up (baseline pre = 45.7 ± 24.5, post = 42 ± 20.3, p = 0.43; follow-up pre = 26.0 ± 22.5 post = 38.8 ±25.0, p = 0.11, two-tail paired ttest). Nonetheless, we could observe a trend in decrease SICI for the post-training (pre = 45.5 ± 20.9 post = 33.0 ±26.9, p = 0.06).

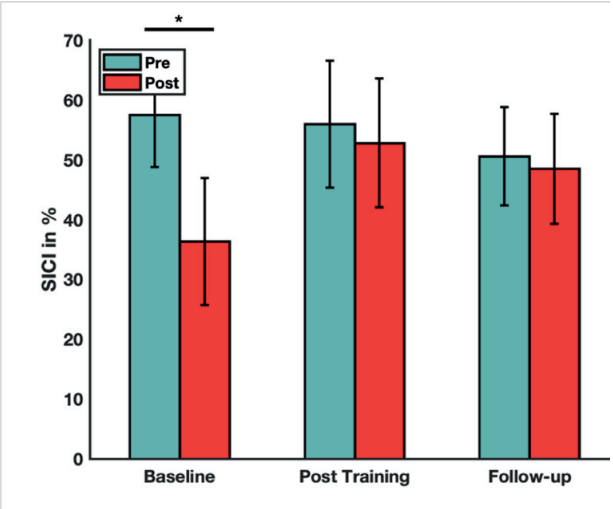

Figure 4:4 SICI in % during rest

Amount of inhibition in % measured by SICI protocol pre (in blue) and post (in red) online BMI session for the three days baselined, post-training and follow-up. The bar plot presents the mean and the standard error of the mean for the averaged amount of SICI across subjects

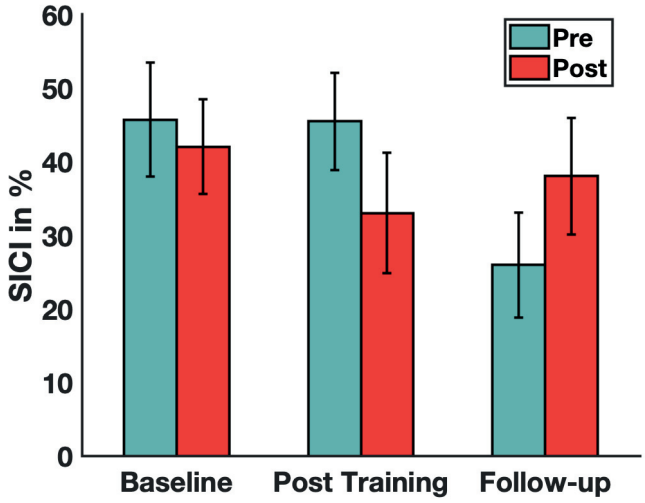

Figure 4:5 SICI in % during MI

Amount of inhibition in % measured during MI task. We compared pre (in blue) and post (in red) BMI session for the three days baselined, post-training and follow-up. A decreased SICI during MI, is a marker of MI good performance. The bar plot presents the mean and the standard error of the mean for the averaged amount of SICI across subjects.

4.3.4 Event related desynchronization (ERD) during MI

ERD is a well-known marker of MI performance. ERD amplitude (in percentage) were recorded in the early phase of BMI training (baseline), and compared to later phase of training (post-training) and after a break of two weeks (follow-up). ERD analyses were performed for offline recordings (without any feedback) and online recordings (with BMI-St-NMES). Figure 4:6 presents ERD in β band [14-26] Hz recorded by FC electrodes, C electrodes, and CP electrodes covering the left sensorimotor network.

For offline recordings, the repeated measure ANOVA showed a significant effect of time over CP electrodes ($F(2,18) = 5.11$, $p = 0.018$) but no effect neither for C ($F(2,18) = 1.52$, $p = 0.24$) nor FC electrodes ($F(1.03,9.31) = 0.8$, $p = 0.40$ Greenhouse-Geisser corrected). Paired-wise comparison (two-tailed paired ttest) between days for CP electrodes revealed significantly larger ERD post-training compared to baseline ($t(9) = 2.47$, $p = 0.03$), and a trend that ERD are larger on CP during follow-up compared to baseline ($t(9) = 1.25$, $p = 0.07$). No significant difference were observed between post-training and follow-up ($t(9) = -1.64$, $p = 0.13$).

During online recordings, ERD were larger compared to offline recordings, indicating that the BMI supported MI performance. However, the ANOVA analyses showed no significant effect of time, but a trend for CP electrodes ($F(2,18) = 3.40$, $p = 0.06$) and no significant effect neither for C ($F(2,18) = 1.95$, $p = 0.17$) not FC electrodes ($F(2,18) = 1.00$, $p = 0.39$).

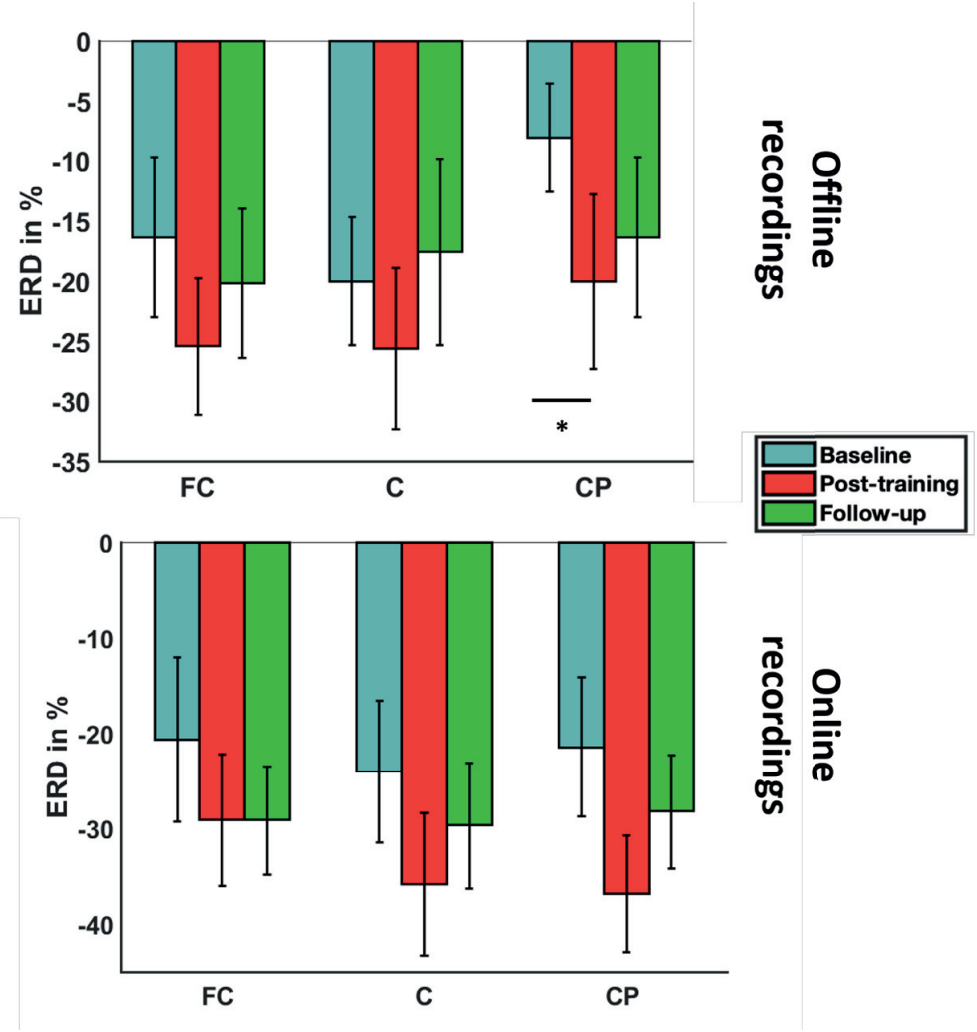

Figure 4:6 ERD during MI task

*ERD for channels FC C and CP electrodes covering the motor network during baseline (blue), post-training (red) and follow-up (green). The bar plot indicates the mean and the error of the mean. ERD were computed during offline recordings (top) and online recordings (down). Statistical analyses were based on a Bonferroni-corrected two-tailed paired t-test. * $p < 0.05$; ** $p < 0.01$.*

