Aalborg Universitet

AALBORG UNIVERSITY

DENMARK

Does feedback based on FES-evoked nociceptive withdrawal reflex condition event-related desynchronization? An exploratory study with brain-computer interfaces.

Tabernig, Carolina B.; Carrere, L. Carolina; Biurrun Manresa, José; Spaich, Erika G.

Does feedback based on FES-evoked nociceptive withdrawal reflex condition event-related desynchronization? An exploratory study with brain-computer interfaces.

Does feedback based on FES-evoked nociceptive withdrawal reflex condition event-related desynchronization? An exploratory study with brain-computer interfaces.

Carolina B. Tabernig[1], L. Carolina Carrere[1], José Biurrun Manresa[1,2] and Erika G. Spaich[3]

[1] Laboratory of Rehabilitation Engineering and Neuromuscular and Sensory Research (LIRINS), Faculty of Engineering, National University of Entre Ríos, Oro Verde, Argentina

[2] Institute for Research and Development in Bioengineering and Bioinformatics (IBB), CONICET-UNER, Oro Verde, Argentina

[3] Department of Health Science and Technology, Aalborg University, Denmark

E-mail: carolina.tabernig@uner.edu.ar

Abstract

Introduction. Event-related desynchronization (ERD) is used in brain-computer interfaces (BCI) to detect the user's motor intention (MI) and convert it into a command for an actuator to provide sensory feedback or mobility, for example by means of functional electrical stimulation (FES). Recent studies have proposed to evoke the nociceptive withdrawal reflex (NWR) using FES, in order to evoke synergistic movements of the lower limb and to facilitate the gait rehabilitation of stroke patients. The use of NWR to provide sensorimotor feedback in ERD-based BCI is novel; thererfore, the conditioning effect that nociceptive stimuli might have on MI is still unknown.

Objective. To assess the ERD produced during the MI after FES-evoked NWR, in order to evaluate if nociceptive stimuli condition subsequent ERDs.

Methods. Data from 528 electroencephalography trials of 8 healthy volunteers were recorded and analyzed. Volunteers used an ERD-based BCI, which provided two types of feedback: intrisic by the FES-evoked NWR and extrinsic by virtual reality. The electromyogram of the tibialis anterior muscle was also recorded. The main outcome variables were the normalized root mean square of the evoked electromyogram (RMS_{norm}), the average electroencephalogram amplitude at the ERD frequency during MI ($\bar{A}_{MI}$) and the percentage decrease of $\bar{A}_{MI}$ relative to rest ($ERD\%$) at the first MI subsequent to the activation of the BCI.

Results. No evidence of changes of the RMS_{norm} on both the $\bar{A}_{MI}$(p=0.663) and the $ERD\%$ (p=0.252) of the subsequent MI was detected. A main effect of the type of feedback was found in the subsequent $\bar{A}_{MI}$(p <0.001), with intrinsic feedback resulting in a larger $\bar{A}_{MI}$.

Conclusions. No evidence of ERD conditioning was observed using BCI feedback based on FES-evoked NWR .

Significance. FES-evoked NWR could constitute a potential feedback modality in an ERD-based BCI to facilitate motor recovery of stroke people.

Keywords: Brain Computer Interface, Event Related Desynchronization, Nociceptive Withdrawal Reflex, Functional Electrical Stimulation, Nociceptive Stimuli

1. Introduction

Hemiplegia or hemiparesis are typical consequences of stroke and lead to lower limb motor impairments such as foot drop [1]. Although motility may be affected, stroke survivors can still perform motor intents (MI) in response to a movement cue, producing the desynchronization of their brain's sensorimotor rhythms (*mu:* 8 to 12 Hz and *beta:* 18 to 30 Hz) [2]. This phenomenon is called event-related desynchronization (ERD) and its temporal and spectral behaviours during MI in post-stroke patients have been described [3,4].

ERD can be used in brain-computer interfaces (BCI) to detect the user's MI [5,6]. An ERD-based BCI is a closed-loop system that records the electroencephalogram (EEG), detects the ERD and generates a command output for controlling the actuator to provide sensory feedback, communication or mobility to the user [7]. BCIs are an emerging technology for motor recovery [8–11]. In these applications, feedback plays a key role as it influences the subject's attention, concentration and motivation. Thus, it must be realistic and similar to the specific motor task, in order to promote neural plasticity [12].

Functional electrical stimulation (FES) is one of the available intrinsic feedback modalities in BCI systems [8,10,13–16]. FES produces or assists movements through the application of electrical stimuli to either mixed or sensory nerves [17] and provides visual, proprioceptive and cutaneous feedback to the patient [18]. FES can also be used to evoke the nociceptive withdrawal reflex (NWR). The NWR is a polysynaptic reflex that integrates afferent sensory signals, descending modulating signals and motor commands to evoke the limb withdrawal motor response. The NWR evoked by electrical stimuli has been previously used to produce functional movements, such as the flexion of the main joints of the lower limb [19] . Since patients with hemiparesis have difficulties performing these same movements, NWR-based FES therapy was proposed for gait rehabilitation, with successful results [20]. Then, it can be hypothesized that motor relearning and motor recovery could be facilitated in hemiparetic people if the NWR is evoked repetitively and synergistically with the activation of the central nervous system with the aid of an ERD-based BCI. A potential problem with this concept is that ERD happens during voluntary MI, whereas the NWR is related to the activation of the nociceptive system and it can be inhibited and/or modulated by the subject. Previous studies investigated changes in brain rhythms in relation to different nociceptive stimuli and pain conditions [21–25]. The relation between the central processing of nociceptive information and the MI is emerging in the BCI context [26]; but the use of NWR as a feedback is still unknown.

In this study, the ERD produced during MI immediately after FES-evoked NWR was assessed in order to evaluate if nociceptive stimulation conditions the ERD of the subsequent MI. To this end, an experiment was carried out in which participants attempted to use an ERD-based BCI which provided two types of feedback: intrinsic, given by the FES-evoked NWR; and extrinsic, provided by a computerized animation by virtual reality (VR).

2. Materials and methods.

The experimental study consisted of two stages: the *Parameters Selection* of the BCI and the electrical stimulator; and the *Feedback* stage in which two BCI were used, each one with a different actuator device. One actuator provided extrinsic feedback

and was based on VR imitating foot dorsiflexion (BCI_VR). The other provided intrinsic feedback and consisted of an electrical stimulator to evoke the NWR and produce visible foot dorsiflexion (BCI_NWR).

2.1. Volunteers

Twelve healthy naïve volunteers without neurological or cognitive conditions (mean age 32 ± 9 years, 6 female) were invited to participate, of whom 8 were enrolled in the study after assessing the following inclusion criteria: ability to modulate their sensorimotor rhythms achieving ERD and visible foot dorsiflexion following FES-evoked NWR. The study was conducted following the Declaration of Helsinki. The protocol was approved by the Central Ethics Committee for Research and Medical Practice of the Entre Ríos, Argentina, and registered in the National Registry of Health Research (RENIS IS001667). All subjects signed a written informed consent prior to participation in the experiment.

2.2. Parameters Selection stage

The purpose of this stage was twofold: 1) to determine the desynchronization frequency (f_{ERD}) to configure the BCI and 2) to identify the NWR stimulation intensity to configure the electrical stimulator. The f_{ERD} was defined as the EEG frequency that showed the largest desynchronization, assessed with the coefficient of determination (r^2) at Cz [27]. NWR stimulation intensity was defined as the minimum comfortable electrical stimulation intensity that achieved visible foot dorsiflexion. The limb with the highest r^2 in Cz for f_{ERD} was selected for further use in the *Feedback* stage.

