Reactivating the dormant motor cortex after spinal cord injury with EEG-neurofeedback: a case study with a chronic, complete C4 patient

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Abstract

Chronic spinal cord injury (SCI) patients present poor motor cortex activation during movement attempts. The reactivation of this brain region can be beneficial for them, for instance, allowing them to use brain-machine interfaces (BMI) for motor rehabilitation or restoration. These BMI generally use electroencephalography (EEG) to measure the cortical activation during the attempts of movement, quantifying it as the event-related desynchronization (ERD) of the alpha/mu rhythm. Based on previous evidence showing that higher tonic EEG alpha power is associated with higher ERD, we hypothesized that artificially increasing the alpha power over the motor cortex of these patients could enhance their ERD (i.e., motor cortical activation) during movement attempts. We used EEG neurofeedback (NF) to enhance the tonic EEG alpha power, providing real-time visual feedback of the alpha oscillations measured over the motor cortex. This approach was evaluated in a C4, ASIA A, SCI patient (9 months after the injury) who did not present ERD during the movement attempts of his paralyzed hands. The patient performed four NF sessions (in four consecutive days) and screenings of his EEG activity before and after each session. After the intervention, the patient presented a significant increase in the alpha power over the motor cortex, and a significant enhancement of the mu ERD in the contralateral motor cortex when he attempted to close the assessed right hand. As a proof of concept investigation, this paper shows how a short neurofeedback intervention might be used to enhance the motor cortical activation in patients with chronic tetraplegia.

Keywords

Spinal cord injury (SCI), tetraplegia, event-related desynchronization (ERD), motor-related cortical activation, neurofeedback, neuroplasticity, electroencephalography (EEG)

Introduction

The quality of life of a person with cervical spinal cord injury (SCI) is tremendously diminished due to the limited upper-limb function[1–3]. Between 6 and 12 months after the injury, the patients reach the chronic stage, where the probabilities of potential recovery are reduced[4]. Brain-machine interfaces (BMI) have been proposed to bypass the injury and restore the lost upper-limb function, for instance by using neuroprostheses or robots[5–9]. Further, there is recent evidence showing that BMI-based rehabilitation therapies can promote lower-limb recovery in paraplegic patients[10], although its feasibility for upper-limb recovery is yet to be demonstrated. These techniques require the activation of the motor cortex to measure and decode the brain activity related to the intended task (e.g., the attempt of grasping)[8,9,11].

However, chronic SCI patients present a significant reduction of the motor cortical activation during the attempts of movement of the affected limbs[12–15]. This is presumably due to the anatomical changes that follow SCI, including reductions in grey matter volume, as well as white matter degeneration in the corticospinal tracts[16–18]. In fact, several studies have reported that functional recovery in SCI patients is associated with the restoration of these anatomical changes and the enhancement of motor brain activation[15,18–20]. The cortical reorganization following SCI can also be measured in the electroencephalogram (EEG), which is the preferred technology to build non-invasive BMIs. On the one hand, these patients present reduced power of the alpha/mu rhythm ([8-13] Hz) in tonic EEG (i.e., event unrelated EEG activity) measured in resting state[21,22]. On the other hand, they show a reduced magnitude of the mu and beta event-related desynchronization (ERD) when attempting to move their paralyzed limbs[13,15]. The ERD is generally used to quantify motor-related activity[23], with stronger ERD implying stronger brain activation[24,25]. Since the motor cortical activation (i.e., the ERD) is a modulation of the idling alpha/mu rhythm, and this rhythm is diminished in the patients, such modulation is affected (i.e., translating into a reduced ERD magnitude). This is in line with previous evidence showing that higher alpha/mu power during rest is associated with higher ERD during motor tasks[26,27].

Despite there is no evidence suggesting that the restoration of brain activation might promote functional recovery in chronic tetraplegic patients, a more easily-decodable activity could, at least, increase the success of BMI-based therapies[28,29], which might have an important clinical repercussion by facilitating motor recovery, even after complete SCI[10]. Therefore, we aimed at enhancing the motor cortical activation of patients with complete and chronic tetraplegia. Our main hypothesis was that artificially increasing the tonic alpha/mu power over the motor cortex might lead to an enhancement of the mu ERD (i.e., motor cortical activation) during movement attempts of a paralyzed limb. In principle, the tonic alpha/mu power can be increased with different interventions: e.g., by transcranial magnetic stimulation, transcranial current stimulation or neurofeedback training[30,31].

We proposed the use of upper-alpha EEG neurofeedback (NF) training, since it does not require expensive equipment and avoids the possible side-effects of brain stimulation. Its basic principle is to decode certain brain pattern of interest and to link it with a real-time feedback, so that the subject learns, by operant conditioning, to self-regulate such brain pattern. NF training has been proven as an effective tool to increase the upper-alpha power over parieto-occipital areas, mainly evaluated in healthy subjects in the context of cognitive enhancement[30,32,33]. In fact, it has been shown that tonic changes in parieto-occipital upper-alpha power can be induced even after one single neurofeedback session[34]. Based on this evidence, it was hypothesized that this upper-alpha NF approach could also be used to increase the upper-alpha power measured over the sensorimotor cortex. Such NF approach was already applied to healthy subjects, reporting the increase of the alpha power over the motor cortex after a one-week intervention, and observing enhancements of alpha desynchronization during the execution of a motor task[35].

