Peripheral Electrical Stimulation Triggered by Self-Paced Detection of Motor Intention Enhances Motor Evoked Potentials

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***Abstract*—This paper proposes the development and experimental tests of a self-paced asynchronous brain-computer interfacing (BCI) system that detects movement related cortical potentials (MRCPs) produced during motor imagination of ankle dorsiflexion and triggers peripheral electrical stimulations timed with the occurrence of MRCPs to induce corticospinal plasticity. MRCPs were detected online from EEG signals in eight healthy subjects with a true positive rate (TPR) of 67.15±7.87% and false positive rate (FPR) of 22.05±9.07%. The excitability of the cortical projection to the target muscle (tibialis anterior) was assessed before and after the intervention through motor evoked potentials (MEP) using transcranial magnetic stimulation (TMS). The peak of the evoked potential significantly ($P = 0.02$) increased after the BCI intervention by 53±43% (relative to preintervention measure), although the spinal excitability (tested by stretch reflexes) did not change. These results demonstrate for the first time that it is possible to alter the corticospinal projections to the tibialis anterior muscle by using an asynchronous BCI system based on online motor imagination that triggered peripheral stimulation. This type of repetitive proprioceptive feedback training based on self-generated brain signal decoding may be a requirement for purposeful skill acquisition in intact humans and in the rehabilitation of persons with brain damage.**

***Index Terms*—Brain–computer interface (BCI), neuromodulation, rehabilitation.**

I. Introduction

In RECENT years, brain–computer interfacing (BCI) has emerged as a technique for providing an alternative tool for individuals with severe motor disabilities to interact with their surrounding environment. BCI has two functionalities: it can serve as an alternative communication channel [1] or a rehabilitation tool [2]. While much research has been devoted to develop BCI as a communication tool, the potential of BCI as a rehabilitation tool has been far less explored.

As a rehabilitation tool, a BCI system becomes a neuromodulatory system, i.e., a system in which neural functions are modulated through feedback that is triggered by decoded brain activities. Although any man–machine interfacing system with visual feedback, including BCI, induces neural changes, even if it is designed only for communication purposes, in this paper a neuromodulation BCI system is defined as a system specifically designed and optimized for inducing neuroplasticity. It has been shown that BCI can restore motor function by inducing use-dependent brain plasticity to facilitate the relearning of lost motor function [2].

After brain lesions, use-dependent plasticity plays an important role in motor relearning and the recovery of motor function [3], for example, in multiple sclerosis and stroke patients [4]. The ability of the central nervous system (CNS) to compensate for the loss of function can be improved as a result of an enhancement in use-dependent plasticity [5]. An essential common characteristic of these studies is that the feedback provided to the users is associated, causally, with specific brain activities. This stems from the Hebbian rule in which synapses increase their efficacy if the presynaptic neuron consistently assists the postsynaptic target neuron to generate action potentials [6]. The pre- and postsynaptic neurons have to be active in order to induce a strengthening of the synapse [7]. In this view, designing a neuromodulation BCI system necessitates the generation of feedback and its appropriate timing with respect to specific brain activities, so that specific corticospinal changes, rather than nonspecific ones, can be induced.

Various intervention approaches can be applied to induce plasticity in the human motor cortex. For example, transcranial magnetic stimulation (TMS) has been applied [8] to enhance use-dependent plasticity while the motor cortex is activated during the performance of a training task. The locus of the effect due to interventions designed to induce plasticity in the nervous system may include various sites such as the motor cortex, the corticospinal tract, other descending tracts, synapses between descending tracts and spinal circuits, spinal neurons, peripheral nerves, and the neuromuscular junction [9]. In this study, we quantify the effect of the intervention by using motor evoked potentials (MEPs) triggered by TMS. In this sense our measure is a direct quantification of the excitability of the cortical projections to the target muscle [10], [11]. Thus, we will

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refer to these changes as changes in corticospinal excitability. Some other noninvasive protocols have also been investigated, such as repetitive transcranial magnetic stimulation (rTMS) [12], pair-associative stimulation (PAS) [13] and transcranial direct current stimulation (tDCS) [14]. These previous studies use (exogenous) triggering methods (rTMS/tDCS, etc.) to activate brain regions. These induce or produce a current within the brain which may spread to areas not normally activated during a voluntary movement. As the stimuli are synchronous there is an added potential disadvantage that the brain regions are activated at the same time rather than following a sequence of activation as during voluntary movement. Here, we are thus proposing to replace the exogenous triggering with an endogenous one, which is normal activity of the brain such as that produced during motor imagination. In our previous study we have demonstrated that motor imagination combined with endogenously triggered afferent feedback can induce alterations in the excitability of the cortical projections to the target muscle [15]. In the current study, we extend this work by asking the subject to imagine a movement when they choose and then combining the resulting brain potential with the afferent inflow that would be generated had the movement been performed rather than imagined. Our previous study has demonstrated that the timing of the afferent inflow in relation to the imagined movement is essential for inducing plasticity.