4.3.5 BMI performance

BMI performance can be assessed by three factors: the number of successful MI and resting trials, the accuracy of the BMI decoder and discriminability of MI features compared to rest.

Figure 4:7 represents subjects' successful trials in percentage per online sessions and the averaged decision threshold used per session. For MI trials, the success was on average (68,8 ± 2.2) no significant difference was recorded over session. The worse performance was achieved during the first online session (66.98 ± 18.2) and the best was the fourth session (72.04 ± 11.4). There was no significant difference between the first and last session (p = 0.77, two-tailed Wilcoxon signrank test) neither between the best and worst session (p = 0.07, two-tailed Wilcoxon signrank test). This result was expected since the decision threshold was manually adjusted in order to keep the task engaging and motivating. Interestingly we can notice that for a similar amount of success, decision thresholds were

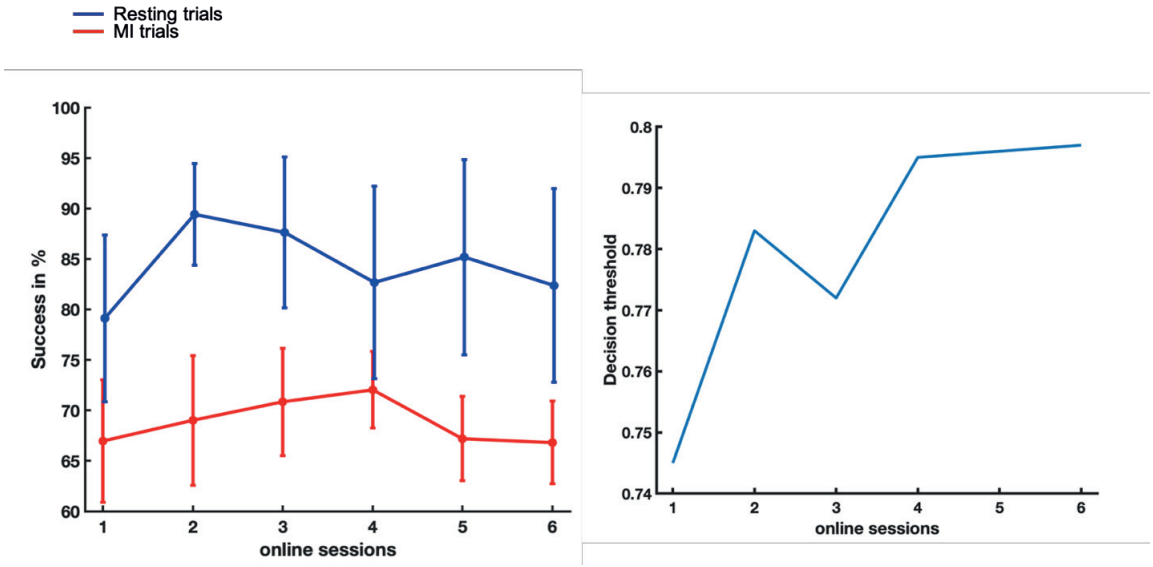

Figure 4:7 Successful trials with the associated decision threshold

The right panel represents the amount of successful trials averaged across subjects. Red line represents MI trials and blue line rest trials. For MI trials the decision threshold was manually selected in order to keep the task engaging and motivated, for resting trial the decision threshold

was the same than MI trials and the objective was not to reach it during 7s. Subjects were able to perform resting trials despite they were receiving St-NMES. The left panel shows the averaged decision threshold used across online sessions.

increased over sessions. The decision thresholds used for the last session was significantly higher compared to the first (online 1: 0.74 ± 0.11, online 6: 0.80 ± 0.08, p = 0.04, two-tailed Wilcoxon signrank test). BMI subjects were able to perform better control at the end of the two weeks BMI training. Moreover, subjects were also able to perform resting trials. The performances were largely variable across subjects but on averaged they reached 84% ± 24% of success. It highlights that BMI was not bias by St-NMES and subjects were able not to cope with St-NMES.

Figure 4:8 represents the single-sample decoding accuracy for the three days of assessment (baseline, post-training and follow-up). Results showed a significant improvement in decoding accuracy after the intensive BMI training compared to before (baseline = 0.66 ±0.2, post-training = 0.75±0.2, p = 0.05), but no remaining effect for the follow-up (follow-up = 0.68 ±0.26). For six participants out of ten, the decoding accuracy was better for the post-training compared to baseline, and the decoding accuracy decreased only for two participants (difference > 0.01). However, for the follow-up, 5 participants obtained higher decoding accuracy compared to baseline, but the 5 other participants decreased decoding accuracy. About the speed to decode MI intention, no difference (p> 0.1) could be measured between the three days. Further analysis would be to be done to understand if BMI training had an impact on speed performance.

Discriminability of MI features compared to rest is represented on Figure 4:9. Results showed that MI patterns were more discriminable after BMI training compared to calibration but the difference was not significant (calibration: 0.11 ± 0.09, post-training:0.18 ± 0.11, p = 0.08). Fisher score remains higher for follow-up compared to calibration but the difference was not significant (follow-up: 0.16 ± 0.08, p = 0.15).

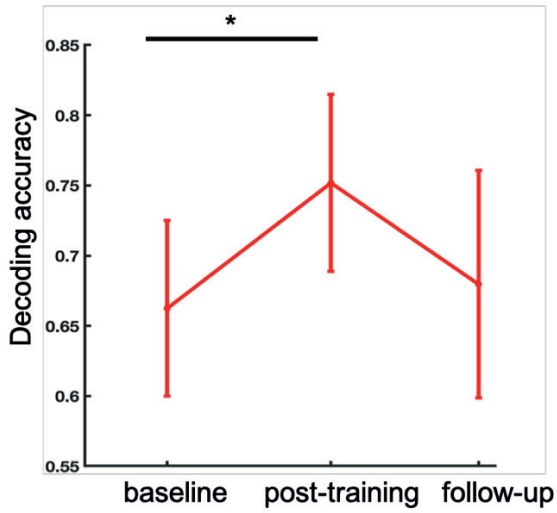

Figure 4:8 Decoding accuracy

Single sample classification of MI trials compared to rest for the three online assessments baseline, post-training and follow-up. Each dot represents the average accuracy with its standard error of the mean. Paired-wise comparison was performed with Wilcoxon signrank test.