2.2.1. Materials

Eight EEG channels were recorded using a g.MOBIlab+® amplifier (Guger Technologies, Austria, sampling frequency: 256 Hz, resolution: 16 bits, filters: 0.5–100 Hz, sensitivity: 500 µV) and the BCI2000 software platform [27]. EEG signals were filtered using a Butterworth bandpass filter between 0.5 Hz and 40 Hz. A notch filter was used to suppress the 50 Hz power line interference. A g.GAMMA® cap was used for positioning the passive electrodes (g.LADYbird®) on the scalp according to the extended version of the international 10-20 system. Electrode positions C3, C4, T7, T8, Pz, F3, F4, and Cz were selected, taking into account the cortical areas of interest for this study [27]. The ground and reference electrodes were placed on the right and left mastoids, respectively.

A computer-controlled pulse generator [28] and a linear current isolated stimulator (STMISOLA, BIOPAC® Systems Inc., USA) were used to deliver electrical stimulation. The active electrode size was 1.5×2 cm (Ambu® Neuroline 700, Denmark) and the indifferent electrode size was 5×9 cm (Pals®, Axelgaard Manufacturing Co. Ltd., Denmark).

2.2.2. EEG signal processing

EEG recording signals were processed using BCI2000 Offline Analysis tool available in BCI2000 Platform [25]. This signal processing consisted in the application of a common average reference filter to remove physiological and non-physiological interferences and the computation of r^2 which was represented in topographic maps within the frequency range from 8 Hz to 30 Hz (sensorimotor rhythms) for the left and right feet [27]. The coefficient r^2 was estimated as the square of the Pearson correlation coefficient between the spectrum of the EEG signal in the resting state and the spectrum of the signal associated with the MI. This coefficient assumes real values between 0 and 1. Values of r^2 close to 1 indicate a very good discrimination between rest and MI conditions, while values of r^2 close to 0 are associated to conditions that can be scarcely distinguished [29]. The cortical localization of the ERD related to MI of foot dorsiflexion was identified by visual analysis of

the EEG at the Cz position and the f_{ERD} was identified for each foot [4]. Finally, the limb with highest r^2 in Cz for f_{ERD} was selected to evoke the NWR.

2.2.3. Protocols

Subjects were first asked to sit in a comfortable and relaxed position. Then, they were instructed to avoid eye blinking and/or muscle movement as much as possible. Finally, they were asked to rehearse foot dorsiflexion without muscle contraction to simulate paretic MI [30]. EEG was recorded based on the experimental protocol proposed by Schalk and Mellinger [27], which consisted of three series with one or two minutes rest intervals in between. Each serie included three randomly distributed different tasks of simulated paretic dorsiflexion of the right foot, the left foot, or both feet in response to a visual cue presented in the middle of the screen. Every task was repeated 10 times during each serie, separated by a 5 to 6 seconds random inter-task interval. During these intervals, subjects were asked to relax. At the end, 30 EEG trials for each task were obtained across the three series (90 trials in total for each volunteer).

To evoke the NWR from the selected limb, the cathode was placed on the medial area of the sole of the foot and the anode was placed on the dorsum of the same foot, which resulted in foot dorsiflexion with minimal discomfort due to the electrical stimulus. The NWR was elicited with a train of 5 pulses of 1-ms duration delivered at 200 pps [19].

The NWR stimulation intensity was determined using a staircase procedure, in which the intensity of the electrical stimulation was initially set at 1 mA, and then it was increased and decreased, in steps of 1 mA, until a visible foot dorsiflexion was obtained or the volunteer manifested intolerable discomfort. Once the desired ankle joint movement was obtained, the intensity was fixed for that volunteer throughout the session and selected as NWR stimulation intensity.

As a result of this first stage, the f_{ERD} for the BCI calibration, the limb to evoke the NWR and the NWR stimulation intensity were selected for each subject.

2.3. Feedback stage

This stage consisted of 2 sessions, in which the two ERD-based BCIs were tested: BCI_NWR and BCI_VR. During these sessions, volunteers performed MI tasks, which consisted of ankle dorsiflexion intention without muscle contraction, to imitate the paresis of the stroke users.

2.3.1. Materials

Figure 1 shows the block diagram of the ERD-based BCI used in this study. It consisted of 3 modules: Signal Sensor and Conditioner, Control Signal Generator and the Actuator Device. The first two modules comprised the following blocks: Acquisition, Filtering, Segmentation, Spatial Filtering, Feature Extraction, Feature Selection, and Classification.
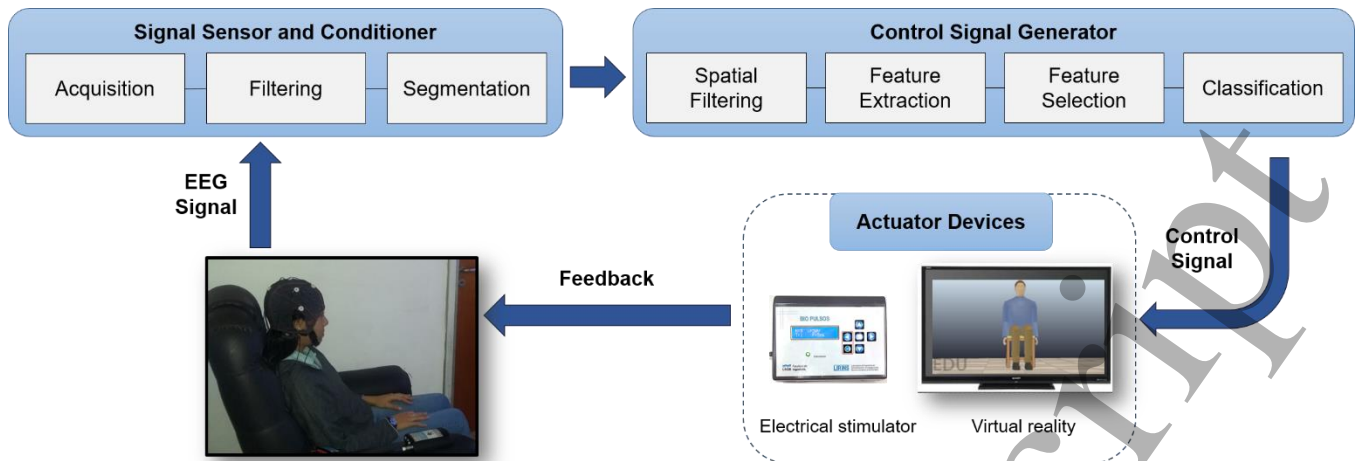
Figure 1: Structure of the ERD-based BCI, with its modules: Signal Sensor and Conditioner; Control Signal Generator and Actuator Devices

The electrodes positions placed in the *Parameters Selection* stage were preserved in this stage. Acquisition and Filtering were the same blocks that were used in the previous stage. Then, data from each channel were segmented and sent to the next module in sets of 8 samples (total length: 31.25 ms) [27]. In the Control Signal Generator module, a Laplacian spatial filter was implemented to improve the signal to noise ratio and to enhance the signal from Cz (Cz' signal) [31]. Then, in the Feature Extraction block, the power spectral density from Cz' was computed in 500-ms epochs via a 16th-order autoregressive model estimated by the Burg Method [32], in the range of 8-30 Hz and using 3-Hz bins. In the Feature Selection block, the spectral amplitude from Cz' corresponding to the f_{ERD} ($A_{f_{ERD}}$) was selected, resulting in 64 $A_{f_{ERD}}$ per task [16]. The first 500 ms after the cue were not used because they can present cue-evoked potentials [33]. The Classification block identified the ERD when the mean $A_{f_{ERD}}$ ($\bar{A}_{f_{ERD}}$) between 0.5 and 2 s after the cue falls below an adaptive threshold. This threshold was set as the lowest of the last two $\bar{A}_{f_{ERD}}$. The initial classification threshold was established as the first $\bar{A}_{f_{ERD}}$. In this way, the strategy to update the detection threshold compelled the volunteers to try decreasing the amplitude of their sensorimotor rhythms to achieve the activation of the BCI, in a trial-by-trial basis. The output of the classification block provided a single activation command for each detected MI task, to trigger the stimulation pulse train [30]. Figure 2 shows the BCI operation protocol.