In this paper, we present a case study with a chronic, complete tetraplegic patient (with the injury at the level of C4), performing a four-sessions NF intervention to up-regulate upper-alpha activity over the motor cortex. By increasing upper-alpha activity (which is normally decreased in chronic SCI[21]), we aimed at inducing a subsequent enhancement of the ERD when the patient attempts to perform an impossible movement[26]. We show the

effects of the training in terms of: *(i)* tonic EEG activity (i.e., changes in upper-alpha power) and *(ii)* motor cortical activation (i.e., changes in ERD during the attempt of movement of his completely paralyzed hand).

Methods

Participant

The criteria for patient recruitment were: (1) SCI with complete loss of motor and sensory function at the level of the hand; (2) chronic phase of the injury, determined by standard medical criteria (i.e., patient discharged from the Hospital); (3) no observable EEG activation over the motor cortex during attempts of movement of the hand; (4) ability to understand and follow instructions; (5) availability to participate in the study during 3-5 consecutive days.

The recruited patient was a 55-year-old male with C4 ASIA A tetraplegia due to a traumatic SCI. He had a complete loss of motor and sensory function below the elbow level. He had no other concomitant neurological or psychiatric conditions. The patient was discharged from the Hospital Nacional de Parapléjicos, in Toledo (Spain), 8 months after the injury. One month after the discharge (i.e., 9 months after the injury), he was recruited for the study. The patient agreed to move each day during the duration of the study from his house to the Hospital to attend to the four experimental sessions. The experimental procedure was designed in accordance with the Declaration of Helsinki and was approved by the Ethics Review Board of the Hospital (C.E.I.C. 89/22-07-2011). The patient was duly informed about the investigation and signed an informed consent before starting the study.

EEG recording

The EEG was recorded from 16 active electrodes placed at FP1, FP2, F3, Fz, F4, C3, Cz, C4, CP3, CPz, CP4, P3, Pz, P4, O1 and O2 (according to the international 10/20 system), with the ground and reference electrodes on FPz and on the left earlobe, respectively. The signals were amplified and digitized using a g.Tec amplifier (Guger Technologies, Graz, Austria) at

a sampling rate of 256 Hz. In real time, a power-line notch-filter at 50 Hz and a band-pass filter at [0.5-60] Hz were applied.

Experimental procedure

Previous NF interventions to up-regulate the upper-alpha EEG activity have been proposed with a duration of 5 consecutive days[32,33,35]. Given the difficulty of involving one patient with high tetraplegia for a NF study during 5 consecutive days, and with previous evidence showing that significant increases in tonic alpha can be induced even in one single NF session[34], we aimed at recruiting a patient for a duration between 3 and 5 days, according to his/her availability (inclusion criteria 5).

The recruited patient agreed to participate in 5 consecutive sessions but could not attend the 5th session due to personal reasons unrelated to the study. Therefore, the patient performed four experimental sessions of one hour each (including preparation time—10 min approximately). He did not have any change in his treatment or personal routine during the course of the study. The sessions were executed in four consecutive days, always in the morning. During each session, the patient was seated on his wheelchair, approximately 1.5 m in front of a computer screen, and he performed the NF training and a series of EEG screenings (related and unrelated to motor tasks) before and after the NF (see Figure 1). The motor-related EEG screenings assessed the effects of the intervention on motor cortical activation, whereas the motor-unrelated ones assessed the effects of the intervention on tonic EEG.

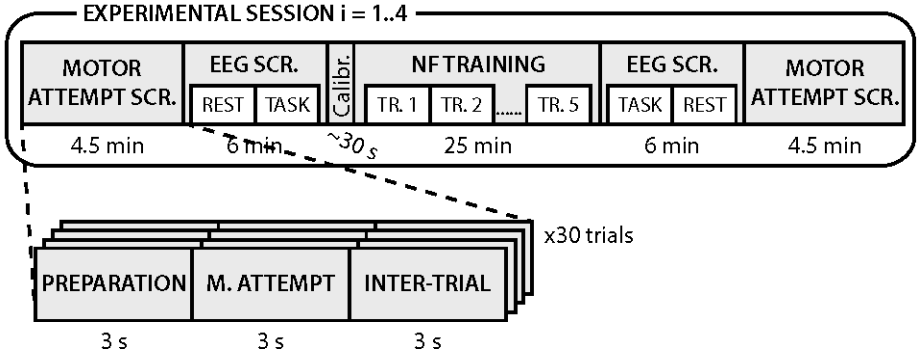

Figure 1. *Experimental design of the study. Four sessions were conducted, each of them including: pre- and post- motor-attempt screening (to quantify the motor cortical activation), pre- and post- motor-unrelated screenings (to quantify the tonic EEG activity), NF calibration, and NF training. The structure of the motor-attempt screening is displayed at the bottom of the figure: it lasted 4.5 min in total, and each of the 30 trials included three intervals: preparation, motor attempt, and inter-trial interval. The tonic EEG screenings lasted 6 min in total and included a resting-state and a sustained-attention task-related EEG activity recording. An automated calibration procedure was executed to set up the NF parameters, taking around 30 seconds. The NF training included 5 blocks of 5 minutes each (25 min in total).*