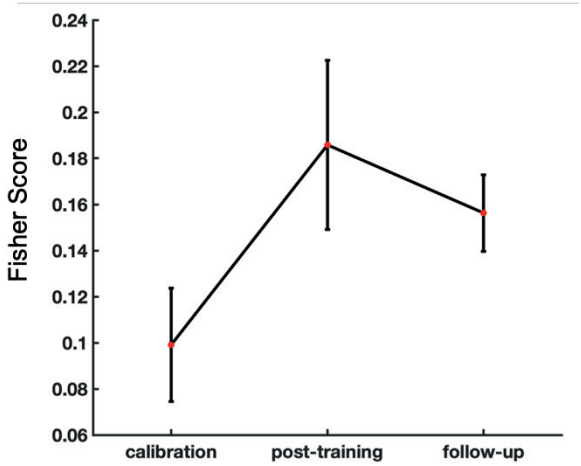

Figure 4:9 Discriminability of MI features

Discriminability of MI features compared to rest during offline recordings was computed with Fisher Score during the first offline recordings (calibration), after BMI training (post-training) and again during the follow-up. The dots represent the mean with its standard error of the mean.

4.4 Discussion

In this study, we investigated the effect of intensive BMI-St-NMES training on BMI learning and CNS adaptation over time. In the early phase of the BMI learning, results showed an increased CST excitability and a decrease local inhibition. After two weeks of training, subjects improved their ability to control BMI. At this time, no more modulation of cortico and corticospinal excitability was recorded. However, during BMI-MI, subjects showed larger physiological markers of MI performance. These results indicated that subjects improved their BMI skills. The skill improvement seemed to be consolidated since all subjects were still able to control their BMI system after two weeks without training. Thus, BMI based on St-NMES is a promising strategy to foster BMI learning.

4.4.1 BMI learning model and adaptation of CNS

Learning to control a BMI is a skill that needs to be acquired with practice [124]. In this new protocol we tested the idea that BMI skill acquisition implies different stages of learning linked to different CNS adaptation.

Halsband et al. [125] suggested that a standard sensorimotor learning consists of three distinct phases: (1) *Initial stage*: Slow and irregular performance under close sensory guidance. During the initial phase we learn by trials and errors. The critical requirement of this phase is the novel establishment of perceived sensory cues with the correct motor commands. The establishment of this novel sensorimotor association is closely related to attention and sensory feedback processing. (2) *Intermediate stage*: With practice, sensorimotor maps become stronger. Sensory cues are transformed accurately and fast to the precise motor response. (3) *Advanced stage*: After long-term practice, movements become automatic and can be performed at high speed and accuracy, even if subjects do not attend to the action. In addition, in their model, Ruffino et al. [107] proposed specific CNS adaptation supporting these learning phases during MI learning: (a) *Early learning:* Cortical map representing trained muscles and the corticospinal excitability would increase during the first sessions of learning. (b) *Later learning and automatization*: General decrease of cortical activity and decrease of CST excitability. Cortical maps would decrease with performance stabilization in the automatic phase. These learning models can be transposed to our BMI learning model: (i) *Initial stage:* Difficulty to perform accurate MI strategy. BMI control is difficult and instable. (ii) *Early learning stage*: increase corticospinal tract excitability due to the establishment of a novel sensorimotor association that is decoding of MI (BMI part) associated to St-NMES feedback. BMI performances are improved. (iii) *Later learning* (intermediate stage): St-NMES feedback is accurately and rapidly

integrated by subject during its performance. It leads to more stable and discriminable MI pattern (ERD). BMI control is increased. (iv) *Advanced stage* should be associated to the expertise of controlling BMI that can be acquired after long use of BMI. This stage has not been investigated yet.

Our findings are in line with our BMI learning hypothesis, except that we did not observe any change in speed decoding. However, further investigation will be needed in order to answer this point. In the early phase of BMI learning an increase in CST excitability and a decrease cortical inhibition was observed. This result confirmed results from our previous experiment. As discussed in the previous chapter (3.4.1) it is known that during MI, an increase CST excitability [44,96,105,109] and that motor cortex inhibition is decreased [126] are described. Also, a prolonged and continuous sensory electrical stimulation and peripheral nerve stimulation, can induce a decrease cortical inhibition [72,127,128]. However, from the best of our knowledge, no MI or BMI studies have shown showed a post-training effect on CNS plasticity. In our two studies involving BMI-St-NMES, the increase of CST excitability as well as the cortical inhibition were sustained after a first BMI-St-NMES session. On the opposite, after two weeks of intensive BMI training, no significant modulation of cortical inhibition and CST excitability was recorded. According to our BMI learning model, we hypothesized that subjects learnt to control the BMI and that their sensorimotor maps were stronger. Indeed, subjects increased their BMI performances with higher decoding accuracy, more discriminable MI patterns and more robust ERD. Interestingly, ERDs were significantly larger over CP electrodes. CP electrodes are covering parietal regions that are linked to somatosensory integration. This result might refer to the idea of a more accurate integration of sensory feedback during MI performance. Although, no correlation between MEP changes and BMI performance could be found, due to a small sample size, the physiological markers of MI performance were increased after two weeks training, reinforcing the idea of a BMI learning. Indeed, ERD were significantly larger, and cortical inhibition was decreased during MI during the post-training evaluation. After two weeks training, subjects probably learnt to perform an appropriate strategy to control BMI-MI.

Interestingly, after two weeks without any practice, subjects were still able to control their BMI. No significant change in CNS was recorded at this time. There were two possible explanations for these results. First, we can hypothesize that subjects preserved their ability to control their BMI similarly to the post-training evaluation. The second hypothesis was that the BMI trained the first day was not aligned anymore with subjects' brain patterns. Thus, there was no association of the feedback with their performance. It might leaded to an inappropriate training and, so, did not support adaptation of CNS. In practice, probably both situations happened. Indeed, no difference was showed in the physiological markers of MI performance compared to baseline. A per subject analyses would be

interesting in order to classify subjects that maintained the ability to perform accurate MI, compared to those that lost this ability and understand what are the predictors factors of BMI skills learning.

4.4.2 BMI skills learning

BMI learning can be measures in different ways: the online success, decoding accuracy and discriminability of brain patterns. The online success is recorded by the amount of successful trials. Although, the decision threshold was manually set-up in order to obtain approximatively 70% of success for MI trials, decision thresholds were increased over time. In other words, subjects learnt to reach more difficult decision thresholds. This can be seen as an improvement in the BMI control. Moreover, the single-sample decoding accuracy (that was not influences by decision threshold) was also significantly higher after BMI training. Interestingly, even in absence of any kind of feedback, the ability to elicit discriminable MI pattern from resting brain pattern was enhanced after BMI training. After two weeks training, subjects learnt the skills necessary to control accurately a BMI. These results are particularly interesting in the BMI field since it pushes back the limits of BMI usability.

Although in literature 10 to 30% of the population has been found not able to control a BMI [49,51] all our subjects except one was able to achieve a decision threshold of 70% after training (20% above random chance level). The subject that did not manage to reach 70% threshold also gradually increased his BMI skills starting from a decision threshold at 0.58 and finished to 0.65. BMI learning environment, including sufficient amount of learning and accurate instructions, are crucial to make every subject being able to learn BMI skills. Similarly to Vidaurre et al. [129], we observed three categories of subjects: subjects for whom (I) a classifier could be successfully trained and who performed feedback with good accuracy directly for the first online. Nonetheless, their performances increased with time and we could observe changes in CNS adaptation over time (II) a classifier could be successfully trained, but feedback did not work well at the beginning but they learnt with training to improve their performance (III) no classifier with acceptable accuracy could be trained after one session. We had to train a classifier again with the data of the first online. Nonetheless, they managed to learn with some training how to control the BMI. We believe that most of BMI studies might neglect this last category of subjects. However, they have the ability to control a BMI but they required more time and more instructions to drive a BMI.