The control signal was sent through virtual ports to the two actuators, so the following two BCIs were available:

- BCI_VR: the actuator was a VR software developed on the V-REP PRO EDU 3.0 platform (Coppelia Robotics GmbH, Zürich, Switzerland) that imitates the foot dorsiflexion in a mirror-like fashion, giving extrinsic feedback [6].
- BCI_NWR: the actuator consisted of the electric stimulation system used in the *Parameters Selection* stage that generates the electrical stimuli to evoke the NWR, producing reflex responses resulting in foot dorsiflexion and therefore, intrinsic feedback [30].

The Filtering, Segmentation, Spatial Filtering, Feature Extraction, and Feature Selection blocks were implemented using the BCI2000 platform [27]. The Classification block and the communication with the actuator devices were implemented in Matlab 9.01, R2016a (The Mathworks, Natick, MA, USA).

2.3.2. Recording protocol

Data were recorded during 2 sessions in the same day, each session with a different feedback in random order. Each session consisted of 3 sets of 11 MI tasks of the selected foot, in response to an auditory cue. The MI task duration was 3 s, followed

by a rest period (inter-task interval, ITI) of 15 s, to avoid habituation of the NWR. The classifier output was generated 2 s after the cue, as can be seen in Figure 2. Volunteers were asked to relax 3 s after the cue. During the ITI, the actuator was disabled.
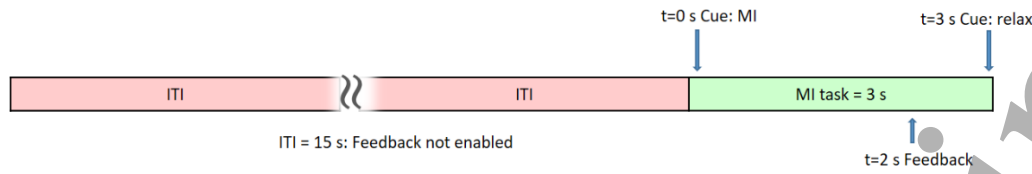

Figure 2: Recording and BCI operation protocol at *Feedback* stage.

2.3.3. ERD quantification

Data from 528 trials of EEG signals were processed. Following the approach put forward by [32,34], the percentage of ERD at f_{ERD} was estimated as:

$$ERD\% = \left(\frac{(\bar{A}_{ITI} - \bar{A}_{MI})}{\bar{A}_{ITI}} \right) * 100$$

where $\bar{A}_{ITI}$ is the $\bar{A}_{f_{ERD}}$ of the ITI and $\bar{A}_{MI}$ is the $\bar{A}_{f_{ERD}}$ during the MI task.

2.3.4. NWR quantification

The NWR response was assessed by surface electromyography (EMG) of the tibialis anterior muscle (TA). Two Ag/ClAg electrodes of 1 cm in diameter, were placed 2 cm apart on the belly of the TA and the ground electrode was placed on the malleolus [35]. A BioAmp amplifier [36] and the BrainBay software platform [37] were used to record EMG. The EMG signals were filtered between 0.5 and 500 Hz and sampled at 2 kHz.

The EMG signal was analysed using Matlab 9.01, R2016a (The Mathworks, Natick, MA, USA). The analysis window, defined as the period of time in which a NWR is expected, was established between 60 and 180 ms after the start of the electric stimulation train [19]. The mean amplitude of the rectified TA EMG signal was calculated by means of the Root Mean Square value (RMS_{NWR}). The baseline RMS ($RMS_{baseline}$) was defined as the RMS amplitude of the TA EMG starting 120 ms before the stimulation onset and ending at the stimulation onset. The $RMS_{baseline}$ was subtracted from the RMS_{NWR} in order to quantify the reflex response and, finally, the difference was normalized with respect to the baseline (RMS_{norm}):

$$RMS_{norm} = \frac{(RMS_{NWR} - RMS_{baseline})}{RMS_{baseline}}$$

To detect the presence of the NWR, a z score was calculated as:

$$z = \frac{(A_{max} - \mu_{baseline})}{\sigma_{baseline}}$$

where A_{max} is the maximum amplitude of the EMG in the analysis window, and $\mu_{baseline}$ and $\sigma_{baseline}$ are the means and standard deviations of the baseline, respectively. A z score greater than 12 indicates the presence of a NWR [38].

2.3.5. BCI performance

To estimate the BCI performance, accuracy was defined as the number of correct classifications of user´s states divided by the total amount of trials (in percentage):

$$Accuaracy\% = \left(\frac{(TP + TN)}{N} \right) * 100$$

where TP is the number of True Positive; TN is the number of True Negative trials and N is the number of the total trials. Then, because the BCI was disabled during the resting trials (ITI), TN was equal to the number of resting trials.

2.3.6. Pain assessment.

At the end of the session, volunteers were asked to assess the pain intensity related to the electrical stimulus. A Numerical Rating Scale (NRS) was used to quantify the level of pain, where 1 was a minimal sensation of discomfort and 10 was intolerable pain. A score of 5 was established as the pain threshold [39].

2.4. Statistics.

Statistics were performed using SPSS® v.23. Summary measures for the data are presented as mean ± standard deviation. Linear mixed models were used to analyze the relationship between the reflex response (i.e. the NWR size estimated by the RMS_{norm}) and both the $\bar{A}_{MI}$ and the $ERD\%$ subsequent the FES-evoked NWR triggered by a MI; and to determine if the type of feedback (extrinsic feedback by RV or intrinsic feedback by NWR) affects the $\bar{A}_{MI}$ or the $ERD\%$ subsequent to the activation of the ERD-based BCI. A compound symmetry structure was used to model the covariance matrix and p values smaller than 0.05 were considered statistically significant.

3. Results

Table 1 shows the f_{ERD} determined during the *Parameters Selection* stage for all volunteers incorporated to the *Feedback* stage. Only one volunteer (S5) presented f_{ERD} in *mu* rhythm while the rest of them evidenced f_{ERD} in *beta* rhythm.