Most of the recent neuromodulation BCI systems reported in the literature, such as the one reported by Mrachacz-Kersting *et al.* [15], are implemented in a cue-based synchronized paradigm. Alternatively, a neuromodulation BCI system can be implemented in a fully asynchronous, self-paced paradigm, which has the advantage that it can be applied continuously by the user, thus providing a more engaging human–machine paradigm. This feature is particularly attractive for the application in stroke rehabilitation. In order to develop such a self-paced BCI system, it is necessary to predict motor intentions reliably and to trigger corresponding interventions, e.g., electrical stimulation, in real time. Such detection should have an appropriate balance between false positive rate (FPR) and true positive rate (TPR). In particular, for the purpose of inducing neural plasticity, if too many "false detections" occur, the delivered stimuli will lose their effectiveness. This is because in the Hebbian learning model, the direction of the change in synaptic connection depends critically not only on the relative timing of pre- and postsynaptic activations, but also on the simultaneous activation of the pre- and postsynaptic neurons. Whenever stimulation is triggered, it should be based on the actual intention of the user. On the other hand, if an insufficient number of intentions are detected, i.e., low TPR, the required output is not generated frequently enough, and the association between the intent and the output may be lost. In either case, the subject will also lose the perception of controlling the triggered stimulation.

In a previous study by our group, it was shown that motor imagination and peripheral stimulation induce cortical plasticity (cue-based, without motor intention detection) [15]. In another study, we developed a motor intention detector (offline) utilizing the initial negative phase of the movement related cortical potential (MRCP), a slow cortical feature of scalp electroencephalography (EEG) [16]. However, it is unknown if a system for which MRCPs are detected online (with acceptable detection errors), and then used to trigger a peripheral stimulation, can still be effective in inducing changes in the excitability of the cortical projections to the target muscle based on Hebbian type of plasticity. This paper proposes the development and experimental tests of a self-paced asynchronous BCI system that detects MRCPs produced by motor imagination (MI) and triggers peripheral stimuli to induce corticospinal plasticity. The purpose is to demonstrate that such a system can induce corticospinal plasticity that outlasts the time span of the intervention.

II. Methodology

A. Subjects

Sixteen healthy subjects (22.3±2.25 years), unaware of the experimental purpose of the study, took part in this study. None of the subjects had any known sensory-motor deficits or any history of psychological disorders. All subjects gave their informed consent before participation and the procedures were approved by the local ethics committee (N-20100067).

B. Experimental Setup

Electromyographic (EMG) signals were recorded from the tibialis anterior (TA) muscle of the right leg (dominant side). Surface electrodes (Ag/AgClNeuroline 720, Ambu, Denmark) were placed in a bipolar configuration following skin preparation by scrubbing with disposable alcohol swabs. A reference electrode was placed on the tibia. The experiment consisted of three parts, a preintervention session, a BCI intervention session, and a postmeasure session, as illustrated in Fig. 1. For all subjects, the three sessions were conducted consecutively, with a 4–5-min interval in between.

During a BCI intervention session, the EMG signals were sampled at a frequency of 500 Hz, bandpass filtered at 10–200 Hz and amplified at 5 k by custom-made EMG amplifiers (SMI, Aalborg University, Denmark). During the pre- and postintervention, the EMG signals were sampled at 4000 Hz and bandpass filtered at 10 Hz–2 kHz. Data was digitized by a 16-bit data-acquisition card (National Instruments, NI6122) and saved by custom-made software in Matlab (R2009b).

Monopolar EEG signals were recorded by custom-made EEG amplifiers (×20 k) (SMI, Aalborg University, Denmark) and digitized by a 16-bit data-acquisition card (National Instruments, NI6122) at 500 Hz (0.1–100 Hz). Signals were acquired from positions FP1, F3, F4, FCz, Pz, P3, P4, C3, C4, and Cz by Ag/AgCl scalp electrodes placed according to the International 10–20 system. The right ear lobe was used as a reference and the ground electrode was placed at nasion. EMG and EEG signals were synchronized during the BCI intervention session, and acquired through the same data-acquisition card.

In the BCI intervention session, stimulation of the common peroneal nerve (CPN) was applied using a NoxiTest isolated peripheral stimulator (IES 230). Stimulating electrodes (32 mm, PALS Platinum, Axelgaard Manufacturing Co., Ltd.) were placed on the skin overlying the deep branch of the right commone peroneal nerve (CPN) (L4 and L5) with the cathode in the proximal location.

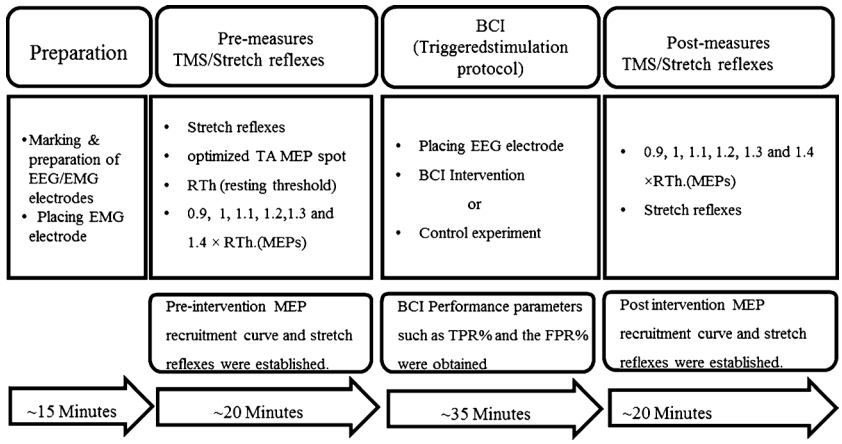

Fig. 1. Experimental protocol.