Moreover, contrary to many BMI protocols, we did not recalibrate subjects' classifier during the two weeks training and neither for the follow-up training. As explained by Perdikis et al [22], frequent

recalibration creates situations in which subject's learning could be hindered by the demand to adapt to a changing decoder. We hypothesized that it also contributed to the BMI learning. However, during the follow-up assessment some subjects decreased their ability to control the BMI. This situation might be explained by two main factors: The amount of training was not enough for subjects to retain the skill. The initial classifier was not adapted any longer to subjects' current performance. The selected features might have changed due to non-stationarity of EEG, and important variability of subjects' performance [130]. Further investigations would be needed to understand when it would be more suitable to update a subject's classifier in order to develop his BMI expertise.

As a conclusion, BMI based on St-NMES feedback is a very promising tool for BMI usage as well as for BMI applied to motor rehabilitation. Indeed, BMI-St-NMES induced CNS plasticity related to the motor task. Several studies already showed that BMI associated to somatosensory feedback could enhance motor recovery after stroke [23,24]. Another study would be needed in order to assess if our BMI-St-NMES could be applicable in the context of upper limb rehabilitation.

Chapter 5 BMI based on St-NMES a promising tool for motor rehabilitation after stroke: a case study.

5.1 Introduction

In Europe, stroke is the third most common cause of death, responsible for over 5 million deaths per year, and it is a major cause of handicap [131]. It has been shown that 80% of patients who suffer from a stroke [132] present an upper limb paresis including motor and sensitive deficit of the upper limb. A study highlighted that six months after stroke 30% to 60% of severely impaired patients do not recover the motor function of the upper limb and only 5% to 20% fully recover [133]. Upper limb rehabilitation after stroke is then, a major concern. However, the impact of current rehabilitation therapies is limited and the advantage at long-term is controversial [134-136]. Moreover, for patients severely impaired, there is only few strategies to enhance upper limb recovery. Most of these patients remain importantly handicapped at the chronic stage [137,138]. In this context, BMI appeared to be a promising tool for upper-limb rehabilitation [23,139]. Interestingly, it has been showed in literature that reactivation of the damaged primary motor cortex and CST excitability improvement are biomarkers of motor recovery [140–143]. In this thesis, we previously showed that BMI based on St-NMES feedback can induce a significant improvement of brain activation within the contralateral sensorimotor cortex, and an increase in CST excitability. BMI-St-NMES could be then a solution to foster motor rehabilitation after stroke.

The purpose of this case study is first to investigate the applicability of our BMI for motor rehabilitation after chronic stroke, and secondly to understand if BMI-St-NMES could lead to enhancement of motor recovery.

5.2 Material and Methods

5.2.1 Presentation of the patient

For this case study, one patient, age: 63 yo, right-handed, was enrolled in the protocol. She suffered from a left ischemic stroke three years ago. As a consequence, she suffered from Brocca

aphasia, right hemi-neglect and severe sensorimotor impairment of the right hemi-body. After 6 months of intensive rehabilitation in a rehabilitation center, she had motor therapy every week. Despite intense rehabilitation, she still suffers from severe motor deficit of the upper-limb. She gave and oral and written informed consent to participate to our study.

5.2.2 Experimental Design

The purpose of this case study was to understand the possible impact of our BMI-St-NMES on motor recovery. The experimental design was comparable to the previous experiment run with healthy participants (see 4.2.1). The differences in the protocol were that clinical evaluations were performed before, after and one month after the BMI experiment (baseline, post-training and follow-up). Moreover, the patient did three weeks of BMI training compared to only two weeks in the previous chapter. The aim was to provide to the patient a similar amount of session than in Biasucci et al.'s experiment [23]. The new experimental protocol is illustrated on Figure 5:1.

5.2.3 Clinical assessment

The primary outcome of this case study was the Fugl Meyer Assessment score (FMA). FMA is an evaluation of motor recovery after score, used to define the severity of motor impairment. For the upper-limb evaluation the maximal FMA score is 66 points. Before the experiment, the FMA score was 14 / 66 points highlighting a severe impairment of the upper-limb at the proximal and distal level. The second clinical outcome was the muscular testing (*Daniels & Worthingham muscle testing*). This test analytically evaluates muscular strength and muscular function. The evaluated functions and muscles were: shoulder flexion, extension and abduction, the biceps and triceps, pronators and supinators of the forearm, wrist extensors and flexors, fingers extensors and flexors, abductor, flexor and extensor of the thumb. The evaluation is evaluated from 0 no muscular contraction to 5 no strength disorder. The other clinical outcomes were the modified Ashworth testing and the visual analog scale (VAS) to evaluate pain. The modified Ashworth score is an evaluation of spasticity by judging the muscle resistance to a stretching movement [144]. The scoring is from 0: no increase in muscle tone to 4: affected part rigid in flexion or extension. The VAS permits the patient to assess his/her pain on a visual scale from 0: no pain to 10: the pain is extreme.

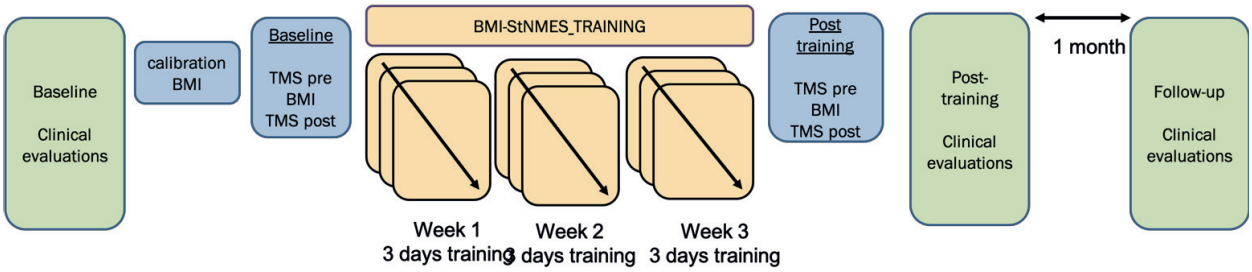

Figure 5:1 Illustration of the experimental protocol

Clinical assessment, in green, were performed before and after the experiment. A follow-up was done one month after the post evaluation. BMI sessions are composed of one calibration session (in blue) and three weeks of training composed of 3 training per week (in yellow). TMS evaluations are represented in blue. Three sessions were performed: baseline, post-training and follow-up. During these days TMS recordings were performed before and immediately after a close-loop BMI session.

5.2.4 BMI training

BMI training was comparable to the previous experimental design (4.2.1) at the exception that the patient had to perform motor attempt instead of MI, to control the BMI. The patient was instructed to perform a wrist and fingers extension despite a complete lack of motor function. The St-NMES feedback was similar to the previous protocol (4.2.2.3). When the decoder confidence was in favor of motor attempt, she received St-NMES on channel 1. When the confidence was closed to reach the decision threshold she received St-NMES on both St-NMES channels. At the time the patient reached the decision threshold, she received NMES eliciting a hand opening. On the opposite, if the decoder was in favor of a resting task no St-NMES was delivered.