Table 1: Desynchronization frequency (f_{ERD}) for BCI calibration

Subject	S1	S2	S3	S4	S5	S6	S7	S8
f_{ERD} (Hz)	24	27	27	30	8	24	15	14

Figure 3 shows an example of the EEG signals recorded during 4 MI tasks. It were observed the start (vertical line marked "1") and the end of the MI tasks (vertical line marked "0"). If there was MI detection (for example after the first 0:15 min., then at 00:33 min. and finally at 1:10 min), the electrical stimulator was activated and consequently the NWR was evoked, eliciting EEG artefacts related to electrical stimulation and a somatosensory evoked potentials also caused by the electrical stimulus, whose intensity for this volunteer was 27 mA.
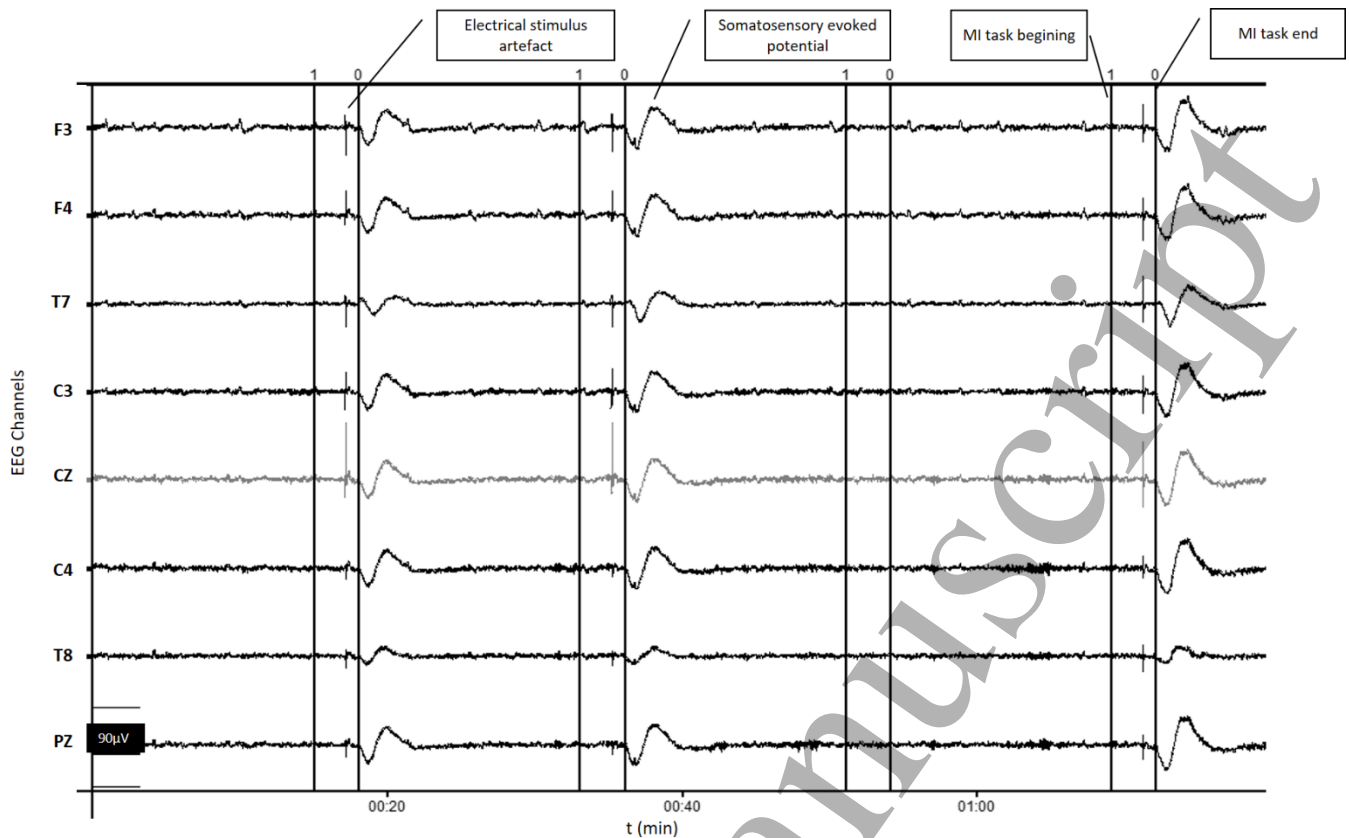
Figure 3: Example of EEG signals recorded during 4 MI tasks.The start of the task (1) and the end of the task (0) are marked with solid vertical lines. Electrical stimulation intensity = 27 mA.

In Figure 4 (a) it can be observed the media and standard deviation (SD) of EMG signals from the TA during the FES-evoked NWR. It highlighted the great variability in the morphology and amplitude of the EMG signal and, therefore, of the NWR. To describe this NWR variability, in Figure 4 (b), can be observed the box plot of all the RMS_{norm} values of the evoked NWR during the *Feedback* stage. The dispersion and the presence of three atypical values are highlighted, which show reflex activity with RMS amplitudes up to almost 50 times the baseline.

(a)

(b)

Figure 4: EMG signals from the TA during the FES-evoked NWR, n = 153. (a) Median (solid line) and standard deviation (SD, shaded boundary). (b) Box plot of RMS amplitudes normalized to baselines (RMS_{norm})

In Figure 5 it can see an example of evolution, during 3 series of a session, of the $\bar{A}_{MI}$ and the RMS_{norm} normalized to the maximum of the series. In vertical lines, the last MI task of each series was indicated. It can be observed the great variability of the $\bar{A}_{MI}$ before each MI and the RMS_{norm}, highlighting in this example that the RMS_{norm} of the third series seem to be of lower value than in the previous two. The full lines indicate the last MI of each series; 11 MI per series.

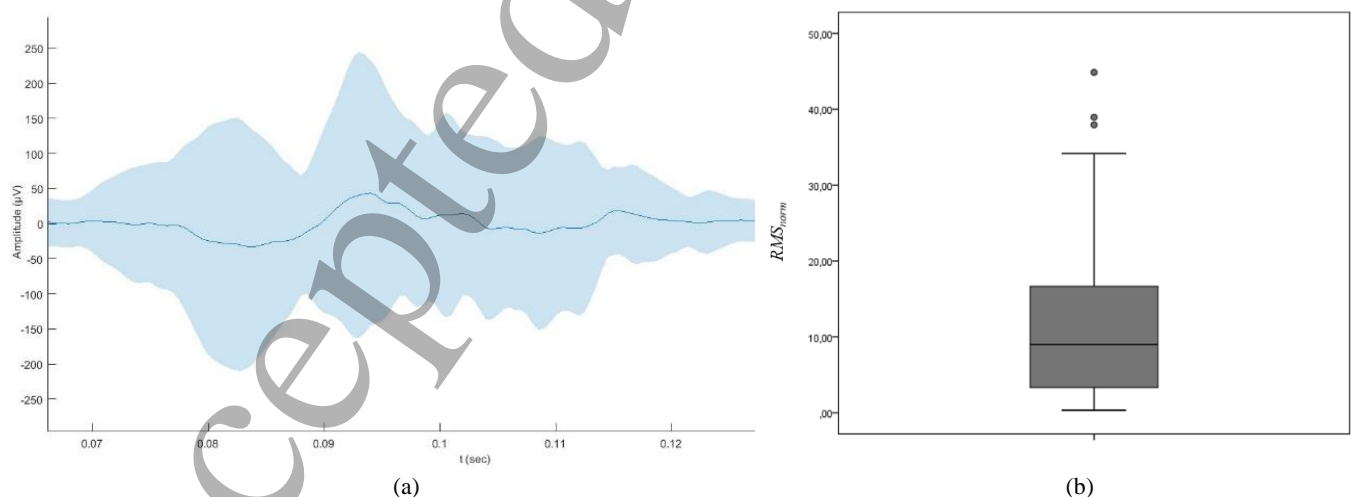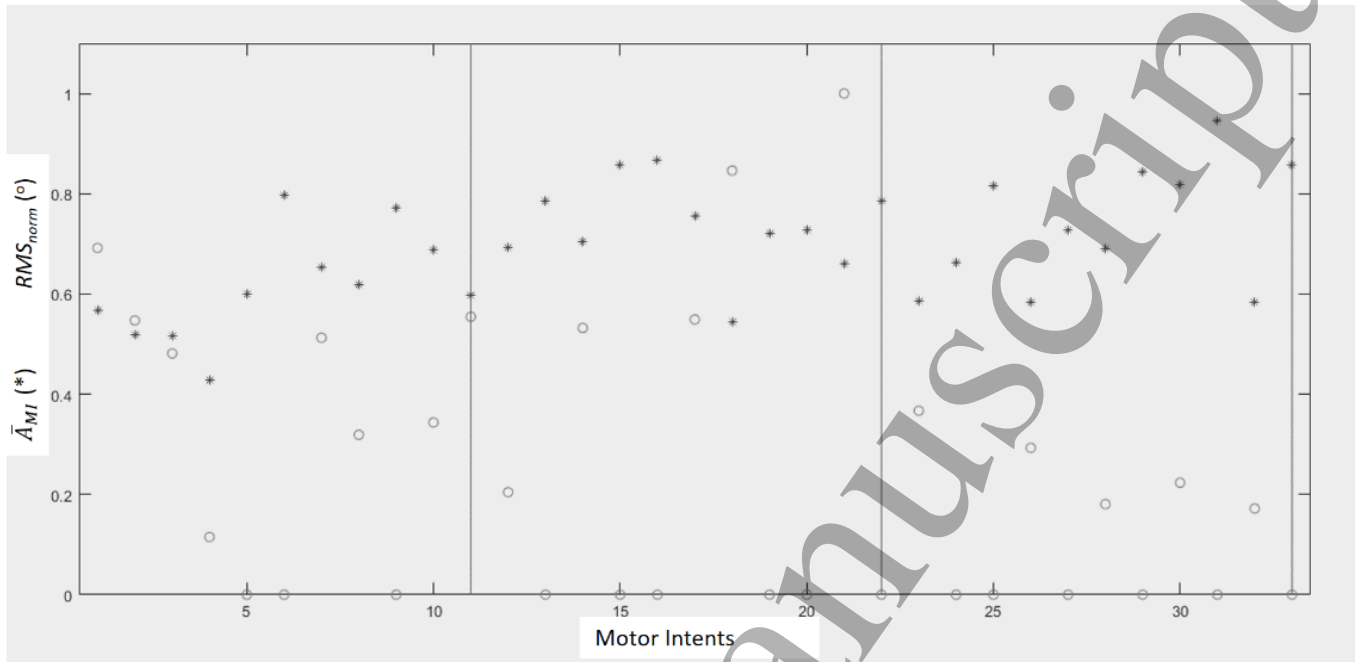Figure 5: Example of evolution of the $\bar{A}_{MI}$ (*) and the RMS_{norm} (°), normalized to the maximum of the series; during 3 series, 11 MI per series.