EEG screenings

The first screening aimed at quantifying the motor cortical activation of the patient during the attempt of movement of a paralyzed limb. This motor-attempt screening was executed at the very beginning (pre-) and at the very end (post-) of each session. It involved the right (i.e., dominant) hand of the patient only, as done in previous studies to quantify motor cortical activity of tetraplegic patients[15,19,36]. The patient was requested to try to close his right hand. He repeated the attempt of movement 30 times, while the EEG was recorded (30 trials collected). Each trial consisted of three intervals of 3 s each, separated by visual cues: *(i)* preparation, in which he was asked to avoid any movement (including head and eye movements) and to be ready for the upcoming cue; *(ii)* motor attempt, in which he had to attempt to close his hand (the resting position was with the fingers extended); and *(iii)* inter-trial interval. The total duration of this assessment was 4.5 min. At the beginning of the first session, the patient was instructed in detail about how to perform the attempt of movement, and he executed some repetitions to get familiarized with the task and the timings within the trials. During the task, the patient was asked to focus his attention on his right hand and to avoid distractions. He was instructed to keep trying to close the hand while the “motor attempt” cue was present. He was also carefully informed on how to avoid artifacts that can contaminate EEG activity (i.e., eye movements, head/neck movements, or compensatory movements with other non-paralyzed body parts) and was requested to minimize those artifacts during the “preparation” and “motor attempt” intervals.

The second type of screenings were conducted to quantify the tonic EEG activity unrelated to motor tasks. They were performed between the motor-attempt screening and the NF training, right before (pre-) and right after (post-) the NF. Two conditions were included: rest and task-related activity. The rest screenings consisted of 3 min of eyes-closed resting-state activity. The task-related activity consisted of 3 minutes in which the patient performed a sustained-attention task. This task, proposed in Zoefel et al., 2011, consisted of a square shown in the screen, randomly changing colors from grey to red or to blue in several saturation steps[32]. The task of the patient was to count the number of saturation steps from grey to red. The tonic EEG activity was afterwards used to calibrate the NF training (in each session) by determining the user-specific upper-alpha frequency band and baseline activity (see NF training section).

NF training

The NF training consisted of 5 blocks of 5 min each (total daily training = 25 min). The training was designed to increase the upper-alpha power averaged over the motor cortex electrodes (C3, Cz, C4, CP3, CPz, CP4; referred to as feedback electrodes). The EEG activity was acquired and processed to provide real-time visual feedback with an in-home software programmed in C++.

Calibration

After the EEG screenings were recorded, a calibration procedure was automatically executed to set up the parameters for the NF training (less than 30 seconds). The tonic EEG activity (i.e., motor-unrelated EEG screenings) was processed to obtain: (1) the individual upper-alpha frequency band (using the Individual Alpha Frequency—IAF—as an anchor point[37]); and (2) the upper-alpha power baseline and the upper/lower thresholds for the feedback computation. The power in the upper-alpha frequency band was calculated through a Fast Fourier Transform (FFT) analysis, with 1 s hamming window and a sliding step of 31.25 ms (i.e., 8 samples at 256 Hz), zero-padded to 1024 points (0.25 Hz resolution). For this calibration step, we automatically filtered out the blinking artifacts from the EEG activity by Independent Component Analysis (ICA), using the FastICA algorithm[38]. This

method transforms the EEG signal from a sensor space (with n dimensions) to a source space that minimizes the statistical dependence between its components. This way, the blinking component can be automatically identified and discarded, and then the EEG signal can be reconstructed filtering out this component[39]. Furthermore, we removed the epochs with amplitude larger than 200μV at any electrode. The individual upper-alpha frequency band was determined as the interval [IAF, IAF+2] Hz, with the IAF computed as the frequency value with the maximum power value in the [7-13] Hz range[37]. The baseline was computed as the mean upper-alpha power averaged across the feedback electrodes, and the 5th-95th percentiles established the lower and upper limits, respectively. Therefore, 90% of the power values were mapped into different saturation tones, while the remaining 10% (i.e., the top 5% and the bottom 5%) were mapped to the maximum/minimum saturation[34].

Training

When the calibration was complete, the patient performed the training blocks. The EEG data was online filtered from blinking artifacts (through the aforementioned ICA filter), and the averaged upper-alpha power of the motor cortex electrodes was mapped into a continuous visual feedback, updated every 31.25 ms on a computer screen in the form of a square with changing saturation colors. The patient was instructed to turn the square into red color (positive feedback, increased upper-alpha power) and to maintain it as long as possible. He was not given any mental strategy nor information about the training parameter, instead he was encouraged to search for mental strategies and to elaborate them whenever he considered he was achieving positive feedback. After the very last session, the patient was asked about the mental strategies used during the whole intervention.