5.2.5 TMS recordings

The position of C3 channel was used as an initial “hot-spot” to elicit a MEP of patient’s paralyzed hand. TMS stimulator intensity was set-up to 90% of maximal intensity. By moving slowly the coil we tried to elicit MEP. No MEP could be recorded for none of the recordings (baseline, post-training nor post-training 2). Ten trials were recorded to document the patient’s situation.

5.2.6 BMI performance analysis

Similarly to the previous experiment, we compared BMI single-sample accuracy (see 4.2.3.4 for method), BMI speed decoding and decoding success (see 4.2.3.5) before and after BMI training.

5.3 Results

5.3.1 Clinical outcomes

The FMA score evaluated before, after and one month after the BMI training showed an improvement of motor function clinically relevant (defined by an increase FMA of 5 points in the case of chronic stroke patients). Indeed, before the experiment the FMA score was 14 / 66. After the BMI training the FMA score increased to 21 / 66. This increase of FMA score was especially reflected in an improvement of shoulder and elbow function. One month after the training, the FMA score was 24 / 66. Although the difference is not clinically relevant, it was good to notice an improvement in wrist extension function.

The MRC evaluations showed an improvement in shoulder flexion and extension as well as elbow flexion and extension (see Table 5:1) before compared to after BMI training. Moreover, we could observe the appearance of thumb abduction, but the movement was not functional. Modified Ashworth showed a decrease of spasticity after the BMI training (see Table 5:2). No change in pain had been observed. The patient also reported in improvement of Gait and a decrease neglect about the right hemi-body.

Name	*Pre-evaluation*	*Post-evaluation*
Shoulder ABD	2+	2+
Shoulder flexion	3-	**3**
Shoulder extension	2+	**3-**
Elbow flexion	2	**3-**
Elbow extension	2-	**3**
Wrist flesion	0	0
Wrist extension	0	0
Thumb opposition	0	0
Thumb ABD	0	**1**
Fingers flexion	0	0
Fingers extension	0	0

Table 5:1 MRC score

MRC score is a muscular testing evaluation.

A value of 0 reflect no muscular contraction, 1 muscular contraction but no movement for the joint, 2 movement in the whole amplitude without gravity, 3 movement against gravity but without resistance, 4 movement against light resistance, 5 movement against maximal resistance. Green values highlight an improvement in MRC score.

Name	*Pre-evaluation*	*Post-evaluation*
Elbow flexion	3	3
Elbow extension	4	**3**
Wrist flexion	0	0
Wrist extension	4	4
Fingers flexion	0	0
Fingers extension	4	**3**

Table 5:2 Modified Ashworth Score

Modified Ashworth score is an evaluation of spasticity.

0 no increase in muscular tone, 1 Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension, 1+: Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM, 2: More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved, 3: Considerable increase in muscle tone, passive movement difficult, 4: Affected part(s) rigid in flexion or extension. Green values highlight a decrease in muscular tone.

5.3.2 BMI outcomes

BMI performances were increase after training. The single sample accuracy was increased after BMI training (baseline 0.84, post-training 1: 0.96, post-training 2: 0.92) as well as decoding success and speed (Figure 5:2). Results highlighted the fact that the patient was able to learn how to accurately control the BMI despite her motor disabilities.

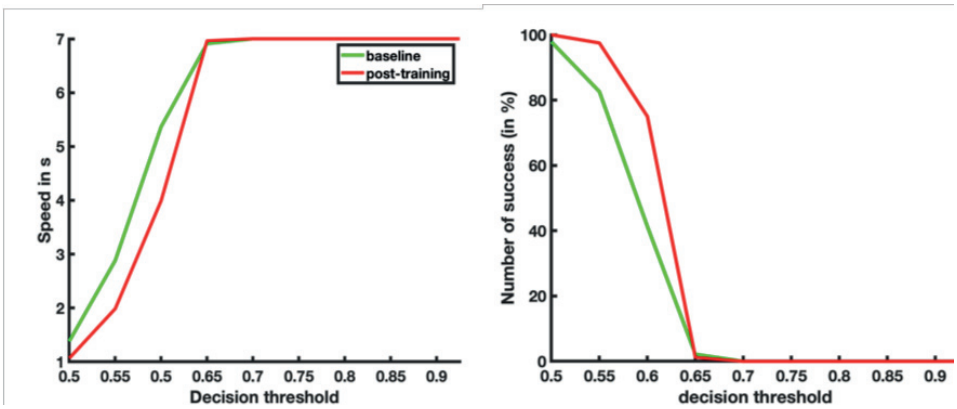

Figure 5:2 Successful decoding and speed of decoder according to decision threshold. Comparison between baseline (in green) and post-training (in red).

5.4 Discussion

In this study case, we have tested the use of BMI St-NMES as an upper-limb therapy for a patient suffering from a chronic stroke. Our results showed that after 10 sessions, the patient improved her upper limb motor function especially at the proximal part. Moreover, the patient was able to control BMI and she even improved her ability to operate it.

Although we could not record MEP, we hypothesized that the patient's motor recovery might be due to cortical and corticospinal reorganization according to results from our previous experiment. BMI-St-NMES is then, a very promising tool for motor rehabilitation. Although, BMI training has been already showed to be valuable for stroke rehabilitation [23–25], we believed that St-NMES feedback might enhance BMI effect on motor recovery especially because it might support CNS adaptation and facilitate BMI control. Moreover, sensory electrical stimulation alone also showed promising results for upper limb rehabilitation [117,118]. The combination of BMI and St-NMES appeared to be extremely interesting at the light of these preliminary results. A study with a larger population and a control group will need to be investigated, in combination with rich CNS imaging, in order to infer about the potential of BMI-St-NMES for stroke rehabilitation.

One main concern to apply BMI-St-NMES for motor rehabilitation might be the possible sensory deficit of patients. In our case, the patient had an impaired sensation but she reported to feel St-NMES at intensities higher for the impaired limb compared to the healthy one. Interestingly the

patient also described a decrease neglect toward her upper limb during and after the BMI-St-NMES sessions. This could be explained because she was feeling her paretic limb and that she needed to intensively focus her attention on it. Finally, a limitation of this study case is that the evaluator was not impartial. For a further experiment it would be important that the clinical assessments are performed by an external evaluator blind to the patient group. A group control will be also needed to compare the use of BMI St-NMES to a standard upper limb therapy.

This single-case study showed that BMI-St-NMES is applicable for motor rehabilitation after stroke and might enhance motor function after intensive BMI training. Nonetheless, a controlled clinical trial will be needed to conclude any effect of BMI-St-NMES on motor recovery.

Chapter 6 Discussion and Conclusion

The goal of this thesis is to provide the scientific rationale, technical details and physiological evidence supporting the use of St-NMES as feedback for BMI applications. Through different experiments, our findings showed that St-NMES is a somatosensory feedback that promoted BMI skill acquisition and improved BMI usability. BMI-St-NMES reduced BMI current limitations by improving BMI accuracy and stability. Moreover, with BMI-St-NMES training, subjects learnt to control a BMI. As explained by Carmena et al. [146], one main challenge for BMI systems is getting the brain to recognize an external "actuator" that is not part of the body, and being able to control it without enacting over physical movements. By coupling the central activation of the imagined movement with peripheral sensation of the limb, this thesis sustains the hypothesis that BMI-St-NMES promotes CNS plasticity and facilitates BMI learning.