The mean BCI accuracy was 74.4% for the BCI_VR and 75.0% for BCI_NWR. The mean electrical stimulation intensity used to evoke the NWR was 13.6 ± 6.4 mA. The average level of discomfort due to electrical stimulation was 3.33 ± 1.37. 75% of the volunteers scored below 5 in the NRS, while the remaining volunteers scored 5. All of them manifested that the feedback was unpleasant but not painful.

No evidence of changes of the amplitude of the NWR response (RMS_{norm}) on the subsequent $\bar{A}_{MI}$ (p = 0.663) or the subsequent $ERD\%$ (p = 0.252) was found.

Figure 6 shows the box plots corresponding to the values of the $\bar{A}_{MI}$ and $ERD\%$ according to the type of feedback, subsequent to the activation of the BCI. A main effect of the feedback type was found in the subsequent $\bar{A}_{MI}$(p <0.001), but no difference between feedback type was found for the subsequent $ERD\%$ (p = 0.961).
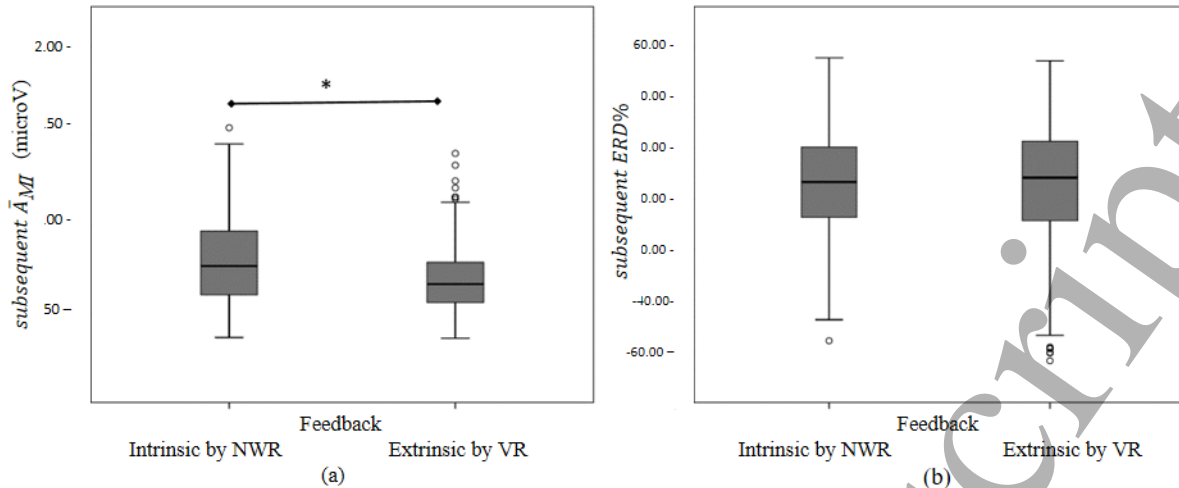
Figure 6: Box plots of (a) $\bar{A}_{MI}$ and (b) $ERD\%$, subsequent to the BCI activation, according to the type of feedback.
The asterisk indicates main effect (*) (p<0.001)

4. Discussion

This study was carried out to determine whether the ERD changes after receiving electrical stimulation of sufficient intensity to produce a NWR with visible foot dorsiflexion. Since the NWR involves the activation of the nociceptive system by means of electrical stimulation using intensities that can cause pain or discomfort, it was hypothesized that this could affect subsequent attempts of sensorimotor rhythms desynchronization, since this would result in activation of the electrical stimulator via the BCI. To test this hypothesis, the $\bar{A}_{MI}$ and $ERD\%$ subsequent to the activation of either a VR animation that provided visual feedback or the NWR that provided cutaneous, proprioceptive and visual feedback were compared across actuator modalities. Regarding the relationship between the reflex response and the subsequent $ERD\%$, results did not show a significant relationship between the RMS_{norm} and the measures of desynchronization. Due to the small sample size, it is an exploratory study.

4.1. NWR and subsequent ERD

The stimulation intensity required to evoke a withdrawal reflex is often sufficient to activate the nociceptive system [19]. Regarding the use of a nociceptive stimuli that may evoke painful sensations, the volunteers in this study were aware that there was a chance that they would receive a nociceptive stimulus to evoke the NWR after a MI. The stimulation intensity selected in our study was high enough to achieve visible ankle dorsiflexion but was not scored as painful by the volunteers, i.e. none of them rated above 5, which was the pain threshold. Also, the mean stimulation intensity was similar to the one used in NWR experiments with healthy subjects (14.6 ± 5.8 mA)[19]. Stroke patients usually present sensory problems with a concurrent decrease in sensitivity [40], so our intensity levels would not be a problem for future application of the method in these patients. In this sense, studies involving stroke patients reported stimulation intensities of 31.7 ± 2.9 mA to evoke NWR and 22.1 ± 2.2 mA for gait re-education based on NWR [41].

