Chapter 6
Neuromodulation on Cerebral Activities

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Abstract During a motor task, a causal relation occurs between the motor command generated in the cortex and the proprioceptive feedbacks that go from the activated muscles through the corticospinal pathway. This causal relation is of interest in neurorehabilitation to improve motor function for people with motor difficulties. Previous neurorehabilitation methods used external stimulation to modify the corticospinal pathway controlling the motor function of the affected body parts. An alternative to these approaches is to reinforce the corticospinal pathway by identifying the cortical motor command naturally generated when a person imagines or attempts a movement, and combine it with peripheral nerve stimulation. The research group of Professor D. Farina has developed a method exploiting Brain–computer Interface technology to detect the cortical motor command and use it to trigger peripheral nerve stimulation in order to reinforce the efficiency of the corticospinal pathway. A detailed description of the method and an interview with Prof. D. Farina is presented in this chapter.

Keywords Corticospinal pathway · Peripheral nerve stimulation · Movement imagination · Motor related cortical potentials

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6.1 Introduction

Neural plasticity is an active topic of research in the field of neurosciences referring to the changes in the neural structures due to modifications in the environment, behavior or body injuries. Gaining knowledge about the mechanisms underlying neural plasticity is of great relevance for neurorehabilitation purposes, i.e. rehabilitation of certain functional abilities that have been lost due to neural damages.

One of the phenomena underlying neural plasticity is the associative long-term potentiation (LTP), which is based on the Hebbian learning theory (Hebb 1949). Associative LTP suggests that the concomitant activation of two connected neurons leads to the reinforcement of the synaptic efficiency of the neural pathway linking them. As part of a rehabilitation procedure, associative LTP can be of interest to restore the functional control of body limbs affected by neural injuries by controlling the activation of two selected neural sources. Based on this concept, several neuromodulation protocols have been proposed using external stimulation in patients with motor disabilities (for a review, see Boroojerdi et al. 2001). On one hand, studies have shown that it is possible to induce brain plasticity by using transcranial magnetic stimulation (TMS). On the other hand, functional and structural changes were also elicited after stimulation of the peripheral nerve of a targeted muscle. Finally, a method called Paired-Associative Stimulation (PAS) combined central and peripheral stimulation to induce LTP. All of these studies have revealed that it is possible to selectively modify the neural structure, and that a temporal association between the brain and muscle activity has to be respected in order to strengthen the corticospinal pathways.

Recently, the research group of Professor D. Farina has proposed an alternative to these neuromodulation protocols using Brain–Computer Interfaces (BCI). The technique relies on the detection of a specific cortical pattern to trigger an external stimulation of the peripheral nerve of a targeted muscle. Their studies revealed that muscle-specific neural adaptations can be achieved and that it is possible to induce cortical plasticity using an asynchronous BCI system. This technique is extensively described in the main body of the present chapter. Additionally, an interview with Prof D. Farina is included at the final part of the chapter, where further information regarding the studies described and future challenges are commented.

6.2 Background

The technique proposed by the research group of Professor D. Farina relies on two distinct fields of research: Neuromodulation protocols and BCI systems. Both fields are presented in order to give the reader a clear perspective of the background underlying the experiments proposed.

6.2.1 Neuromodulation Protocols

Previous studies have shown the possibility of inducing neuroplasticity in the nervous system using different kind of stimulation on the peripheral targeted nerve and/or over the targeted sensorimotor cortical regions. Protocols applying TMS alone have proven to be useful to modify deliberately the neuronal excitability, synaptic plasticity or behavioral function outlasting the stimulation period. In this case, several configurations of the stimulation pulses lead to different motor cortex plasticity protocols, such as repetitive TMS, transcranial Direct Current Stimulation, or Theta Burst Stimulation (for a review, see Ziemann et al. 2008). On the other hand, protocols applying only peripheral nerve stimulation (Ridding et al. 2000, 2001) have revealed changes in the excitability of the primary motor cortex in normal human subjects. In this case, a period of at least 1.5 hours of peripheral nerve stimulation is necessary to produce significant changes of the cortical excitability. Stefan et al. (2000) proposed to use together cortical and peripheral nerve stimulation. In their study low-frequency peripheral nerve stimulation is paired with TMS over the contralateral motor cortex inducing plasticity in the motor cortex. Their results highlighted the importance of the time interval left between the peripheral and the cortical stimulations (Kumpulainen et al. 2012). More recently, Thabit et al. (2010) developed a movement-related cortical stimulation protocol in which the motor cortex is stimulated with TMS at specific times with respect to the mean expected reaction time of voluntary movement performed by the subjects measured. Their results revealed that the timing of the stimulation with respect to the reaction time expected of the voluntary movement plays a critical role on the consequences over the motor cortex. This was one of the first studies in which artificial stimulation, applied by TMS, is paired with endogenous cortical activity, i.e. cortical activity when a subject performs a movement, supporting the possibility of its use for rehabilitation of neurological disabilities.