EEG data analysis

The effects of the training were quantified with two analyses. Firstly, we evaluated if the intervention succeeded in inducing tonic EEG changes (i.e., enhancing the upper-alpha power) over the motor cortex: see **Effects of the intervention on tonic EEG** below. Secondly, we evaluated if such enhancement potentiated the cortical activation during the

motor-attempt screening (i.e., the attempt of movement of the hand): see **Effects of the intervention on motor cortical activation** below. The main variable for the first analysis was the absolute upper-alpha power measured in the motor-unrelated EEG screenings, whereas the main variable for the second analysis was the mu ERD measured during the motor-attempt screening.

For these two variables (i.e., tonic EEG upper-alpha power and mu ERD), we evaluated the inter-session and the within-session effects. The inter-session effects measured the trend of the variables across sessions and were computed as the Spearman correlation between the tonic EEG upper-alpha power or the mu ERD (on each session, measured in the pre-NF screenings) and the session number. In addition, we conducted post-hoc pairwise comparisons between the data of session 1 and sessions 2, 3 and 4, (independent-samples *t*-test). Notice that, as a single-subject analysis, these independent-samples *t*-tests considered the whole set of values obtained from the pre-NF screenings of each session: i.e., all the 1-second epochs for the EEG upper-alpha power, or all the trials for the mu ERD. The within-session effects were assessed by comparing the tonic EEG upper-alpha power or the mu ERD (averaged within each session) before (pre-) and after (post-) the NF training (dependent-samples *t*-test). All the analyses were performed in Matlab 2012b (Mathworks, Natick, MA, USA), using the integrated Signal Processing and Statistics toolboxes, and with the Fieldtrip open-source toolbox for computing the time-frequency ERD maps[40]. The *p*-values were corrected by multiplying them by the number of comparisons performed in the analysis (equivalent to Bonferroni correction), and therefore, statistical significance was considered when the corrected *p*-values were below 0.05.

Effects of the intervention on tonic EEG

The inter-session and within-session effects of the NF training in tonic EEG (i.e., upper-alpha power) were assessed over the whole motor cortex, averaging all the electrodes used to provide feedback (i.e., C3, Cz, C4, CP3, CPz, CP4), to measure the global effect induced in the motor cortex by the intervention. These analyses were separately applied to the EEG recorded during resting-state (eyes-closed) and the sustained-attention task (eyes-open).

The EEG power distributions were computed by applying a Fast Fourier Transform (FFT) to 1 s epochs (zero-padded to 1024 points, 0.25 Hz resolution). The upper-alpha band was determined as the [IAF, IAF+2] Hz interval using the same procedure as in the NF training. The power values were log-transformed prior to statistical testing to approximate a normal distribution[41].

Effects of the intervention on motor cortical activation

The inter-session and within-session effects in motor cortical activation (i.e., mu ERD) were assessed in the contralateral hemisphere (i.e., left) to the involved (i.e., right) limb, since that is the brain region controlling the movements of the hand that the patient tried to move (i.e., C3 electrode). The trials with prominent artifacts were discarded by visual inspection. We first computed, for each session, the time-frequency ERD maps using Morlet Wavelets[42]. The significant time-frequency pairs of the ERD maps in the entire alpha band ([7.5-12.5] Hz) were obtained using a bootstrap resampling method (with α = 0.01, and baseline [-3, 0] s)[43]. From these significant maps, we identified the subject-specific mu rhythm from the average map of the last session (i.e., session 4), where it was more prominent. A time-frequency window covering the subject's mu frequency band and the time interval [0.5, 2.5] s was defined, averaging the values inside it to quantify the user-specific mu ERD. A mu ERD value was then computed for each trial of each session of the motor-attempt screening. In addition, we also assessed the inter-session and within-session effects in absolute mu power in the preparation and motor attempt trial intervals. Finally, we performed two additional secondary analyses. Firstly, we quantified the ERD in other frequency bands: delta ([0.5-4] Hz), theta ([4-7] Hz) and beta ([12-30] Hz), in order to see if bands unrelated to the training were also affected. Secondly, we repeated the analyses considering the activity of C4 electrode (i.e., ipsilateral activity).

Results

Effects on tonic EEG

The patient successfully performed the four sessions, completing the 25 minutes of NF training in each session. The average IAF over sessions was 9.6±0.2 Hz (9.4 in Session 1; 9.6 in Session 2; 9.9 in Session 3; 9.6 in Session 4). Hence, on average, the upper-alpha frequency band was [9.6-11.6] Hz. Figure 2 shows the evolution of upper-alpha power averaged over the motor cortex electrodes during eyes-closed resting-state (Figure 2a), and during the sustained-attention task and the NF blocks (Figure 2b). The inter-session analysis revealed that the upper-alpha power significantly increased over time, both in resting-state (r_{263} = 0.41, p < 0.0001) and in the sustained-attention task (r_{122} = 0.3, p < 0.0001). The post-hoc comparisons showed significant power increases in resting-state for sessions 2, 3, and 4 with respect to session 1 (Figure 2a and Supplementary Tables 1 and 2); as well as significant power increases in task-related activity for sessions 3 and 4 (Figure 2b and Supplementary Tables 1 and 2). We found no significant within-session effects, either in resting-state or in task-related activity. In addition, we measured the within-session effects across the NF training blocks (grey dots in Figure 2b) and found a significant power increase over time (r_4 = 0.97, p = 0.0028), measured as the Spearman correlation of the power values in the pre- EEG screening and the five NF blocks with respect to their execution order.