In the pre- and postintervention sessions, to assess the excitability of corticospinal projections to the TA, a TMS (Magstim 200, Magstim Company, Dyfed, U.K.) with a focal figure of eight double-cone coil (110 mm diameter) was used to apply single pulses to elicit a MEP in the TA. The stimulation current was directed from the posterior to anterior. As a control parameter, stretch reflexes were also measured to assess the spinal contribution.

C. Experimental Procedures

The experimental protocol of the current study is described with special focus on the online detection of the initial negative phase of MRCPs and on the timed delivery of the electrical stimulation. The details of other aspects of the protocol can be found in Mrachacz–Kersting *et al.* [15]. The subjects were seated comfortably in a chair, with the right leg secured in a custom-made fixture. In the preintervention measure session, TMS was applied to assess the baseline of corticospinal excitability, quantified by the peak-to-peak amplitude of the generated TA MEP. For two subjects, stretch-reflex recordings were also acquired to assess the possible spinal contribution to any changes in MEP size. In the following BCI intervention session, the subject was asked to perform a self-paced voluntary movement task of dorsiflexion of the TA muscle. They were specifically instructed to make the movement whenever they wanted to. Furthermore, the subject was asked to keep all muscles, other than those in the performing leg, relaxed, and to remain relaxed between any two successive movements. Eye movements, blinks, body adjustments, throat clearing and other movements were to be avoided as much as possible. A computer monitor delivering visual information to the subject was placed approximately 1.5 m in front of the subject. After the BCI intervention session, TMS (for all subjects) and stretch reflexes (for two subjects) were again applied to determine changes in cortical and spinal excitability. The general protocol is illustrated in Fig. 1.

1) TMS: TMS was used to measure the corticospinal excitability before and after the all intervention. The intensity for the magnetic stimulation was set to 50% of the stimulator output to find the optimal site for evoking an MEP in the TA. The optimal stimulation site was taken as the coordinate where the peak-to-peak amplitudes of the MEPs were greater in the TA muscle than the amplitudes of adjacent coordinates for a given stimulus intensity. For all subjects this site was approximately two to three centimeters anterior to the vertex. Once identified, it was marked (on the scalp) to ensure that the coil position was maintained so that the stimulation was always applied over the same area of the motor cortex for both pre- and postintervention. Subsequently, the resting threshold (RTh) was identified. The RTh was defined as the highest stimulus intensity that in no more than 5 of 10 consecutive stimuli evoked an MEP with amplitude of $\sim$50 μV while the muscle was at rest. Next, 10 MEPs were elicited in the resting TA at six TMS intensities: 90%, 100%, 110%, 120%, and 130% of RTh. The stimuli were delivered randomly every 5–7 s. The mean peak-to-peak TA MEP amplitudes measured pre- and postintervention for each subject were extracted. The average MEPs were plotted against the TMS intensity and the Boltzman sigmoidal function applied by using the Levenberg–Marquard, nonlinear, least-mean squares algorithm fit (as previously described by Devanne *et al.*. [17]).

2) BCI (Intervention): The BCI intervention consisted of two phases. The first was a training phase for the online MRCP detector [16], followed by an applying (testing) phase of the trained MRCP detector. In this session, the purpose of the current online BCI paradigm was to trigger peripheral stimulation by movement intentions extracted from the self-paced EEG signals. This combination of imagined movement and peripheral stimulation is the BCI intervention.

3) Training Phase: In the first phase, subjects were instructed to perform ballistic ankle dorsiflexions at random intervals. No external stimuli or cues were presented to the subject for task execution. However, the subjects had feedback on their ankle dorsiflexion torque on a computer screen, depicted as a moving vertical bar. They were asked to reach a torque level corresponding to 20%–30% of the maximum voluntary contraction (MVC) torque, as determined during a practice presession. This procedure resulted in a fully self-paced set of movement executions. During this phase, two runs ($\sim$5-min duration) were recorded, with a 2–3 min of rest period in between. These two runs were used as a training set for the movement-intention detector based on the initial negative phase of the MRCP (Fig. 2) with an optimized spatial filter (OSF) technique. In summary, the analysis was divided in two steps:

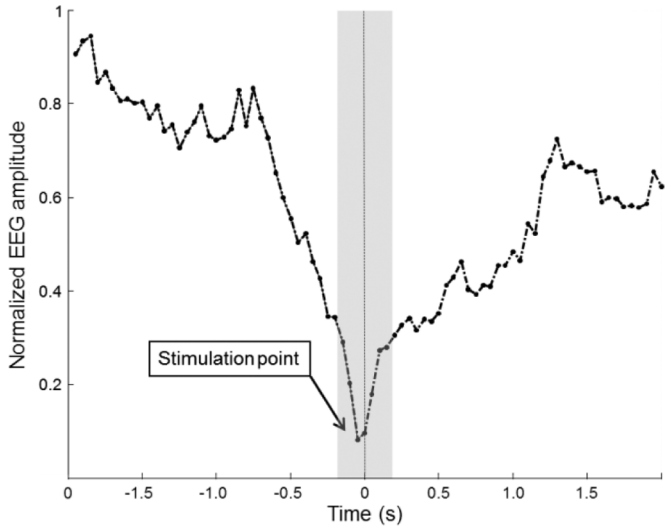

Fig. 2. Template of initial phase of MRCP (training phase). Subject 2: MRCP signal at Cz shown after being preprocessed with OSF technique for improving SNR. Signal (initial negative phase of MRCP; *not shown*) before dashed vertical line was used as template. Arrow is point at which the electrical stimulation was delivered. Shaded region is the second negative deflection, also called motor potential (MP).