6.2.2 BCI Systems

During the last decade, BCI systems have been proposed to help patients with neurological disabilities communicate with the environment and to move with the help of assistive technologies like wheelchairs or neuroprosthetic devices. Recently, a greater attention has been given to the development of BCI systems on electroencephalographic signals (EEG) for neurorehabilitation purposes (Daly and Wolpaw 2008). On one hand, protocols proposed neurofeedback training, that is, the visualization of the cortical activity along the expected cortical activity during specific task in order to recover a “normal” cortical activity leading to functional recovery (Buch et al. 2008). On the other hand, protocols aim at using the BCI-based control of an external assistive device to generate a proprioceptive feedback. The afferent information generated by these feedbacks is expected to induce corticospinal plasticity leading to functional recovery. In this case, the use of the EEG signal is of interest due to its intrinsic capacity to characterize subject's intentions to move.

6.3 Using EEG/BCI to Induce Brain Plasticity

The previous section showed that, on one hand, the combination of endogenous cortical activity and external stimulation can induce cortical plasticity and, on the other hand, the intention to move can be detected by EEG-based BCI systems. By combining these two approaches, the research group of Professor D. Farina proposed an alternative technique to induce neuromodulation. This technique combines a novel EEG-based BCI approach for the detection of the intention to move with peripheral electrical stimulation in order to induce corticospinal plasticity. For this purpose, three goals are addressed: (1) detect and identify the cortical potentials related to the motor task; (2) accurately define the timing to send the peripheral stimulation; (3) development of a self-paced BCI system detecting online the optimal instant at which peripheral stimulation has to be generated to increase the excitability of the corticospinal pathway.

The level of activity of the motor cortex prior to and during the execution or the imagination of a voluntary motor task can be characterized by the movement-related cortical potentials (MRCP), which refers to the changes of the direct current amplitude of the EEG signal before and during a motor task. The MRCP for voluntary motor tasks consists of an initial negative potential, that is, a slow decrease of the EEG amplitude occurring before the onset of the movement, and followed by a positive potential (Fig. 6.1). This negative potential can be separated into a readiness potential (RP), that is, a first slow decrease occurring 2 s before the movement onset and a steeper decay 0.4 ms before the movement onset. In addition, the RP presents a stable time pattern synchronized with the onset of voluntary movements, which makes the RP perfectly suited to detect a movement intention before it starts (for details see Sect. 6.4 Q2).

In order to maximize the plasticity-induced of the corticospinal pathway, the time at which the stimulation is delivered is crucial (Kumpulainen et al. 2012). The research group of Professor D. Farina proposed to use the MRCP to decide the best timing to send the peripheral stimulation (Mrachacz-Kersting et al. 2012). In this experiment, three groups had to perform imaginary movements as described in Fig. 6.2. During the imaginary movement, single peripheral nerve stimulation was applied at three different latencies according to the movement detection: (1) before the movement execution phase (RP), (2) at the peak negativity of the RP and (3) during the holding phase. Changes in the excitability of the corticospinal pathways were assessed by TMS before and after the experimental procedure. Results revealed that the corticospinal excitability significantly increased when the peripheral stimulation was applied during the peak negativity of the RP only. These results demonstrated that the peripheral stimulation combined with