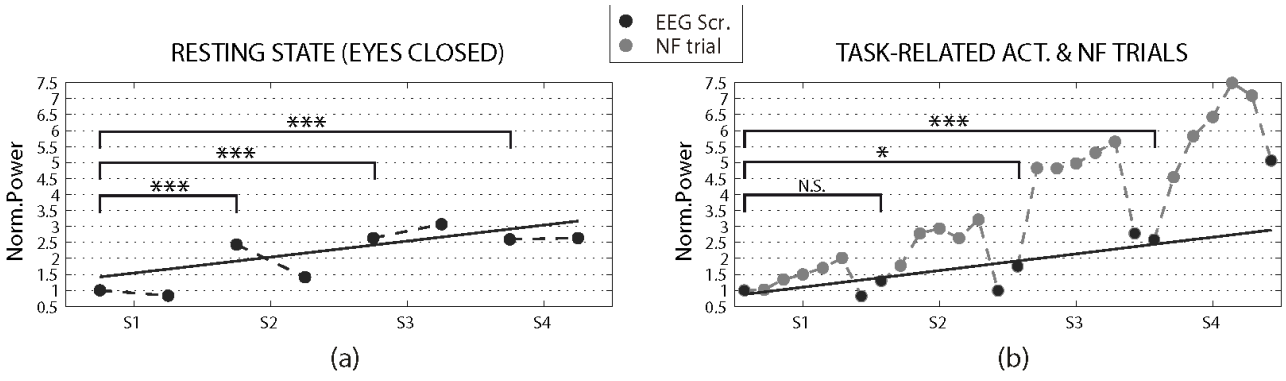

Figure 2. *Tonic EEG power in the upper-alpha frequency band, averaged over the motor cortex electrodes (C3, Cz, C4, CP3, CPz, CP4). The left panel corresponds to the eyes-closed resting-state EEG screenings, with the black*

*dots representing the averaged power in the pre- and post- EEG screenings of each session. The right panel corresponds to the sustained-attention task screenings and the NF blocks, with the black dots representing the averaged power in the pre- and post- EEG screenings within each session, and the grey dots the power during the NF blocks. The power was normalized to the pre-NF EEG screening of the first session for illustration purposes. The solid black lines represent the inter-session trend of the pre- screening power values. The results of the post-hoc pairwise comparisons between the pre- screenings of session 1 and sessions 2, 3 and 4 (independent-samples t-test, Bonferroni corrected) are also depicted. N.S.: $p > 0.05$; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.*

After the last session, the patient was interviewed about the mental strategies followed during the whole NF intervention. He reported the use of different types of relaxation thoughts, as they (according to the self-report of the patient) allowed him getting positive feedback more easily.

Effects on motor cortical activation

Figure 3 depicts the evolution of the ERD maps in C3 electrode, and Figure 4 quantifies the changes in mu ERD and in mu absolute power (for the preparation and motor attempt intervals). We observed in the ERD maps that a clear desynchronization appeared throughout the training. Using that result, we determined the user-specific mu rhythm as the [8.6-12.1] Hz frequency interval (see rightmost map in Figure 3).

Subsequently, we computed the averaged mu ERD for each session. There was a significant enhancement of mu ERD over time ($r_{86} = -0.50$, $p < 0.001$; Figure 4a). Notice that the mu ERD, which represents cortical activation, is measured with negative values[23], and an enhancement of mu ERD corresponds to the increase of its absolute value. Hence, as the ERD enhancement consists of getting more negative values, a negative change implies a mu ERD enhancement, which in turn denotes an increase in motor brain activation. The post-hoc comparisons between sessions revealed a significant mu ERD enhancement in sessions 3 and 4 with respect to session 1 (Figure 4a and Supplementary Tables 3 and 4). The ERD was not significantly modified within sessions.

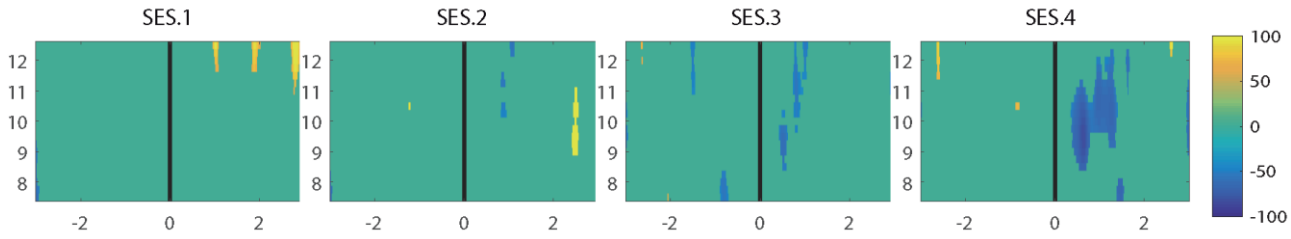

Figure 3. *Significant time-frequency ERD maps of C3 electrode, reflecting the motor cortical activation during the motor-attempt screenings performed at the beginning of each session. These maps represent the average contralateral cortical activation of the patient when he attempted to move his paralyzed right hand. Maps cover the entire alpha ([7.5-12.5] Hz) frequency range in the [-3, 3] s time interval (i.e., preparation + motor attempt). Time-frequency pairs that did not reach statistical significance in the bootstrap resampling procedure were assigned a value of 0.*