MRCP template extraction and motor imagination detection. First, the OSF coefficients [16] were computed to maximize the signal-to-noise ratio (SNR) from the training data set. Based on these OSF coefficients, a surrogate channel (linear combination of nine acquired EEG channels) was obtained from which the template of the initial negative phase of MRCPs (from the start of the depression phase to its peak negativity, as illustrated in Fig. 2) was extracted. Before the detection of movement in the testing set, a receiver operating characteristic (ROC) curve was obtained through cross validation on the training data set to find a working point. After that, the extracted MRCP template was used to detect movement intentions by a matched filter algorithm in the testing data.

4) Applying (Testing) Phase: In this phase, subjects were asked to imagine the kinaesthetics of ballistic ankle dorsiflexion, instead of executing it. During the self-paced motor imaginary task, the initial negative phase template of MRCP obtained from the training phase was used to detect the presence of the motor potential (MP) phase of MRCPs in real time by a matched filter [16]. Once a positive detection was triggered, a single electrical stimulus was delivered and was timed to arrive at the peak negativity of the MRCPs. The subjects were instructed to disregard the sensation of this stimulation (which was kept at motor threshold level to keep interference to minimum) as much as possible and to focus on performing the imaginary movements. During this phase, since no torque signal could be recorded to identify the occurrences of motor imaginary tasks, the subjects were asked to extend their right index finger approximately 2 s after they had received the electrical stimulation if they were performing motor imagery (true positives, TPs). If they did perform motor imagery, but did not receive the electrical stimulation, they had to extend their left index finger after 2 s (false negatives, FNs). Whenever the stimulator was triggered without the subject's movement intention, it was counted as false positive (FP). This phase continued until 50 TPs had been completed. The subject was provided with a short pause of 1–2 min at their request during this phase.

5) Peripheral Electrical Stimulation: The site for the CPN stimulation was at the level of the fibula head. The pulsewidth was set to 1 ms. Stimuli were delivered every 3–5 s starting at an intensity of 5 mA and increased in increments of 5 mA until a recognizable M-wave was seen in the TA EMG trace. The intensity was then adjusted downwards again in steps of 1 mA until the M-wave disappeared. This procedure was repeated three times to ensure reproducibility and the intensity set to that level which induced a recognizable M-wave. This intensity will from now on be referred to as $1\times$ motor threshold. Palpation of the antagonist soleus (SOL) and peroneal muscles was performed during stimulation trials to ensure that these were not activated as it is known that their activation has an inhibitory effect on the TA.

6) Stretch-Reflex Recording: TA stretch reflexes were elicited prior to and following the intervention in two subjects to assess alterations in these spinal pathways. The right leg was fixed to a servo-controlled hydraulic actuator (MTS-systems Corporation, 215.35; Voigt *et al.*[18]), such that the anatomical ankle axis of rotation was closely aligned with the fulcrum of the actuator. The foot segment of the right leg of the subject was firmly strapped to a custom-made plate that extended from the actuator, thus producing a tight interface between the arm of the motor and the foot of the subject, ensuring that the movement of the actuator was transmitted solely to the ankle joint. The angular position of the actuator was monitored by an angular displacement transducer (Transtek, DC ADT series 600). Initially, the subjects were asked to produce an MVC by contracting their TA as hard as possible. Subjects were instructed to pull their toes upwards as powerfully as possible on the word "go", and to maintain this position until instructed to relax. They were then allowed to relax for 1–3 min prior to the next trial. The best of a total of three collected trials was deemed as the subject's MVC. The root mean square (rms) value of the rectified TA EMG for the MVC over a 1-s period was calculated. Subsequently, the subjects were provided with visual feedback via a computer screen displaying horizontal markings set at 5% MVC and via a vertical bar displaying the subject's current level of TA activation. Subjects were asked to maintain the bar between the horizontal markings while the perturbations were applied, without interfering with the imposed plantarflexion perturbation.

Thirty stretches were randomly applied at intervals ranging from 5 to 7 s (velocity of $200°s^{-1}$ to $240°s^{-1}$; amplitude: 6° to 8°; hold-time 460 ms). The angular velocity and the amplitude of the imposed perturbations were adjusted for each subject so that three discernible peaks were seen in the EMG trace. The latency of the first response peak (termed M1 or alternatively SLR in the literature) was extracted from the data both in the pre- and postintervention sessions. The rms value of a window extending 10 ms on either side of M1 was calculated and used as an indication of the size of this component of the TA stretch reflex.