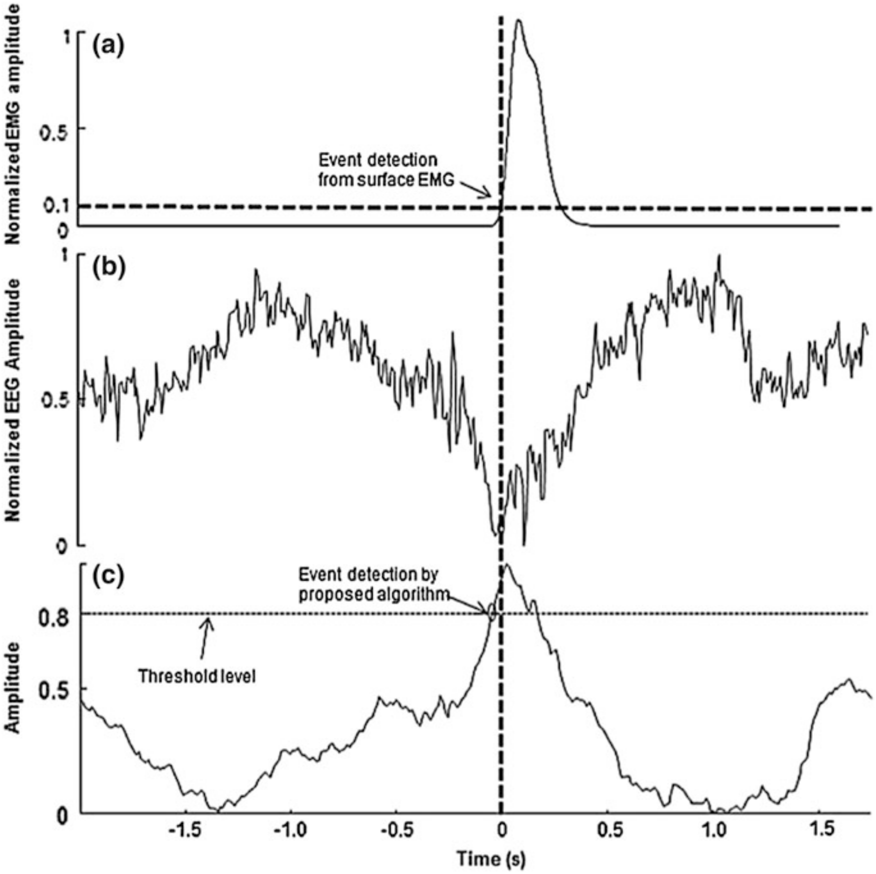

Fig. 6.1 General scheme of detection during movement execution task. Representative sample from one subject: detection of an initial negative phase of MRCPs in an EEG channel obtained through the set threshold. **a** Rectified and averaged EMG trace for event detection, the *horizontal dashed line* is the EMG detection threshold and the *vertical line* is the reference point for detection latency. **b** Single trace of MRCP in the EEG channel, obtained by the optimized spatial filter during self-paced motor execution task. **c** Output of the matched filter. The *horizontal dashed line* is the detection threshold of the proposed algorithm. All *vertical axes* are in arbitrary units. Original figure is presented in Niazi et al. (2011)

movement imagination could strengthen the corticospinal pathway only when the peripheral stimulation is applied during the negative peak of the movement potential (for details see Sect. 6.4 Q1).

In order to get a self-sufficient system to induce neuroplasticity, the research group of Professor D. Farina (Niazi et al. 2012) proposed to combine peripheral stimulation (Mrachacz-Kersting et al. 2012) with a BCI system that detects online the movement onset in an asynchronous way (Niazi et al. 2011), i.e., when the subjects perform movement executions/imageries at their own pace. Several