In order to achieve a BMI learning two components have to be considered: motor and sensory [146]. The motor side is represented by the performance of BMI systems based on both neural adaptation (brain plasticity) and machine adaptation (machine learning). With training, the goal is to achieve high accuracy with a minimum of cognitive resources and permits any user (with or without motor impairments) to effortlessly control a BMI in daily life activities. In theory, the user simply needs to imagine a limb movement and the BMI will perform the associated action. However, in practice the BMI usability is limited by major technical and human factors. On the sensory side, the goal is to provide realistic sensory feedback that would mimic the natural input or, in the case of MI, emphasize the motoric and kinesthetic memory of a movement. Nonetheless the sensory feedback should not interfere with the BMI decoding. This thesis provided evidences that both motor and sensory aspects of BMI learning are increased with the usage of St-NMES as BMI feedback.

6.1 BMI learning: motor aspects

From the motor aspects, this thesis has shown that compared to a standard visual feedback, St-NMES improved BMI performance. Subjects were able to learn how to perform the task and to control the BMI assuming both machine and CNS adaptation. From a machine learning point of view, this learning is defined by the fact that the decoder can accurately predict subjects' brain state (MI or rest) from the recorded neural activity. Through our different experiments we could indeed, observe

that St-NMES feedback improved decoders' accuracy and stability. Interestingly, BMI based on St-NMES offered a faster decoder compared to visual feedback, which is also a component of skill acquisition. However, more investigations are needed to understand the relationship between BMI learning and speed decoding improvement. Moreover, subjects were able to use the same BMI system over a month without any re-calibration. In principle this can be viewed as an antagonism for machine learning adaptation since we consider the machine system as fixed. However, training a new decoder regularly, even with the same features, might eliminates cortical map formation and the associated performance improvements [147]. Ganguly and Carmena [147] showed with an invasive BMI study on monkeys that the stability of the decoder is a crucial component in the development of a new motor map and BMI skill acquisition. Compared to a BMI with visual feedback, features selected for BMI-St-NMES decoder were more stable over time and subjects could be trained across sessions with a constant decoder. We hypothesize that it facilitated the consolidation of new cortical maps and promoted the acquisition of BMI skills.

The development of new maps is due to the second aspect of motor learning, namely, the neural adaptation. Brain plasticity supports the formation of decoder-specific pattern of cortical activity and the associated feedback. Different stages of learning could be observed through our experiments supported by different phases of neural adaptation. In the early stage, BMI-St-NMES induced an increase CST excitability and a decrease cortical inhibition. This adaptation could be linked to the early process of motor and sensory coupling. At this stage this coupling was crucial to induce plasticity since neither BMI with visual feedback nor St-NMES alone induce CST modulation. Moreover, the fronto-parietal network was significantly more involved with BMI-St-NMES. In later learning phase, no modulation of CST excitability could be recorded after BMI training suggesting that this neural adaptation mechanisms were not needed any longer. We hypothesized that cortical maps were already formed and subjects were already in a later learning stage. This idea was sustained by the fact that after two weeks training, the cortical activation during MI task was significantly increased as well as the decoding accuracy. From our results, we suggest that the observed neuroplasticity mechanisms may have created a specialized BMI control network that allows skillful control.

However, Ganguli and Carmena [147] also showed that once a cortical map became consolidated, a second map could be learned and stored. Once subjects acquired BMI skills, it would be interesting to adapt the BMI decoder to the new acquired patterns. Indeed, in the early stage subjects' performance and motor strategies are highly variable. The preliminary decoder might be then, not optimal for long-term training. As example, Perdikis et al. [22], although also considering that the

decoder stability is essential for BMI learning, had to retrain their decoder twice over months for the training of their users. An efficient re-training of decoder might enhance BMI learning and more specifically BMI performance over time. In the future, further investigations would be needed to understand how and when to adapt BMI decoders according to subjects' expertise. Following this idea, another possible solution to enhance BMI learning is the development of BMI St-NMES with more complex decoding algorithms. In this thesis we used simple LDA algorithm. Due to the non-linearity of brain mechanisms maybe and adaptive decoder and complex mathematical models would be able to characterized better EEG signals to develop subjects' expertise.

6.2 BMI learning: sensory aspects

The somatosensory system plays an essential role in motor learning [148–150]. St-NMES provides somatosensory afferences to the brain by depolarizing sensory nerves. BMI based on MI might be considered as a central activation of a "potential" movement triggered from the integration of sensory stimuli from the motoric memory of the movement [86]. As explained before, to control a BMI it is well known that we should emphasize kinesthetic imagery of the movement. According to Stinear et al. [44] only kinesthetic imagery can modulate CST excitability compared to visual feedback. In this thesis, we showed that BMI based on St-NMES induced an increase CST excitability compared to BMI based on visual feedback. St-NMES feedback probably promoted kinesthetic strategies and the integration of somatosensory information of the "potential" movement. In addition, subjects reported that the tingling sensations in the limb helped them to drive and keep their attention toward limb sensation contrary to the visual feedback. St-NMES also permitted to enhance peripheral activation by depolarizing sensory nerves. Thus, the physiological activation of the peripheral pathway during BMI-MI was reinforced. BMI-St-NMES not only mimic but also strengthen the natural sensorimotor loop by combining central and peripheral activation. The association of sensorimotor mapping and the facilitation of attentional resources were probably key components to support the learning process. That is the reason why we believe that St-NME is currently the most suitable modality of non-invasive feedback to sustain BMI learning and brain plasticity.

Somatosensory feedback has been already reported to be better than visual feedback for BMI control. However, from our knowledge, no study was able to prove that a somatosensory feedback had no direct impact on BMI decoding. Our experiment showed that St-NMES alone did not induce significant ERD and our BMI decoders correctly classified passive delivery of St-NMES as rest. This aspect of somatosensory feedback is very important because the decoder should predict subjects'

intention and not the brain response to the feedback. If the somatosensory feedback induces detectable patterns, the decoder risk to fail to couple subjects' motor intention with the feedback, but to couple brain evoked response to the feedback. Thus, subjects might not be able to learn to control the device. Regarding this statement, most of the previous BMI studies investigated somatosensory impact only during the MI task without considering resting trials. To assure that the BMI is not biased by the feedback, and that the user is "voluntary" in control of the BMI, it is important to verify that users are able to control both mental states (MI and rest). Throughout our different experiments, subjects reported that at the early stage of the experiment, performing resting trials with St-NMES was more difficult than with visual feedback. Receiving St-NMES, subjects' attention toward the upper-limb was strong, whereas for resting trials they had to quickly disengage from the task and change their attentional strategy. With a relatively short amount of practice (after one day of training) subjects managed to control both mental tasks with St-NMES feedback. Therefore, St-NMES can be considered as a usable somatosensory feedback for BMI applications.

One limitation of the used somatosensory feedback is that we defined a fixed St-NMES configuration for all subjects. St-NMES was then, very limited in term of amount of information it provided to the user, and might limit BMI learning. Changing St-NMES parameters according to BMI decoding does not appear to be a solution since parameters like waveform, stimulation intensity, frequency, the time course might influence changes in sensorimotor cortex [120]. On the contrary, the use of multimodal feedback and multisensory inputs might be a solution promote BMI learning. Indeed, in order to develop subjects' expertise, the feedback used should be richer over time. Our idea is that in the early phase of training, low amount of information about BMI decoding through binary St-NMES feedback seems to be sufficient. However, later in the training, the development of skill expertise might require higher amount of information thanks to multi-sensory inputs. For example, combining St-NMES with more detailed visual information could be a solution to enhance subjects' skills. This multi-sensory combination needs to be investigated in the future to promote different phases of BMI learning.