The right part of Figure 4 shows the evolution of the absolute mu power in C3 electrode for both the preparation ([-3, 0] s, Figure 4b) and the motor attempt ([0.5, 2.5] s, Figure 4c) intervals. For the preparation interval, the inter-session analysis revealed a significant effect (increase) across sessions (r_{86} = 0.43, p < 0.001), as well as significant power increases in sessions 3 and 4 with respect to session 1 (Figure 4b and Supplementary Tables 3 and 4). For the motor-attempt interval, there were no significant changes across sessions. The within-session analysis showed no power changes in the preparation interval, but a marginally significant power increase for the motor attempt interval (t_3 = -2.55, p = 0.08). All these analyses showed an enhancement of contralateral ERD with the training.

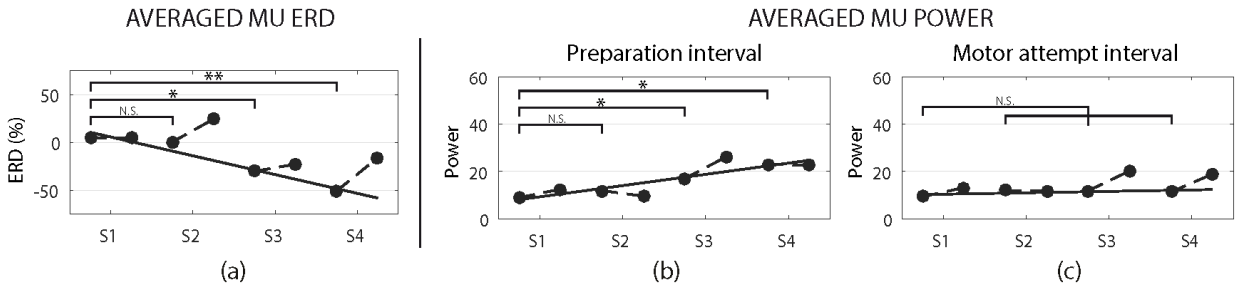

Figure 4. *Evolution across sessions of the brain activity during the motor-attempt screening in C3 electrode (i.e., contralateral hemisphere). (a) Evolution of the mu ERD; (b) evolution of the mu absolute power during the preparation interval (i.e., resting baseline); (c) evolution of the mu absolute power during the motor attempt interval. Each black dot in (a) represents the average mu ERD across all the trials, considering the time-frequency window [8.6-12.1] Hz and [0.5, 2.5] s (see Figure 3). The dots in (b) and (c) were computed averaging the absolute*

*power values (instead of ERD values), considering the time window [-3, 0] s for the preparation interval (b), and the time window [0.5, 2.5] s for the motor attempt interval (c), using the same frequency window of [8.6-12.1] Hz in both cases. The solid black lines represent the inter-session trend of the pre- screenings of each variable. The results of the post-hoc pairwise comparisons for each variable between the pre- screenings of session 1 and sessions 2, 3 and 4 (independent-samples t-test, Bonferroni corrected) are also depicted. N.S.: p > 0.05; *: p < 0.05; **: p < 0.01; ***: p < 0.001.*

These results indicate that the ERD enhancement across sessions was due to a change of the brain activity during the preparation (i.e., resting baseline) intervals, but not during the motor-attempt intervals. To show this in a more visual fashion, we display in Figure 5 the ERD and the absolute power time-courses in the mu frequency band at the beginning and at the end of the study. A stronger ERD was revealed at the end of the study (Figure 5, left). This was due to a power increase in the baseline interval, while the power values did not vary significantly during the motor attempt interval (Figure 5, right).