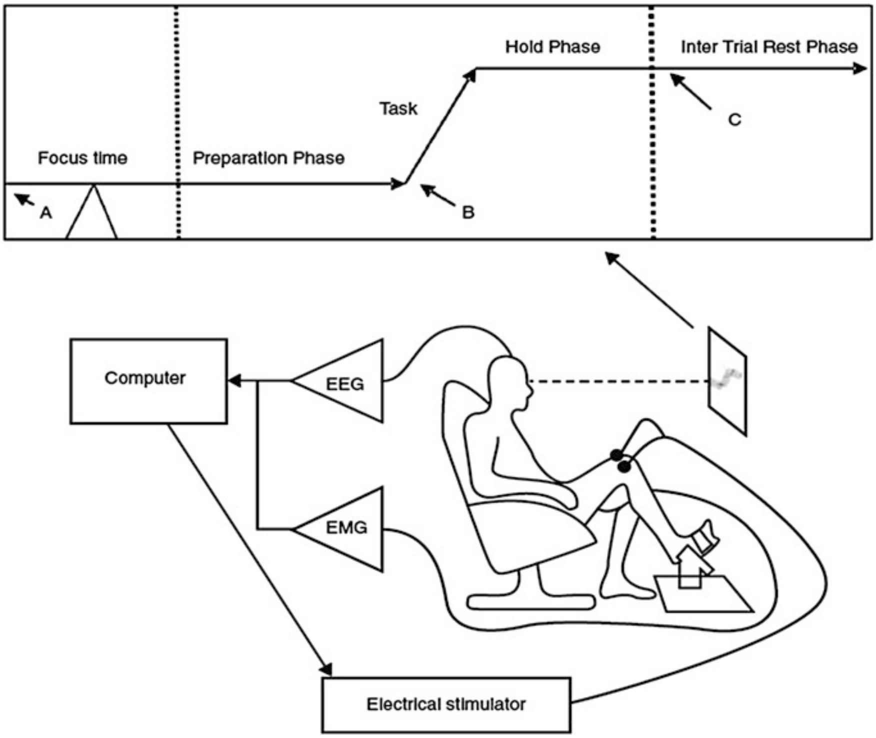

Fig. 6.2 The visual cue—the interface instructing the subjects to perform the imaginary movements: A *moving cursor* starts from point A at the beginning of each trial. In the focus time subjects concentrate on the screen, in the preparation phase subjects mentally prepare for performing the imaginary dorsiflexion, while the movement should be executed at the time instant when the cursor hits point B. The imaginary contraction is held throughout the hold phase and released after point C. Original figure is presented in Mrachacz-Kersting et al. (2012)

techniques were compared to correctly detect the RP during self-paced movement executions and imaginations in healthy and stroke patients (Niazi et al. 2011). Results demonstrated that an optimized spatial filtering technique and matched filters allow the detection of the movement intention based on the RP detection with a good performance.

An experimental procedure to test the reliability of this neuromodulation paradigm based on a BCI system was realized over 16 healthy participants. The accuracy of the BCI system was evaluated by comparing the true positives versus false positives rate, i.e., the actual detection of movement intention versus false detection. Changes of the excitability of the corticospinal pathway were assessed using TMS before and after the experimental procedure (Mrachacz-Kersting et al. 2012). Results revealed that the BCI algorithm was sufficiently accurate in the detection of the movement intention to increase the corticospinal excitability

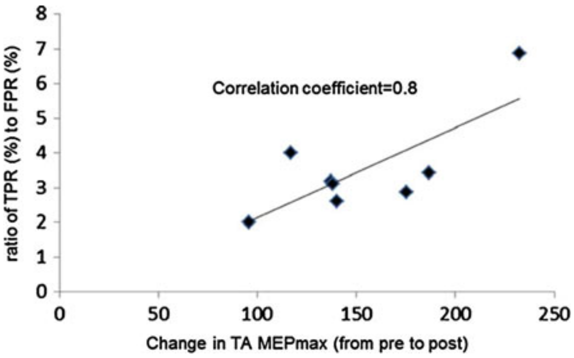

Fig. 6.3 Correlation graph. Correlation between change in the maximal motor evoked potentials (MEP) of the tibialis anterior (TA) from pre- to postmeasure of TMS and ratio (%) of True Positive Rate (TPR) to False Positive Rate (FPR). The change in MEP (*horizontal axis*) refers to the change in the corticospinal excitability while the ratio of TPR to FPR (*vertical axis*) refers to the ability of the BCI system to detect movement intention. Original figure is presented in Niazi et al. (2012)

(Fig. 6.3). This type of technique may be used in rehabilitation procedures in order to increase motor skills.

However, even though this technique showed its efficiency to increase the excitability of the corticospinal pathway, no study has yet revealed that this increase is correlated with an increase of the functional abilities (for details see Sect. 6.4 Q3 and Q4). Future studies should assess the links between the corticospinal excitability and functional abilities in order to confirm the usefulness of this, or any other, technique as neurorehabilitation protocols.

6.4 Interview Part 1: Methodological Aspects and Procedure

Q1: *The timing for triggering the stimulation is important. Could it be better optimized?*

Dario Farina (D.F.): We put a lot of emphasis on the latency of the external stimulus with respect to the cortical activity measured with EEG because we have shown that if the stimulation is later or earlier than 500 ms nothing seems to happen in the cortical structures. However when we stimulated at the peak negativity, we had a variance of possible detection of that peak negativity which was in the order of 100 ms. So I would not say that further improving the latency is a critical aspect in this technological development.

Q2: *Why did you choose the MRCP rather than other EEG-measurable cortical patterns like for example the Event Related Desynchronization?*

D.F.: If we are looking at the whole cortical potential, MRCPs are the only neurophysiological processes that allow prediction of the movement.