Another limitation in this thesis is the lack of evidence that St-NMES need to be accurately linked to the BMI decoding to induce BMI learning compared to a sham BMI-St-NMES. A sham BMI-St-NMES would imply similar involvement of participants with similar amount of St-NMES, but the St-NMES will not be correlated to subjects' brain activation. However, Biasucci et al. [23] compared the use of BMI based on motor NMES to a sham BMI with NMES for stroke rehabilitation. Results showed that only patients using BMI-NMES significantly improved their motor function as well as increase the connectivity within the damaged motor cortex. No plastic changes and no motor

improvement were observed in the sham group. Thus, we hypothesize that a BMI training not coupled to a correlated St-NMES will not induce efficient plasticity or learning skills.

6.3 Improvement of BMI usability

Ideally, any kind of user, with or without motor disability, should be capable to use a BMI to augment their daily-life activities. A usable BMI can be defined as efficient, accurate and user-friendly. The current lack of usability can be explained by the fact that significant efforts have been dedicated to improve decoding efficiency and accuracy however, BMI studies have generally ignored the user-training component of BMI operation [124]. In this thesis, we showed that St-NMES feedback enhanced BMI usability by improving decoder efficiency and, more importantly user-training aspects.

St-NMES feedback enabled subjects to develop an appropriate strategy to control BMI and to foster kinesthetic imagery. All subjects reported that the task was mentally demanding but that the way to focus their attention was easier compared to the visual feedback. Thus, St-NMES improved the "user-friendly" aspects of BMI in the sense that it made our BMI accessible to all participants. Although in literature 10 to 30% of the population has been found not able to control a BMI, this was not the case in the experiments reported in this thesis. With current EEG-based BMI technology, the only exception are perhaps patients with involuntary movement disorders because of muscular artifacts interfering with EEG recordings. The environment, the experimental conditions and the feedback are crucial elements to achieve BMI control. However, in order to improve the BMI usability, it would be interesting to distinguish fast learners from slow learners and to adjust the training and the BMI, according to subject's current ability. For example, for a fast learner an enriched environment and a more complex feedback might improve their BMI skills. On the contrary, slow learners might need simple somatosensory feedback, more frequent adaptation s of their decoders, and a longer training period.

While the development of St-NMES feedback showed improvement in BMI usability, more challenges remain to be investigated. For example, in our experiments we used the decoding of analytical movement. It would be interesting to decode more complex movements like different synergia or different kinds of grasps. Importantly the transfer to daily-life activities need to be developed. Technological limitations also need to be tackled like EEG usability (dry electrodes, easy to use, decrease signal to noise ratio). Although further improvements are still necessary for BMI-St-NMES to move the technology outside the laboratory, it is a very promising tool for certain BMI

applications especially for motor rehabilitation where it will be deployed in rather controlled conditions and by trained professionals.

6.4 Therapeutic perspectives

BMI coupled to St-NMES feedback might be a promising tool for motor rehabilitation. Indeed, using high-density EEG, BMI-St-NMES showed previously to increase brain connectivity and brain activation in the contralateral hemisphere to the MI limb [67] and to enhance CST excitability. These properties are especially relevant for stroke rehabilitation since reactivation of the damaged primary motor cortex and CST excitability improvement are biomarkers of motor recovery [140,142]. Our BMI approach can combine real-time decoding of MI (or even motor attempt in the case of plegic patients) supported with St-NMES and deliver a peripheral therapy such as a robotic orthosis or NMES at the end of the trial. It has been shown that the combination of MI-BMI with a robotic orthosis has the potential to improve motor performance for moderate to severely impaired chronic stroke patients [24,33,151]. Similarly, combining a MI-BMI with NMES is also a promising alternative for motor rehabilitation [68]. Recently, Biasucci et al. [23] compared a BMI-NMES intervention with sham NMES for motor rehabilitation of chronic stroke patients. The experimental group was based on contingent delivery of NMES upon BMI decoding of patients' motor attempt of the paretic hand. On the contrary, in the sham group NMES delivery was not contingent with patients' brain activity. As a result, they observed a significant, clinically relevant and lasting motor recovery of arm and hand function only for the BMI group (6.6 points in the Fugl-Meyer score, which remained 6-12 months after the end of therapy). Authors hypothesized that the observed motor recovery was probably due to plasticity in the corticospinal projections. Their hypothesis is in line with our results. Although we could not show that BMI-St-NMES increase CST plasticity after stroke, we accumulated evidences that BMI-St-NMES can directly impact CST and cortical plasticity. Further experiments comparing with TMS protocols and diffusion MRI before and after BMI-St-NMES for motor rehabilitation will be needed to understand the impact of this new BMI on CNS plasticity and motor recovery.

As a conclusion, BMI-MI based on St-NMES are a very promising tool to induce motor recovery and motor learning. This new BMI modality could become a future opportunity for several fields of research including mental training during assistive scenarios as well as motor rehabilitation of patients with CNS lesions.

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Curriculum Vitae

TIFFANY **CORBET**

PhD student in Neuroscience, EPFL

PROFIL

I started my career as a physiotherapist. I was always curious about neuroscience and technologies applied to rehabilitation. I quickly became passionate about interdisciplinarity. That is why I started a master in neuroscience and I naturally continued with a PhD at EPFL. Nowadays, I have good experience in rehabilitation, neuroscience and engineering. In the future I would like to continue and promote interdisciplinarity. I am an enthusiastic, self-motivated, responsible and hard-working person. I like to collaborate with people coming from different backgrounds. I work well both in a team environment as well as using own initiative. I am always enthusiastic to learn and undertake new challenges.

CONTACT

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EDUCATION

2015 - 04/2019	**PhD student in neuroscience** Chair in Brain Machine (CNBI), Center for NeuroProsthetics (CNP) École polytechnique fédérale de Lausanne (EPFL)
2015	**Master in neuroscience** Geneva University (UNIGE), Switzerland
2012	**Bachelor in Science of rehabilitation and brain plasticity** Lyon University, France
2012	**State diploma in physiotherapy** Institut Rockfeller Lyon, France
2009	**Validation of first year of medical school** Lyon University, France
2007	**Scientific Baccalaureate** International High School of Ferney Voltaire, France

SKILLS & EXPERTIZE

Clinical neuroscience	■■■■■■■■■■	EEG	■■■■■■■■■■
Neuroscience	■■■■■■■■□□	TMS	■■■■■■■□□□
Rehabilitation	■■■■■■■■■■	fMRI	■■□□□□□□□□
Brain-Machine Interface	■■■■■■■■■□	NMES/FES	■■■■■■■■□□
Neuro-prosthetics	■■■■■■□□□□	EMG	■■■■■■■□□□
Signal analysis	■■■■■■■■□□	MatLab	■■■■■■■■□□
Statistical analysis	■■■■■■□□□□	SPSS	■■■■■□□□□□
Physiotherapy	■■■■■■■■■■	R	■■■■■□□□□□