In this study, it was observed that volunteers achieved ERD even after receiving an unpleasant stimulus 15 seconds earlier. In other words, they did not suppress the oscillations of their sensorimotor rhythms (at *alpha* and *beta* frequencies), perhaps because the electrical stimuli were annoying but not painful. Phasic pain stimuli transiently suppress oscillations at *alpha* and *beta* frequencies [24]. Nociceptive stimulation produces transient and strong *alpha*-ERD at latencies between 150 and 1000 ms after stimulation with ITI ranging from 8 to 12 s [23]. It was also reported that this short latency nociceptive-induced *alpha*-

ERD reflects the summation of sensory-related and task-related cortical processes [21]; but the effects on ERD induced by unpleasant stimuli have not yet been reported.

4.2. Type of feedback

In the BCI context, feedback can be given intrinsically or extrinsically, as a response to the MI. The feedback informs the person about their performance while the motor task was being performed. Extrinsic feedback is defined as the information provided by an external source, for example a therapist or a display [42–44]. Intrinsic feedback is related to sensory information from changes in the body, given for example by orthotic or FES [8,10,11]. Intrinsic feedback activates visual, auditory, proprioceptive and tactile pathways and enables an appropriate sensory context to facilitate cortical reorganization. For BCIs in rehabilitation, this feedback is generally richer than extrinsic feedback [45,46], particularly with FES-evoked NWR since afferent sensory signals, descending modulating signals and motor commands are integrated by the central nervous system into a motor output. Moreover, the electrical stimulation needs to be combined with simultaneous voluntary effort to potentially provide an artificial way that ensures synchronized activation of the residual corticospinal tract [18]. This voluntary effort involves the sensorimotor rhythms modulation as a response to the motor task, i.e. ERD which was detected by the BCI. No reports about ERD-BCI with FES-evoked NWR have been found.

In this study a main effect of the feedback type was found in the subsequent $\bar{A}_{MI}$, with intrinsic feedback resulting in a larger $\bar{A}_{MI}$ (Figure 6-a-), but it was not found for the subsequent *ERD%* (Figure 6-b-). Attention to unpleasant stimuli could have influenced the $\bar{A}_{MI}$ [47], but it is not clear. On the other hand, *ERD%* takes into account the resting condition ($\bar{A}_{ITI}$). The 15 s duration ITI avoided the habituation of NWR and allowed the volunteers to prepare for a new ERD but, perhaps, it was not long enough to reach the resting state during the use of BCI_NWR. The role of mental states in determining individual post-stimulus brain activity, perception and behaviour is a key in this type of studies [24]. Future studies are necessary to explore the influence of the attention to unpleasant stimuli and to determine whether the volunteers went back easier into rest with RV feedback than with NWR feedback.

The mean BCI accuracies (74.4% for the BCI_VR and 75.0% for BCI_NWR) showed that both of the BCI were higher than the chance level of 63.3% [48] and they were in the range reported by other authors for lower limb ERD_based BCI [6].

4.3. ERD-based BCI

Although the development of the BCI_NWR was not the aim of this study, the concept of eliciting the NWR by a BCI was also explored using an ERD-based BCI with FES-evoked NWR in the *Feedback* stage.

Regarding the applied ERD-based BCI, the Acquisition, Filtering, Segmentation, Spatial Filtering, Feature Extraction and Feature Selection blocks were based on those proposed by Schalk and Mellinger [27] and used by several authors [50–52]. A 16th-order autoregressive model was used to estimate power spectral density because it performs better than Fast Fourier Transform in short data segments [53].The order of the model was selected as it is suggested in the literature for scalp EEG sampled at 256 Hz [27,54]. In future studies, it could be interesting to compare the advantages and disadvantages of different feature extraction methods.

The BCI recorded the EEG in monopolar configuration, filtered it, and then used a Laplacian spatial filter to generate a single signal that highlights the signal coming from the electrode Cz (Cz' signal). Other authors recorded the EEG in bipolar configuration and chose the most convenient pair of electrodes for the best BCI control, placed in different areas of the cerebral cortex [15]. However, in the context of neuro-rehabilitation, the aim is to achieve motor recovery. Then, it is essential to record the EEG signal originated in the injured motor cortical area which is expected to recover through training (in our study, the

lower limb and therefore Cz). Although in stroke people the EEG signal to noise ratio is likely reduced, there are studies that report that it is possible to identify ERD and control a BCI with signals from the affected hemisphere [6,11,55,56].

Regarding spatial filters, in a review reported by Bashashati *et al.* [57], the authors reported that 32% of the studies used Laplacian filters, 22% used principal component analysis (PCA) or independent component analysis (ICA), 14% common spatial patterns (CSP) and 11% used common average reference (CAR) filters. In filters based on PCA, ICA or CPS the weights are adapted from data of all the EEG channels [58], which may not be those corresponding to the cerebral cortex to recover. On the other hand, the use of CAR filters tends to reduce the impact of artefacts common to all channels, but they do not fulfil the objective of enhancing the signal coming from a specific EEG channel. For these reasons, and given that the filter seeks to highlight spatially localized brain activity [31], it is considered that the choice of the Laplacian filter is appropriate for the application in neuro-rehabilitation.

The used BCI detected the MI estimating the average energy of the EEG signal at f_{ERD} in Cz' in each MI and then compared it with an adaptive threshold established as the lowest of the last two $\bar{A}_{MI}$. This strategy was similar to those used by other authors who established an adaptive threshold as the mean of the means of the populations of the $\bar{A}_{f_{ERD}}$ during the MI and during rest [59]. The used BCI generated a binary output to command the actuator, for each detected ERD during a MI. Similarly, others studies proposed a BCI that provided a binary command signal for the control of a FES device. These BCIs were based on ERD with a double threshold configured for each subject with an empirical procedure [15].

All of the modules of the BCI used in this study could be modified or optimized by using other machine learning strategies [60] but always taking into account the feasibility of use in a clinical rehabilitation setting, that is, being of rapid configuration and calibration and easy-to-use by the therapist/operator.

4.4. Other observations

Seven of the eight healthy naïve volunteers showed f_{ERD} (table 1) in *beta* rhythm, while only one participant evidenced ERD in *mu* rhythm. These results coincide with the bibliography where it was reported that there is a desynchronization of the both sensorimotor rhythms [2,4,5,32,33].

After each activation of the electric stimulator by the BCI, somatosensory evoked potentials were registered, as shown in Figure 3. When using electrical stimulation at high-intensity levels just like in this study (13.6 ± 6.4 mA; needed to overcome the threshold for NWR evocation and to perform joint movement), somatosensory evoked potentials reflect the simultaneous activations of large-diameter, lower threshold non-nociceptive fibers (type Aβ) and small-diameter, higher threshold nociceptive fibers (Aδ) [61].

In the example of the evolution of the RMS_{norm} during 3 series of a session shown in Figure 5, the intra-subject variability is observed during a session and at a constant stimulation intensity. Likewise, there is a tendency to decrease the RMS_{norm} (relative to the maximum of the series) during the third series. This could be due to the habituation of the NWR that, although the ITI of 15 seconds was established to avoid it, might not be enough for this subject. These considerations should be taken into account at the time of the implementation of a rehabilitation therapy. Also it would be interesting to estimate the ERD latency both as a biomarker and as a detector of the onset of ERD in order to give feedback to the user at the earliest possible time [62].