Sensory-motor rhythms allow a good detection of the movement with much later latency. In the previous question we said that the latency may not be important but in this case we are talking about latencies bigger than hundreds of milliseconds. We would lose too much time by using the sensory-motor rhythm. On the other hand, the MRCPs have a bandwidth from Direct Current to 1 Hz, so it is an extremely small amount of information that we are extracting from the EEG signal. There is no doubt that if we used an entire bandwidth, which means information from the sensorimotor rhythms, we would detect the desired events with much better accuracy. This could be useful for an asynchronous BCI but it would not be useful for our application because you would lose too much time, making this technique completely useless in order to induce neural plasticity.

Q3: *Movement normally includes more than one muscle. How is this taken into account in your experiments if stimulations are only delivered to one muscle?*

D.F.: It would be interesting to investigate if the intervention is more effective the more you approach functional tasks. Our single electrical stimulus is very far from the functional task, the foot doesn't even move. We literally just have an afferent volley, artificially produced by the electrical stimulation. If we can reproduce the entire movement, that would be much closer to what our brain areas would normally receive when they execute the functional gait movement.

Q4: *How do you think the changes regarding cortical excitability will improve functional ability to perform daily living activities?*

D.F.: That's the one-million-dollar question. In healthy subjects, it is not even clear how the corticospinal excitability changes are related to functional performance of the task. The corticospinal excitability should be related to the excitability of the corticospinal pathway, which is certainly responsible for the neural coding of the movement. The expectation is, if that changes, maybe a movement will be executed with a better strategy in terms of lower motor neurons recruitment. Of course, all of this has to be proved. On a very global level, a new study with stroke patients has shown that there are some functional improvements in some clinical scales that come in parallel with the increase of the enhancement of the cortical excitability. For example, the group of stroke patients that tried the intervention was able to walk the 10 m path faster, on average, than the control group. Now, how these improvements are correlated between each other and what are the neurophysiological mechanisms that make such improvements are completely open questions.

6.5 Interview Part 2: Applications and Future Challenges

Q5: *What is the main contribution of these studies?*

D.F.: These studies belong to the large category of neurofeedback and neuromodulation, in which you record a neural signal and you provide a feedback associated to this signal. The feedback is an afferent electrical stimulation but the specificity of this feedback is not too relevant, it could also be the movement of a robotic hand, a vibration, etc. The idea is to relate a motor imagination with an afferent stimulation precisely delayed with respect to the mental task. By doing that the corticospinal pathway will be strengthened. The main novelty of these studies is putting together a completely self-paced system for which a computer algorithm interprets the cortical activity and send a peripheral stimulation with a very precise delay. This has been demonstrated to increase the corticospinal excitability in healthy subjects and in stroke patients. It is a new approach for neuromodulation based on EEG recordings and also one of the few applications of BCI for neuromodulation.

Q6: *Which impairments would benefit from these techniques?*

D.F.: Naturally we thought that the obvious targets would be brain-damaged patients because the technique is devoted to increase the excitability of the brain areas. I could think of several other possible applications, for example, neurological tremor is another pathology in which you may want to provide enough afferent stimulation to desynchronise pathological cortical oscillations with respect to afferent input. I could see similar techniques applied for tremor suppression, which has also a cortical origin. Therefore pathologies that are related to cortical impairment or brain damage should benefit from this technique.

Q7: *What results do you expect to obtain when applying this technique on stroke patients?*

D.F.: There are always more difficulties in applying this, or any other, technique in patients. The signals that you are recording may be different and may not even be present. These differences are interesting because they could be used as biomarkers of the excitability without using TMS. One could follow the cortical recovery by only looking at the characteristics of the MRCP in comparison to healthy individuals but it has not yet been tested. However, I don’t exclude that there would be a number of patients with whom we could not use this technique. On the other hand, the technique could be also extended in various ways. We were trying to enhance the normal physiological pathway but, in the same way, you can enhance alternative pathways. For example, you can make a connection by recording the cortical activity and stimulating the ipsilateral side, trying to strengthen a pathway as an adaptation strategy. Of course, this is just a speculative kind of statement. What I am saying is that, there is so much to do, especially from the clinical side, and it is impossible to predict how much these techniques can impact the rehabilitation in the long term. Certainly there will be a long time period before these kinds of technology will be used as clinical applications. I think that it is reasonable to expect that this strategy should be helpful in the rehabilitation process. The important thing is what these results may trigger. Here (Summer School on Neurorehabiliation, ed.), we were discussing about translating these results to robotics, exoskeletons or orthosis which seems to me much more reasonable from the functional point of view. One thing is to give an electric tap to the nerve, which is very unnatural; another thing is to move the foot passively or partly passively exactly as it would be executed with that motor command. My expectation is certainly not that the techniques should be taken as they are, immediately employed by a number of hospitals, which decide that these results are extremely interesting, and they want to try them [smile]. This is only a proof-of-concept. There are still many steps to do but I am convinced that the way, at least, is correct.