REWARDS

2018	**Selected for 1st Engineering PhD Summit** Summit theme: Data Driven Engineering in the Life Sciences 2018 Ecole Polytechnique Fédérale de Lausanne, Switzerland
2018	**Best presentaition for Le Fond Jean Falk-Vairant** 15th meeting of the Lemanic Neuroscience Annual Meeting 2018 Les Diablerets, Switzerland
2018	**First place for Overall Poster Presentation** The Seventh International Brain-Computer Interface Meeting BCI 2018 Pacific Grove, California
2016	**Second place for Overall Poster Presentation** The Sixth International Brain-Computer Interface Meeting BCI 2016 Pacific Grove, California

TIFFANY **CORBET**

PhD student in Neuroscience, EPFL

ABOUT ME

Field of interest

- Neuroscience
- Neuroprosthetic
- Cognitive psychology
- Interdisciplinarity
- Translational medicine
- Experimental design
- Scientific communication
- Teaching and education

Languages

- French - Native
- English - C1
- Spanish - A1
- Portuguese - basics

Personality

- Dynamic
- Pro-active
- Social
- Passionate
- Team-player

Hobby & Interests

- Ski
- Fitness
- Cooking
- Gaming
- Music

EXPERIENCE

2015 - present — **PhD student**
Research topic : Usage of brain-machine interfaces for motor rehabilitation
Professor : J. d. R. Millán
CNBI, École polytechnique fédérale de Lausanne (EPFL), Switzerland

2017 - 2018 — **Teacher Assistant**
Course : Fundamentals of NeuroEngineering (Master course, EPFL)
Professor : José del R. Millán and Sylvestro Micera
Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland

2016 — **Teacher Assistant**
Course : Brain Computer Interaction (Master course, EPFL)
Professor : José del R. Millán
Ecole Polytechnique Fédérale de Lausanne (EPFL), Suisse

2013 - 2015 — **Master internship in clinical research**
Master thesis : Enhancement of functional connectivity a new way to promote motor recovery after stroke
Professor : A. Guggisberg
Hôpital de Beau Séjour, UNIGE, Switzerland

2015 — **Master internship**
Cognitive Neuroscience Lab UNIGE, Switzerland
Professor : D. Bavelier

2012 - 2013 — **Physiotherapist in neuro-rehabilitation**
Institution de Lavigny, Switzerland

2011 - 2012 — **Bachelor thesis**
Title: Robotics and hemiplegia : what are the perspectives ?
Hôpital Henry Gabriel Lyon, France
Professor : Marie-Odile Girard

PUBLICATIONS - journal papers

in prep. — **T. Corbet**, M. Wessel, T. Morishita, F. Hummel and J.d.R. Millán, *"Sensory threshold neuromuscular electrical stimulation supports differents stages of BMI skills learning."*

submitted — **T. Corbet**, I. Iturrate, M. Wessel, T. Morishita, F. Hummel and J.d.R. Millán, *"Sensory threshold neuromuscular electrical stimulation promotes the acquisition of BMI skills."*

2019 — R. Krauth, J. Schwertner, S. Vogt, S. Lindquist, M. Sailer, A. Sickert, J. Lamprecht,S. Perdikis, **T. Corbet**, J.d.R. Millán, H. Hinrichs, H. J. Heinze, C.m. Sweeney-Reed, *" Cortico-muscular coherence is reduced acutely post-stroke and increases bilaterally during motor recovery: a pilot study."* ***accepted in Frontiers in Neurology***

2018 — **T. Corbet**, I. Iturrate, M. Pereira, S. Perdikis and J.d.R. Millán, *"Sensory electrical stimulation fosters motor imagery performance"* ***NeuroImage 176:268-276.***

2018 — A. Biasiucci, R. Leeb, I. Iturrate, S. Perdokis, A. Al-Khodairy, **T. Corbet**, A. Schnider, T. Schmidlin, H. Zhang, M. Bassolino, D. Viceic, P. Vuadens, A.G. Guggisberg, J.d.R. Millán. *"Brain-Actuated Functional Electrical Stimulation Elicits Lasting Arm Motor Recovery After Stroke"* ***Nature Communication 9(1):2421***

2018 — I. Iturrate, R. Chavarriaga, H. Zhang, M. Pereira, **T. Corbet**, R. Leeb and J.d.R. Millán, *"Human EEG reveals distinct neural correlates of hand grasping types"* ***NeuroImage 181:635-644***

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2018 A. Mottaz, **T. Corbet**, N. Doganci, C. Magnin, P. Nicolo, A. Schnider and A. G. Guggisberg, *"Modulation of functional connectivity through neurofeedback: effect on motor function in a controlled cross-over study"*
Neuroimage Clinical 2018; 20: 336–346

2015 A. Mottaz, M. Solcà, C. Magnin, **T. Corbet**, A. Schnider, A. G. Guggisberg, *"Neurofeed back training of alpha-band coherence enhances motor performance"*
Clinical Neurophysiology, 126(9):1754:1760

PUBLICATIONS - conference papers

2018 **T. Corbet**, I. Iturrate and J.d.R. Millán *"Sensory threshold electrical stimulation a novel feedback modality for BMIs"* Proceedings of the 7th International Brain-Computer Interface Conference

2018 K. Lee, **T. Corbet**, R. Aydarkhanov, L. Randazzo, R. Chavarriaga, J.d.R. Millán *"Online decoding of gait-related lower-limb movement intention"* Proceedings of the 7th International Brain-Computer Interface Conference

2017 **T. Corbet**, I. Iturrate, M. Pereira, S. Perdikis and J.d.R. Millán *"Sensory threshold electrical stimulation enhances classification of motor imagery performance"* Proceedings of the 7th Graz Brain-Computer Interface Conference

2016 **T. Corbet**, I. Iturrate, M. Pereira, S. Perdikis and J.d.R. Millán *"BCI-NMES therapy enhances effective connectivity in the damaged hemisphere in stroke patients"* Proceedings of the 6th International Brain-Computer Interface Meeting

2016 R. Leeb, A. Biasiucci, T. Schmidlin, **T. Corbet** and J.d.R. Millan *" BCI controlled neuromuscular electrical stimulation enables sustained motor recovery in chronic stroke victims"* Proceedings of the 6th International Brain-Computer Interface Meeting

PhD COURSES

- Data analysis and model classification (4 credits)
- Scientific writing (2 credits)
- Design of experiments (4 credits)
- Diffusion MRI (2 credits)

OTHER ACTIVITIES

Reviewing Journal: Frontiers in Behavioral Neuroscience (review editor), Clinical Neurophysiology, Behavioural Brain Research.
Conference: The Seventh International BCI Meeting2018, IEEE International Conference on Systems, Man, and Cybernetics 2018, International Conference on Neurorehabilitation 2018

Invited speaker The 19th international day of rehabilitation of AHREK Valence (France) 2018. *"Usage of brain-machine interface for motor rehabilitation after spinal cord injury"*

Physiotherapy Institution La Musse, Saint Sébastien De Morsent France (2018), *"New technologies and rehabilitation "*

The 18th international day of rehabilitation of AHREK Valence (France) 2017, *"Usage of brain-machine interface for motor rehabilitation after stroke"*

Thesis advisor Two students in physiotherapy at Institut Rockfeller Lyon, France (2018-2019)

**Ce document a été imprimé au Centre d'impression EPFL,
imprimerie climatiquement neutre, certifiée myClimate.**