5. Conclusions

Results showed that the cutaneous, proprioceptive, tactile and visual, although unpleasant, feedback given by the foot dorsiflexion obtained by FES-evoked NWR did not condition the subsequent ERD and that it was possible to elicit the lower

limb NWR by an ERD-based BCI to produce a visible foot dorsiflexion. FES-evoked NWR could therefore be used as feedback in an ERD-based BCI for motor recovery of stroke people. The NWR causes the flexion of the affected lower limbs joints and, if it is performed repetitively and synergistically with the central commands activation (thanks to the use of an ERD-based BCI), it is expected to facilitate motor relearning.

Acknowledgements

References

[1]   Winstein C J, Stein J, Arena R, Bates B, Cherney L R, Cramer S C, Deruyter F, Eng J J, Fisher B, Harvey R L, Lang C E, MacKay-Lyons M, Ottenbacher K J, Pugh S, Reeves M J, Richards L G, Stiers W and Zorowitz R D 2016 Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals *Stroke* **47** e98–169

[2]   Neuper C and Pfurtscheller G 2010 Electroencephalographic characteristics during motor imagery *The neurophysiological foundations of mental and motor imagery* vol 6, ed G Aymeric and C Collet (University Press Scholarship Online Oxford) pp 45–66

[3]   Billinger M, Daly I, Kaiser V, Jin J, Allison B Z, Gernot R M and Brunner C 2012 Is It Significant ? Guidelines for Reporting BCI Performance *Towards Practical Brain-Computer Interfaces* ed B Z Allison, A Nijholt, S Dunne, R Leeb and J D R Millán (Springer) pp 333–54

[4]   Tabernig C, Carrere L C, Gentiletti G and Spaich E G 2019 Post-stroke injured cerebral cortex: frequency analysis of the desynchronization of its sensorimotor rhythms during motor intent *IFMBE Proc. Ser. Springer Verlag*

[5]   Müller-Putz G R, Schwarz A, Pereira J and Ofner P 2016 From classic motor imagery to complex movement intention decoding: The noninvasive Graz-BCI approach *Prog. Brain Res.* **228** 39–70

[6]   Carrere L C, Escher L G, Gentiletti G G and Tabernig C B 2021 A foot motor imagery brain-computer interface with realistic visual feedback: preliminary evaluation in healthy and stroke subjects *Res. Biomed. Eng.*

[7]   Brunner C, Birbaumer N, Blankertz B, Guger C, Kübler A, Mattia D, Millán J del R, Miralles F, Nijholt A, Opisso E, Ramsey N, Salomon P and Müller-Putz G R 2015 BNCI Horizon 2020: towards a roadmap for the BCI community *Brain-Computer Interfaces* **2** 1–10

[8]   Biasiucci A, Leeb R, Iturrate I, Perdikis S, Al-Khodairy A, Corbet T, Schnider A, Schmidlin T, Zhang H, Bassolino M, Viceic D, Vuadens P, Guggisberg A G and Millán J D R 2018 Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke *Nat. Commun.* **9** 2421–34

[9]   Cervera M A, Soekadar S R, Ushiba J, Millán J del R, Liu M, Birbaumer N and Garipelli G 2018 Brain-computer interfaces for post-stroke motor rehabilitation: a meta-analysis *Ann. Clin. Transl. Neurol.* **5** 651–63

[10]   Tabernig C B, Lopez C A, Carrere L C, Spaich E G and Ballario C H 2018 Neurorehabilitation therapy of patients with severe stroke based on functional electrical stimulation commanded by a brain computer interface *J. Rehabil. Assist. Technol. Eng.* **5** 1–12

[11]   Romero-Laiseca M A, Delisle-Rodriguez D, Cardoso V, Gurve D, Loterio F, Posses Nascimento J H, Krishnan S, Frizera-Neto A and Bastos-Filho T 2020 A Low-Cost Lower-Limb Brain-Machine Interface Triggered by Pedaling Motor Imagery for Post-Stroke Patients Rehabilitation *IEEE Trans. Neural Syst. Rehabil. Eng.* **28** 988–96

[12]   Jeunet C, Kaoua B N, Lotte F, Jeunet C, Kaoua B N and Lotte F 2016 Advances in User-Training for Mental-Imagery Based BCI Control : Psychological and Cognitive Factors and their Neural Correlates

[13]   McCrimmon C M, King C E, Wang P T, Cramer S C, Nenadic Z and Do A H 2015 Brain-controlled functional electrical stimulation therapy for gait rehabilitation after stroke: A safety study *J. Neuroeng. Rehabil.* **12**

[14]   Chung E, Kim J-H, Park D-S and Lee B-H 2015 Effects of brain-computer interface-based functional electrical stimulation on brain activation in stroke patients: a pilot randomized controlled trial *J. Phys. Ther. Sci.* **27** 559–62

[15]   Vŭcković A, Wallace L and Allan D B 2015 Hybrid brain-Computer interface and functional electrical stimulation for sensorimotor training in participants with tetraplegia: A Proof-of-Concept Study *J. Neurol. Phys. Ther.* **39** 3–14

[16]   Carrere L C, Escher L and Tabernig C B 2019 A Wireless BCI-FES Based on Motor Intent for Lower Limb Rehabilitation *CLAIB 2019* pp 1162–70

[17]   Popović D B 2014 Advances in functional electrical stimulation (FES) *J. Electromyogr. Kinesiol.* **24** 795–802

[18]   Young W 2015 Electrical stimulation and motor recovery *Cell Transplant.* **24** 429–46

[19]   Ole K. Andersen and Spaich E G 2013 Gait rehabilitation using nociceptive withdrawal reflex–based functional electrical therapy in stroke patients *Introduction to Neural Engineering for Motor Rehabilitation* ed D Farina, W Jensen and M Akay (IEEE Press) pp 497–582

[20]   Spaich E G, Svaneborg N, Jørgensen H R M and Andersen O K 2014 Rehabilitation of the hemiparetic gait by nociceptive withdrawal reflex-based functional electrical therapy: A randomized, single-blinded study *J. Neuroeng. Rehabil.* **11** 1–10

[21]   Hu L, Peng W, Valentini E, Zhang Z and Hu Y 2013 Functional features of nociceptive-induced suppression of alpha band electroencephalographic oscillations *J. Pain* **14** 89–99

[22]   Peng W and Tang D 2015 Pain related cortical oscillations: Methodological advances and potential applications *Front. Comput. Neurosci.* **10** 1–10

[23]   Michail G, Dresel C, Witkovský V, Stankewitz A and Schulz E 2016 Neuronal Oscillations in Various Frequency Bands Differ between Pain and Touch *Front. Hum. Neurosci.* **10** 1–8

[24]   Ploner M, Sorg C and Gross J 2017 Brain Rhythms of Pain *Trends Cogn. Sci.* **21** 100–10

[25]   Peng W, Huang X, Liu Y and Cui F 2019 Predictability modulates the anticipation and perception of pain in both self and others *Soc. Cogn. Affect. Neurosci.* **14** 747–57

[26]   Zhang S, Yoshida W, Mano H, Shibata K, Kawato M, Seymour B, Zhang S, Yoshida W, Mano H, Yanagisawa T, Mancini F and Shibata K 2020 Article Pain Control by Co-adaptive Learning in a Brain- Machine Interface Article Pain Control by Co-adaptive Learning in a Brain-Machine Interface *Curr. Biol.* 1–10

[27]   Schalk G and Mellinger J 2010 *A practical guide to brain-computer interfacing with BCI2000: General-purpose software for brain-computer interface research, data acquisition, stimulus presentation, and brain monitoring* (Springer-Verlag London)

[28]   Vértiz D, Filomena E and Tabernig C B 2018 System of generation and amplification of electrical stimulation pulses for evocation of nociceptive withdrawal reflex *Rev. Argentina Bioingeniería* **3** 1–6