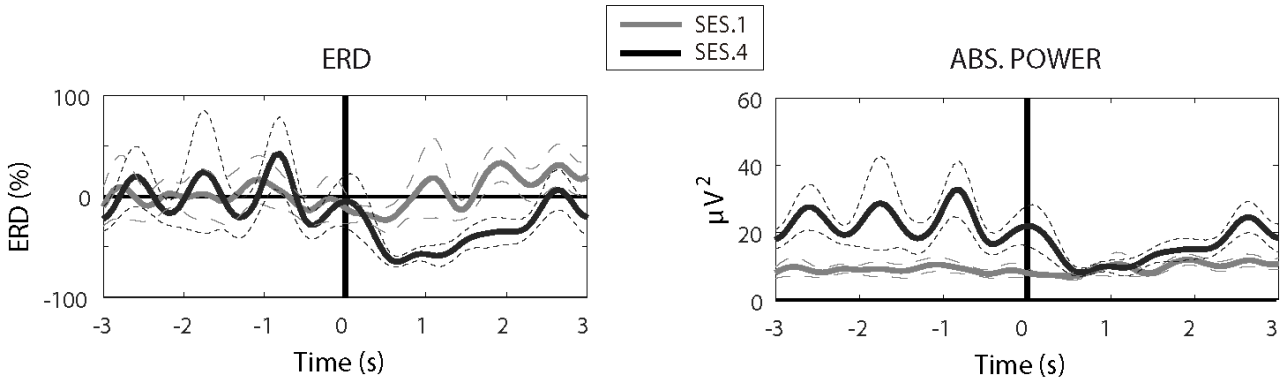

Figure 5. *Comparison of the patient's brain activity between the beginning and the end of the study in terms of mu ERD (left) and mu absolute power (right), measured in C3 electrode (i.e., contralateral hemisphere). Each panel shows the time-course including the preparation interval ([-3, 0] s) in which the patient was relaxed, and the motor attempt interval ([0, 3] s) in which he attempted to move his paralyzed hand. The grey lines represent the mu ERD (left) or mu absolute power (right) averaged across trials for the pre- motor-attempt screening of the first session (session 1), and the black lines represent the post- motor-attempt screening of the last session (session 4). The dashed lines represent the standard error of the mean.*

The exploratory analysis in delta, theta and beta bands showed no significant effects in the ERD either inter- or within-sessions. Finally, we evaluated the effects of the intervention on ipsilateral activity (C4 electrode). This analysis provided similar results to what was found in C3 electrode, showing a significant enhancement in ERD across sessions (see

Supplementary Material for more details about the analysis of ipsilateral motor cortical activation).

Discussion

The present study aimed at enhancing the motor cortical activation of a patient with chronic tetraplegia. Our hypothesis was that increasing the tonic alpha power (i.e., the extent of alpha synchrony in the basal state of the brain[44]) over the motor cortex of the patient would enhance his cortical activation (i.e., the modulation of the alpha/mu rhythms[23]) during the attempts of movement of his paralyzed limbs. We proposed a neurofeedback (NF) intervention that positively rewarded the up-regulation of the tonic upper-alpha activity over the motor cortex, without any mental strategy provided[32,34]. The effects of the NF training in motor cortical activation were quantified by measuring the mu ERD when the patient attempted to move one of his completely paralyzed hands. This proof-of-concept study confirmed that, as the tonic upper-alpha power of the patient increased during the course of the NF intervention, his mu ERD was also bilaterally enhanced.

The enhancement of motor cortical activation has been suggested to improve motor performance in healthy subjects, and even to induce motor improvements in stroke population[45,46]. Regarding chronic, complete SCI (and especially tetraplegia), we did not expect that the reactivation of the motor cortex might be associated with any functional improvement by itself, since there is no evidence to support that modifying supraspinal structures (reflected as the enhancement of brain activation) could restore the damages in the spinal cord that disrupt the connection between the brain and the paralyzed limbs. However, Cramer and colleagues hypothesized that the normalization of the brain motor system after chronic SCI "*might be useful as an adjunct to therapies aiming to restore movement after SCI*"[28]. For instance, a higher and more easily-decodable cortical activity would facilitate the use of brain-machine interfaces (BMI) for rehabilitation or motor substitution[6,7,10,47]. The mu ERD is commonly used as a brain indicator of motor intention, and it has been used to decode motor actions in complete[48,49] and incomplete[50,51] SCI

patients. Since some of these patients lose the mu ERD patterns[13,15], they may not be able to use this technology with an acceptable accuracy. A pre-intervention aiming at the restoration of cortical activation might boost the success of BMI therapies[10]. This intervention could be used as a previous step before BMI usage in this population. Indeed, there is evidence supporting that higher levels of tonic alpha power lead to higher BMI performances to decode motor tasks[52].

Previous investigations suggested that the motor cortical activity of SCI patients could be enhanced by the use of motor imagery (MI), which is a way to activate the motor cortex[53], relying on the hypothesis that repetitive cortical activation may induce neuroplasticity[54]. In fact, MI has been shown to improve the performance of non-paralyzed movements in SCI patients[55]. More specifically, in tetraplegic patients with C6-C7 injuries, tenodesis grasp (a compensatory action to regain grasping function[56]) can be trained by MI, leading to behavioral improvements and neuroplastic changes[57,58]. However, for completely paralyzed movements, no behavioral improvements should be expected by only training with MI[55]. Still, the study by Cramer et al. targeted the increase of motor brain activation in tetraplegia, proposing a 7-day MI training of one possible (tongue) and one impossible (foot) movement with no feedback. After the training, they found that during the attempts of movement of the foot there was an enhancement in fMRI activation in a deep brain structure (left putamen), although no changes appeared in the motor cortex[28]. Afterwards, a study by Enzinger and colleagues underlined the importance of feedback to change the brain activity, showing that the prolonged use of a MI-based BMI over 8 years leaded to a strong activation of the motor cortex in a tetraplegic patient, which was comparable to the activation during the execution of movements in healthy controls[29]. It is important to note that these studies trained one or various specific tasks (e.g., motor imagery of the hand or foot), and evaluated the changes in brain activity during the performance of the same tasks[28,29], without reporting any possible generalization effects to other limbs or tasks.