The stretch reflex changes were quantified in this protocol since it is well known that H-reflexes may only be elicited in

the resting TA muscle in approximately 10% of the population. It is also known that the H-reflex is the electrical analog of the M1 component of the stretch reflex and thus the transmission within the same pathway can be assessed. However, given the difficulty in H-reflex recordings, the stretch reflex is a reasonable alternative to rule out alterations in the Ia afferent spinal pathway.

D. Control Experiment 1–2: Imagery and Electrical Stimulation Alone

Two additional control experiments were performed. In four subjects the intervention performed consisted of only self-pace imagined movements (50 times) to quantify the effects of imagination alone. In the second control experiment the CPN nerve of four subjects was stimulated randomly (50 times, 8–12 s apart). The purpose of these control experiments was to investigate the individual effect of the motor imagination and electrical stimulation on altering the excitability of the corticospinal projections to the TA, which was measured using TMS.

E. Statistical Procedures

A three-way ANOVA with factors interventions (BCI, imagine and electrical stimulation only), time (pre and post), and stimulus intensity (90%, 100%, 110%, 120%, and 130% RTh) was used to investigate the effects of the BCI intervention on the changes in the MEP amplitude. The Tukey's post hoc test was used to reveal the significance of the intervention factor. Also, paired t-tests were used to assess changes in the parameters of the input-output curve (S50, the slope and the r2 value) and TA MEPmax before and following the BCI intervention and control experiments. For all experiments, statistical significance was assumed if $P<0.05$.

III. Results

All the subjects performed, on average, a minimum of 15 movements per run in the training phase of the BCI intervention. The mean duration of the complete testing phase for all subjects was 26.38±4.9 min. The experiment, took on average, 1 h and 30 min. Impedance during the EEG experiment was under 5 KΩ. Epochs with EOG activity exceeding 125 μV were discarded.

A. BCI Performance

All results shown in this section are based on the entire testing phase of the BCI intervention. The average results of the self-paced BCI system based on OSF in all subjects are given in Table I. The average (across subjects) TPR obtained for the motor imagery (MI) task was 67.15±7.87. The FPR was 22.05±9.07%. The mean detection time latency with respect to the onset (determined offline) of the task was −125±309 ms. Subjects had to perform, on average, 75.38±9.01 (TP+FN) motor imagery task to get 50 TPs.

TABLE I
DETECTOR PERFORMANCE RESULTS

Sub	BCI performance based on optimized spatial filter			
	Detection TPR %	False positives rate %	Duration of testing session (minutes)	Total number of tasks attempted
1	69.44	24.13	27	72
2	54.35	7.92	23	92
3	66.67	16.67	25	75
4	75.76	37.89	21	66
5	65.79	20.63	22	76
6	61.73	18.03	32	81
7	79.37	30.56	35	63
8	64.10	20.63	26	78
Mean	**67.15±7.87%**	**22.05±9.07 %**	**26.38±4.90**	**75.38±9.01**

B. Changes in Excitability of Corticospinal Projections to TA

As the intention of the current study was to investigate whether a user-driven online BCI system could alter corticospinal excitability, we assessed the input–output properties of the TA MEP prior to and following the intervention in a small sample of subjects ($n = 8$). The TA MEP was elicited at six intensities of TMS, ranging from 90% to 130% of RTh. A Boltzman fit was applied to the extracted peak-to-peak TA MEP data. Fig. 3 shows the averaged raw data as well as the fitted data for two representative subjects prior to and following each intervention. The Boltzman fit accounted for more than 80% of the total variance in the data ($r^2 \geq 0.8$). Three variables were extracted from the fitted data: the maximum value (TA MEPmax), the slope of the steepest part of the curve (k) and the stimulus intensity required to obtain a response that is 50% of the maximum (S50). For the two subjects shown in Fig. 3, the postmeasures of TA MEPmax increased by 75% and 15%, respectively, from the preintervention measures, while the slope did not change. The S50 values were shifted towards the left of the curve by 3% in both subjects, implying a change in the threshold for inducing a TA MEP.

Across all subjects, the maximum MEP varied widely across individuals due to the TA representation deep in the inter-hemispheric fissure. We thus normalized the peak to peak TA MEP for each subject and all stimulation intensities to the maximum TA MEP recorded in the preintervention.

A three-way ANOVA with factors interventions (BCI, imagine and electrical stimulation only), time (pre and post), and stimulus intensity (90%, 100%, 110%, 120%, and 130% RTh) revealed a significant effect of intervention ($F = 10.47$; $p = 0.0001$) and time ($F = 15.07$; $p = 0.0002$). The Tukey's post hoc test revealed that the BCI intervention was significantly different from the control interventions and there was no significant difference among the control interventions. Paired t-tests revealed that TA MEPmax in post-TMS measure of MEP's increased significantly by 53±43% ($P = 0.02$) as compared to that of premeasure of MEP's for the BCI intervention (Fig. 5), the S50 variable of the Boltzmann fitted data