[29]   Aldea R and Eva O D 2013 Detecting sensorimotor rhythms from the EEG signals using the independent component analysis and the coefficient of determination *ISSCS 2013 - Int. Symp. Signals, Circuits Syst.* 13–6

[30]   Tabernig C B, Carrere L C, Biurrun Manresa J A, Gentiletti G G and Spaich E G 2019 Is it possible to use the FES-evoked nociceptive withdrawal reflex as feedback in a BCI system? *IFESS 2019* (London)

[31]   McFarland D J 2015 The advantages of the surface Laplacian in brain-computer interface research *Int. J. Psychophysiol.* **97** 271–6

[32]   Pfurtscheller G and Mcfarland D 2012 BCIs that use sensorimotor rhythms *Brain-computer interfaces: principles and practice* ed J R Wolpaw and E Wolpaw (Oxford, Reino Unido: Oxford University Press) p 227

[33]   Pfurtscheller G and Neuper C 2010 Dynamics of sensorimotor oscillations in a motor task *Brain-Computer Interfaces: Revolutionizing Human–Computer Interaction* (New York: Springer) pp 47--64

[34]   Pfurtscheller G and Neuper C 2003 Movement and ERD/ERS *The Bereitschaftspotential : movement-related cortical potentials* (Springer) pp 191–206

[35]   SENIAM Project 2020 Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles

[36]   Filomena E and Reta J M 2017 BioAmp Biopotentials Amplifier

[37]   Brain Bay 2017 BrainBay Plataform

[38]   France C R, Rhudy J L and McGlone S 2009 Using normalized EMG to define the nociceptive flexion reflex (NFR) threshold: Further evaluation of standardized NFR scoring criteria *Pain* **145** 211–8

[39]   Andersen O K, Sonnenborg F A and Arendt-Nielsen L 1999 Withdrawal Reflexes Elicited By Electrical Stimulation of the *Muscle and Nerve* 1520–30

[40]   Tyson S F, Crow J L, Connell L, Winward C and Hillier S 2013 Sensory Impairments of the Lower Limb after Stroke: A Pooled Analysis of Individual Patient Data *Top Stroke Rehabil* **20** 441–9

[41]   Spaich E G, Svaneborg N, Jørgensen H R M and Andersen O K 2014 Rehabilitation of the hemiparetic gait by nociceptive withdrawal reflex-based functional electrical therapy: a randomized, single-blinded study *J. Neuroeng. Rehabil.* **11** 81

[42]   Ahn M and Jun S C 2015 Performance variation in motor imagery brain-computer interface: A brief review *J. Neurosci. Methods* **243** 103–10

[43]   Morone G, Pisotta I, Pichiorri F, Kleih S, Paolucci S, Molinari M, Cincotti F, Kübler A and Mattia D 2015 Proof of principle of a brain-computer interface approach to support poststroke arm rehabilitation in hospitalized patients: Design, acceptability, and usability *Arch. Phys. Med. Rehabil.* **96** S71–8

[44]   Grimm F, Walter A, Spler M, Naros G, Rosenstiel W and Gharabaghi A 2016 Hybrid neuroprosthesis for the upper limb: Combining brain-controlled neuromuscular stimulation with a multi-joint arm exoskeleton *Front. Neurosci.* **10** 1–11

[45]   Vidaurre C, Ramos Murguialday A, Haufe S, Gómez M, Müller K R and Nikulin V V. 2019 Enhancing sensorimotor BCI performance with assistive afferent activity: An online evaluation *Neuroimage* **199** 375–86

[46]   Bhattacharyya S, Clerc M and Hayashibe M 2019 Augmenting Motor Imagery Learning for Brain–Computer Interfacing Using Electrical Stimulation as Feedback *IEEE Trans. Med. Robot. Bionics* **1** 247–55

[47]   May E S, Butz M, Kahlbrock N, Hoogenboom N, Brenner M and Schnitzler A 2012 Pre- and post-stimulus alpha activity shows differential modulation with spatial attention during the processing of pain *Neuroimage* **62** 1965–74

[48]   Jeunet C, Debener S, Lotte F, Mattout J, Scherer R and Zich C 2018 Mind the Traps! Design Guidelines for Rigorous

BCI Experiments *Brain--Computer Interfaces Handbook* (CRC Press) pp 639–60

[49] Schalk G and Mellinger J 2010 *A Practical Guide to Brain-computer Interfacing with BCI2000* (New York: Springer)

[50] Darvishi S, Ridding M C, Abbott D and Baumert M 2015 Does feedback modality affect performance of brain computer interfaces? *International IEEE/EMBS Conference on Neural Engineering* vol July (Montpellier, France) pp 232–5

[51] Abdalsalam E, Yusoff M Z, Malik A, Kamel N S and Mahmoud D 2018 Modulation of sensorimotor rhythms for brain-computer interface using motor imagery with online feedback *Signal, Image Video Process.* **12** 557–64

[52] Kasahara K, Hoshino H, Furusawa Y, Sayo DaSalla C, Honda M, Murata M and Hanakawa T 2018 Initial experience with a sensorimotor rhythm-based brain-computer interface in a Parkinson's disease patient *Brain-Computer Interfaces* **2621** 1–9

[53] Krusienski D J, McFarland D J and Principe J C 2012 BCI Signal Processing: Feature Extraction *Brain-computer interfaces: principles and practice* (Oxford University Press)

[54] McFarland D J and Wolpaw J R 2008 Sensorimotor rhythm-based brain-computer interface (BCI): Model order selection for autoregressive spectral analysis *J. Neural Eng.* **5** 155–62

[55] Aguilar C B, Carrere L C and Tabernig C B 2020 Lower limb motor intention : ERD time-course analysis in stroke and healthy subjects *Rev. Argentina Bioingenieria* **23** 19–23

[56] Ramos-Murguialday A, Broetz D, Rea M, Yilmaz Ö, Brasil F L, Liberati G, Marco R, Garcia-cossio E, Vyziotis A, Cho W, Cohen L G and Birbaumer N 2013 Brain-Machine-Interface in Chronic Stroke Rehabilitation: A Controlled Study *Ann. Neurol.* **74** 100–8

[57] Bashashati A, Fatourechi M, Ward R K and Birch G E 2007 A survey of signal processing algorithms in brain-computer interfaces based on electrical brain signals. *J. Neural Eng.* **4** R32-57

[58] Tanaka T and Arvaneh M 2018 *Signal Processing and Machine Learning for Brain--Machine Interfaces* ed T Tanaka and M Arvaneh (London: The Institution of Engineering and Technology)

[59] Ramos-Murguialday A, Schürholz M, Caggiano V, Wildgruber M, Caria A, Hammer E M, Halder S and Birbaumer N 2012 Proprioceptive Feedback and Brain Computer Interface (BCI) Based Neuroprostheses *PLoS One* **7**

[60] Lotte F, Bougrain L, Cichocki A, Clerc M, Congedo M, Rakotomamonjy F and Yger A 2018 A review of classification algorithms for EEG-based brain computer interfaces: a 10 year update *J. Neural Eng.* **4** R1–13

[61] Arguissain F G, Biurrun Manresa J A, Mørch C D and Andersen O K 2015 On the use of information theory for the analysis of synchronous nociceptive withdrawal reflexes and somatosensory evoked potentials elicited by graded electrical stimulation *J. Neurosci. Methods* **240** 1–12

[62] Mrachacz-Kersting N, Ibáñez J and Farina D 2021 Towards a mechanistic approach for the development of non-invasive brain-computer interfaces for motor rehabilitation *J. Physiol.* **599** 2361–74