Q8: *Are there any drawbacks to use this technique in a clinical setting?*

D.F.: I cannot see big drawbacks, not even in the practical implementation. Many drawbacks in neuro-rehabilitation techniques are the practical implementation on a daily basis because it had to be robust and so on while this kind of approaches wants only to retrain. This is not something that one has to aim to give at the hospital or at home to the patient. It can be just a rehabilitation strategy on top of many others—maybe not implemented with the strategy described here but implemented with the same kind of concept. So, something hospital-based is a good perspective.

Q9: *Would the experimental protocols used be suitable in a clinical environment?*

D.F.: Everything we are including in our experiments is already available in most hospitals. EEG and peripheral stimulation are done continuously. The rest is a computer analysis and the requirements are minimal because the processing is not very complex. For this kind of intervention, there are no elements that are completely stranger to the clinics. Mounting the EEG always takes a bit of time because you have to check signals quality, etc. If you want something faster, the EEG part could be improved, for example, with the inclusion of active electrodes, with systems that imply a minimal time in the mounting and in checking the signal quality. My main message is that everything used in our experiments is not different from what is done in a clinical environment. On the other hand, there is an open question on the clinical applicability in terms of how much our proposed system will be accepted by the patients, how easy will it be to explain to them what to do, how much time the clinicians will need to mount the electrodes etc. This is a whole thing that one can discuss with the clinician.

Q10: *At which stage of the rehabilitation would this intervention be applied?*

D.F.: Naturally it would be more effective the closer the interventions are performed with respect to the stroke event. After a certain limit though, because you have to recover from the brain damage and the subject, in the very first period, is usually not available for rehabilitation or for training. I would say that the intervention we are proposing should be applied to stroke patients as soon as the standard physiotherapy starts. When the medical staff says that the patient can go under a rehabilitation treatment, this kind of intervention could be easily added. The patients that we have analyzed started the interventions for our clinical study after they had already started a number of interventions but that was a clinical study and we needed to recruit stroke patients in collaboration with a hospital, taking into account their conditions.

Q11: *How is this intervention going to be applied to a certain kind of stroke patient that presents a lesion over a certain hemisphere and region? How can it be asserted that the reinforced corticospinal pathways are the optimal ones?*

D.F.: It's reasonable to think that if you try to reinforce the physiological pathway that was working in that way before the damage you cannot induce any additional damage. I mean that the subject can also employ additional strategies but still he has a pathway reinforced which is responsible for a movement that is physiologically optimal, because it corresponds to the healthy conditions. The adaptation strategies in stroke are so heterogeneous that it is difficult to say what is best in a general sense. Probably the best would be to analyze the patients individually in collaboration with the medical staff. Sometimes the best intervention may even be to learn a completely different neural strategy, which is functionally not very different from the healthy condition. However, it's not excluded that you can use this kind of technique to do that.

6.6 Conclusions and Future Challenges

During the last decade a number of therapies based on stimulation of the central and peripheral nervous system have been proposed to induce changes in the corticospinal pathways by increasing the cortical excitability in specific regions. A novel intervention developed by the research group of Prof. D. Farina, exploited EEG-based BCI technology to detect the cortical motor command generated when a person imagines or attempts a movement and combined it with electrical stimulation of the targeted muscle. This intervention obtained positive results with both control and stroke patients and demonstrated its efficiency to increase the excitability of the corticospinal pathway. In the case of stroke patients, unpublished results from the research group of Prof. D. Farina suggested that this intervention improved functional abilities in clinical tests, for example the time spent in a 10 m walk.

As Prof. Farina pointed out in the interview, this intervention is a "proof-of-concept". Future developments in this framework will be oriented in proving the system's performance under clinical conditions, taking into account different muscles, limbs and/or more functional tasks, and testing alternative ways to deliver proprioceptive feedback. In conclusion, "there are still many steps to do but the way, at least, is correct".

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