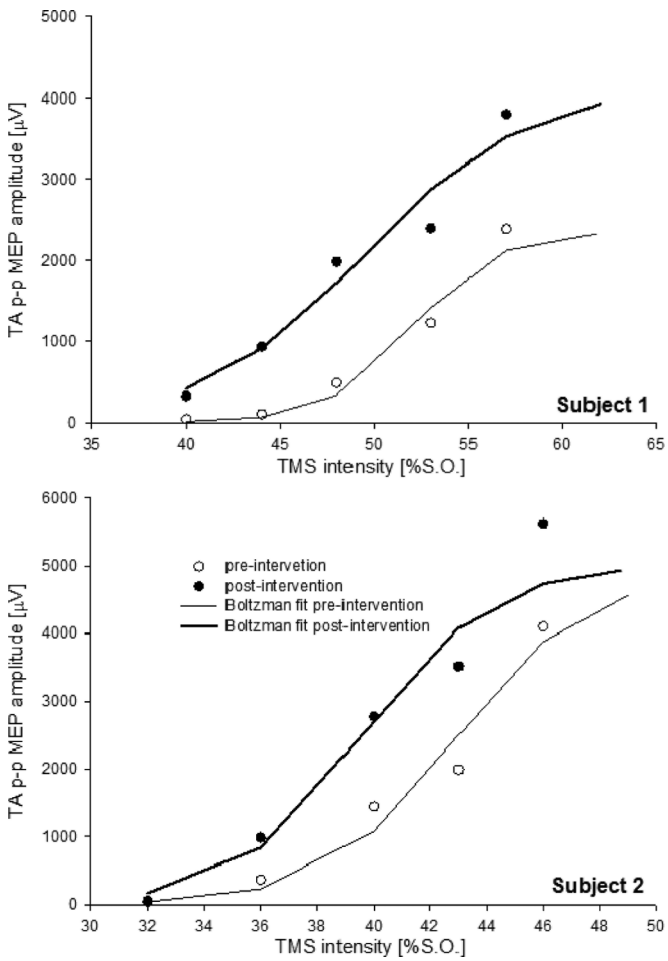

Fig. 3. Changes in motor output after conditioning. TA MEP recruitment curve prior to and following the BCI intervention for two subjects, as indicated. Also shown are curves fitted using Boltzman sigmoidal function by the Levenberg–Marquard nonlinear LMS algorithm. Each data point represents the average of ten stimuli of stimulator output (%SO).

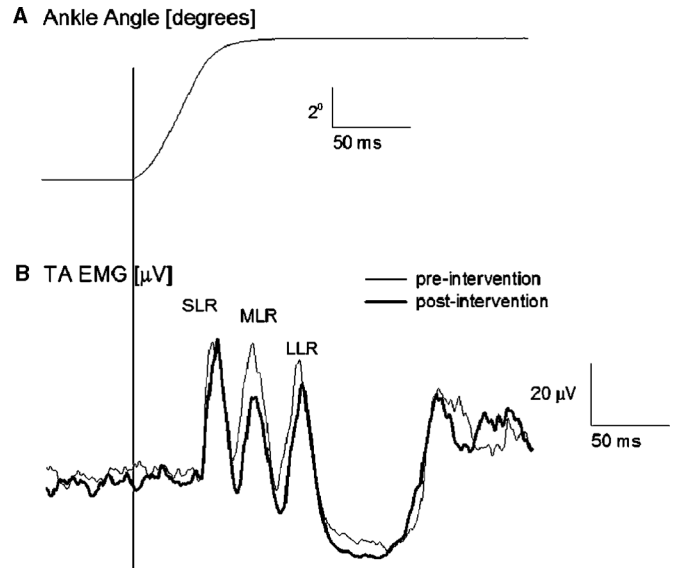

Fig. 4. Stretch-reflex data. Top A: right ankle angle (°). Vertical line indicates onset of imposed planar-flexion perturbation. B: TA-rectified EMG trace prior to (thin line) and following (thick line) the BCI intervention. Each trace is the average of 30 trials. Data are for one subject.

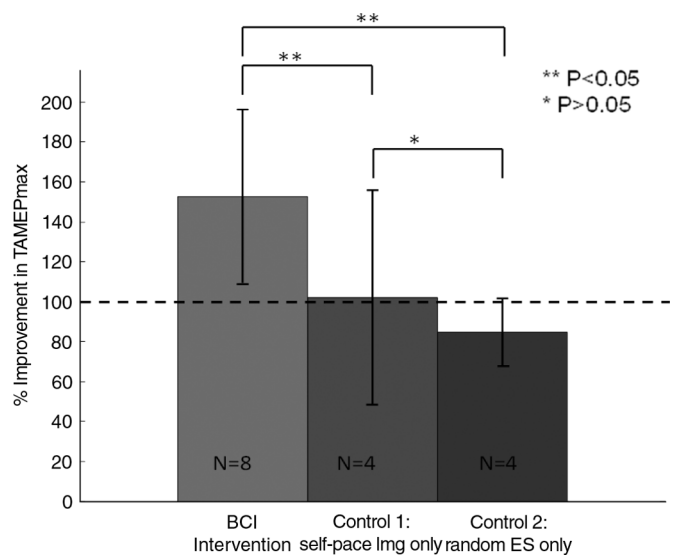

Fig. 5. Group Data TA MEPmax. Average data for TA MEPmax across all subjects expressed as a percentage of premeasures for the intervention, self-paced motor imagination (50 times) only and random electrical stimulation (ES) experiment. N indicates the number of subjects in each experiment. Also shown are standard deviations.

was significantly different between pre and post of the BCI intervention ($p = 0.01$).

Across all subjects the S50 had a value of 43.2 ± 6.7% RTh prior to and 41.8 ± 7.0% RTh post intervention, while the slope parameter k remained unchanged ($p = 0.138$). The correlation coefficient was 0.8 calculated between change in TA MEPmax from pre- to post-BCI intervention measure of TMS and ratio of TPR(%) to FPR(%) as shown in Fig. 6.

Because the changes observed in corticospinal excitability in the BCI intervention could have been elicited by imagination or electrical stimulation only, a control in four subjects (in each group) was carried out by collecting TA MEP recruitment curves prior to and following an intervention. Subjects were either asked to only imagine the task at their own choice of pace (without electrical stimulation) or they received electrical stimulation randomly only. Paired t-tests revealed TA MEPmax increased by 2±53% ($P = 0.59$) and −15±17% ($P = 0.16$) for the self-paced motor imagination and the electrical stimulation respectively, the S50 variable and the slope parameter k remained unchanged ($P > 0.05$) for both control experiments.

These control experiments reveal that individually (i.e., on their own) the imagination or electrical stimulation is not effective in increasing corticospinal excitability, however, the paired relationship between specific afferent inflow from the muscle and its imagination is the cause of corticospinal excitability in BCI experiments as depicted in correlation coefficient value.

C. Changes in Spinal Excitability

To assess potential changes in spinal excitability, reflex responses in the TA to sudden plantar-flexion rotations were investigated prior to and following the intervention in two subjects. The changes in ankle angle as well as the EMG recordings

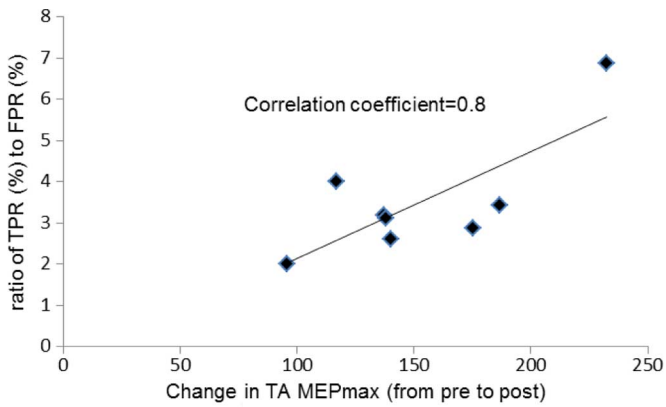

Fig. 6. Correlation graph. Correlation between change in TA MEPmax from pre- to postmeasure of TMS and ratio of TPR (%) to FPR (%).

of the TA both prior to and following the intervention is shown for one subject in Fig. 4(a) and (b). Each trace is the average of 30 imposed rotations. The TA responds with three peaks, as seen in the EMG trace [Fig. 4(b)], and the Short-latency stretch reflex (SLR) component is generated exclusively through spinal circuitries. For this subject, the SLR amplitudes before and after the triggered stimulation (BCI intervention) session was 122.6 μV and 122.8 μV, which indicates the absence of spinal excitability changes following the BCI triggered stimulation. For the second subject the values were 90.3 μV and 78.1 μV.

IV. Discussion

The main finding of this study was that the asynchronous BCI system based on motor imagination triggering peripheral stimulation can induce an alteration in the corticospinal projections of the target muscle (TA). These changes are the result of the online detection of the motor potential (MP) of MRCPs. The stimulation of the CPN occurred with detection accuracy (TPR %) greater than 67% and FPR was 22.05%, on average, across all subjects. For induction of neural plasticity accuracy of the BCI system is still an open question [19]; however, the accuracy of the current system is comparable to other existing BCI systems discussed in [16]. The changes in values of TA MEPmax and the S50 can be used to speculate indirectly changes in the corticospinal tract. In addition, results from the stretch reflex session suggested that the changes observed are likely supraspinal, as the SLR component of the stretch reflex remained unchanged.

A. Previous Studies

In the literature, different features of EEG signals have been explored to predict an impending movement, including localized changes in spectral power of spontaneous EEG signals related to sensorimotor processes [20], [21], slow cortical potentials [22] and various types of event-related potentials [23], [24]. MRCP's in the past have been used for classification purposes [25]. We aimed at exploiting the second negative deflection, referred to as MP, which occurs 50–60 ms prior to the movement onset [25] and [26], which is thought to be related to the execution of the movement. For a detailed comparison between OSF treated and raw MRCP refer to Niazi *et al.* [16].

One interesting result of this study is that only 50 TPs of 20%–30% of MVC motor imagery task were required to observe the changes in corticospinal projection. This is similar to the number of paired TMS and peripheral nerve stimuli applied to subjects in Kujirai *et al.* [27]. However in that study, the target muscle was a hand muscle. In the current study, motor imagery of 20%–30% of MVC was performed with consideration to the comfort (fatigue) of the subjects. As the potential users of this protocol will be patients with neurological disorders (e.g., stroke) and they may not be able to perform the movements at a higher MVC. In everyday movements such as walking, muscle contraction levels rarely attain values close to the MVC. If the current results can be achieved using low levels of MVC, it may be speculated that at higher levels of MVC the results may be further improved due to a better signal to noise ratio (SNR) of MRCP signals [28]. An improved SNR is likely to result in a more precise detection of the MRCP, hence enhancing the paired relation between movement intention and peripheral input.

In another study by Häusler *et al.* [29], using the contingent negative variation (CNV) paradigm the authors demonstrated an increase in the MEP amplitude when the TMS pulse was timed to arrive immediately after the second stimulus (s2) was presented to the subjects. The target muscle in this previous study was an upper limb muscle and the protocol consisted of an exogenously generated stimulus (TMS) and its pairing with the CNV's component. In the current study it is hypothesized that replacing TMS with a more natural volitional generated signal (the MRCP) within the human brain and pairing this with afferent feedback (i.e., an electrical stimulation of the deep branch of the CPN in the current study) will open new noninvasive protocols of altering corticospinal excitability. It is important to note that the origins of the various components of the two potentials (CNV and MRCP) are quite different, as discussed in a recent study by Ziemann *et al.*. [30]. The current study can help in choosing the right type of naturally generated signal(s) for achieving a causal relationship (as discussed previously) in a neuromodulatory approach-based rehabilitation system.

In the past, protocols, such as PAS, have required a greater number of paired stimuli [13], [31] when targeting lower limb muscles. One possible reason for a higher number of stimuli in these previous studies is that TMS has a low spatial resolution [32]. It not only activates the targeted regions in the brain but also activates other nearby regions within the range of the TMS coil. In contrast, the origins of the self-generated brain signals are known, such as in the MP phase of MRCP, i.e., placed in the Broadmann's area 6 (composed of the premotor cortex and, medially, the supplementary motor area, SMA) and area 4 (the primary motor cortex [33]), possibly making them more suitable for Hebbian-based neuroplasticity. Other invasive studies, e.g., [34], have shown that stimulation in real time triggered by neural recordings during volitional movements generated motor cortex plasticity. This study corroborates our findings that the proposed noninvasive method of involving the motor cortex (use-dependent) could provide an effective method of selectively strengthening specific neural pathways during rehabilitation.

B. Neuroplasticity

Motor training leads to encoding motor memories in the CNS [35]. Here, we investigated if it is possible to alter the corticospinal projection of the targeted muscles by self-paced generated MRCPs and by giving proprioceptive feedback to the motor cortex engaged in the training motions via CPN stimulation—a proposal consistent with the Hebbian principle that long term potentiation (LTP) of synaptic efficacy occurs when its pre- and postsynaptic elements are simultaneously active [6]. Neural plasticity can be induced when two inputs act together onto a target neural structure in temporal synchrony [36], [37]. Based on the above, a self-pace motor imagination triggered peripheral stimulation system may also be effective for the rehabilitation of stroke patients, where it has already been shown that motor training can induce use-dependent plasticity [38].

C. Relations With FET

Functional electrical stimulation (FES) and functional electrical therapy (FET) are assistive technologies used to improve functional and motor recovery, e.g., in stroke patients. In FES, muscles are activated passively through the stimulation. The use of FES combined with passive exercises, such as grasping and releasing objects, has been shown to improve functional recovery in the upper extremities and can be superior to the use of task-oriented therapies in isolation [39]. More recent studies have explored FES and its ability to reorganize and strengthen corticospinal connections in patients with strokes (FET). In subjects with chronic strokes and associated foot drop, long-term use (3–12 months) of a foot stimulator has been associated with improved voluntary contraction of the TA along with increased MEP mapping with TMS [40]. This suggests that FES used in chronic cases may strengthen motor corticalareas and associated descending cortical connections [40]. Based on these results and on the results of the present study, it can be hypothesized that a system based on an online asynchronous motor imagination/FES can be beneficial for rehabilitation purposes.

V. Limitations

The conclusion that changes induced by the BCI intervention were at a corticospinal level has to be interpreted with caution. By quantifying the changes in the M1 component of the TA stretch reflex, the results may be compared to similar studies which have implemented the H-reflex to assess alterations in spinal excitability. However, both these measures test only one spinal pathway and indeed it is possible that changes may have occurred in other pathways. However, it was not the main aim of this study to elucidate on the exact sites of the plastic changes and one might speculate that alterations at one site will inevitably lead to modifications at another site. At least in studies on operant conditioning to modify the simple H-reflex, it has repeatedly been demonstrated that plasticity occurs at numerous levels of the nervous system (for a review, see [41]). Also the different aspects of triggered stimulation are not fully explored in this study, such as paired versus unpaired stimulation, or different parameters of the delivered electrical stimulation. Further studies targeting the above-mentioned aspects need to be carried out before the full extent of the proposed paradigm is understood.

VI. Conclusion

We demonstrate for the first time that it is possible to alter the corticospinal projections to the TA muscle by using an asynchronous BCI system based on online motor imagination triggering peripheral stimulation. This type of repetitive proprioceptive feedback training based on self-generated brain signal decoding may be a requirement for purposeful skill acquisition in intact humans and in the rehabilitation of persons with brain damage. The results in the current study demonstrated the exciting possibility that peripheral stimulation combined with patient-driven rehabilitative treatment could lead to more prominent behavioral gains than passive rehabilitative treatment with cortical lesions, such as those found in stroke.

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