In contrast, the present study proposed a different approach to enhance motor cortical activity with a motor-unrelated intervention. The basic principle of the NF intervention is to

establish a causal link between a brain pattern of interest (in this case, the upper-alpha power over the motor cortex) and a visual feedback, so that the subject can learn to self-regulate his/her brain oscillations[32]. The patient was not provided with any specific strategy, but was instructed to find his own strategy to maximize the positive reward[59]. We used a motor task (i.e., the attempt of movement of one of his completely paralyzed hands) to evaluate the effects of the intervention in terms of motor cortical activation. However, notice that the mental strategies of the patient during the NF should not rely on motor commands (e.g., movement attempts, or motor imageries of explicit or implicit nature—such as in mental rotation), since this would have induced an upper-alpha desynchronization[23,60], and therefore, would have been negatively rewarded. When the patient was inquired after the last NF session about the mental strategies used, he reported the use of different relaxation strategies for the self-regulation of the activity, which is in line with previous evidence[59].

The first reason motivating the proposed NF approach is that chronic SCI patients can show pathologic or null cortical activation during movement attempts, which makes difficult to measure and characterize the activity that has to be reinforced. For instance, since the patient recruited for this study did not present any mu ERD at the time of his recruitment, it seems an unsuitable approach to reinforce such ERD. Some EEG studies have also shown cortical activation patterns in paraplegic and tetraplegic patients that differ from those of healthy individuals, especially in the event-related synchronization of the beta band[61,62]. Therefore, for patients that present altered brain activations during motor tasks, reinforcing such activations may lead to maladaptive neuroplasticity[63]. Different abnormalities of the brain motor system have been described after SCI, including sub- and supra-normal activations[13,28,61,62] and alterations in cortical connectivity[64]. One of these abnormalities is the reduction of tonic EEG alpha power over the motor cortex, as well as in parietal and occipital areas[21].

We hypothesized that the upper-alpha NF could target this abnormality, and that this would lead to changes in the mu rhythm, since there is an overlap between mu and alpha

rhythms. While the NF focused on [9.6-11.6] Hz frequency range (upper-alpha), we found a significant power increase in tonic EEG in a wider frequency range ([7-12.5] Hz), in agreement with previous NF studies using similar protocols[32,34,65]. The patient did not have significant mu ERD during motor attempt at the study entry, which is in line with previous research[13,15]; and this activation was fostered during the intervention. The strongest effects were found in the frequency range [8.6-12.1] Hz, which is within the alpha interval modified in the tonic EEG.

Interestingly, the significant enhancement on ERD was bilateral. The enhancement of motor cortical activation over the ipsilateral hemisphere was similar to what was observed in the contralateral hemisphere (cf. Supplementary Material). Bilateral ERD during voluntary movement is a known phenomenon in healthy subjects[66]. In paraplegic patients, bilateral ERD has also been reported during foot movement attempts, being it broader than in controls subjects[61]. Since the NF intervention targeted the whole motor cortex, the bilateral increase in tonic alpha activity resulted in an enhanced bilateral modulation of the mu rhythm (i.e., mu ERD) during the attempt of movement. However, it is difficult to ascertain, on the basis of one single patient, the origin of this effect in ipsilateral activity, and further research is required to elucidate the principle behind it.

The second reason supporting this NF approach is that it aims at modifying the basal state of the brain, instead of training a specific limb or task. A change in ERD magnitude (i.e., in motor brain activation) can be due to a power increase during the baseline interval or to a power decrease during the attempt of movement (or a combination of both). This is not generally studied in the literature and may be of great importance to find the optimal way to enhance the brain activation. Our results showed that the NF training modified the tonic activity of the brain (i.e., the baseline; cf. Figure 5), which should translate into an enhancement of the motor cortical activation of any motor task[30]. Since we only measured the activation patterns during the attempt of grasping of one of the hands, we can only speculate about if this activity was also enhanced for movement attempts of the other paralyzed limbs (e.g., the legs), and it will require further research to validate this

hypothesis. Notice that, on each day, the patient performed the NF intervention and the pre- and post- motor-attempt screening (i.e., trying to move his paralyzed right hand, without any feedback). Therefore, it is not possible to ascertain whether the motor attempt also had some effect in the enhancement of motor cortical activity. We suspect that the contribution of this motor task, if any, was minimal for two reasons. Firstly, because the time that the patient spent attempting to move the hand during these screenings was notably shorter than the time of the NF training (only 60 trials per day—30 before and 30 after—with 3 seconds of movement attempt per trial; i.e., 3 minutes versus the 25 minutes of NF). Secondly, because there was no feedback during the movement attempt, which makes unlikely that the cortical activity was reinforced by this task. Self-reports of patients indicate that they attempt to move their paralyzed limbs hundreds of time every day, but still their motor cortical activity significantly decreases over time[15].

As a proof of concept investigation, these results show that using EEG neurofeedback training to up-regulate the alpha power over the motor cortex also induces as a short-term effect an enhancement of the motor cortical activation in chronic, complete tetraplegia. It would be interesting to investigate the duration of the changes and the long-term effects of a continued training. Although it is very likely that the induced effects can disappear at some point after ceasing the intervention[15], we hypothesize that a long-lasting training or the repeated use of BMI systems after the reactivation of the motor cortical activity would prevent such new degeneration[10]. Following the hypothesis of Cramer et al., we speculate that the use of this NF technique may induce a more easily-decodable cortical activity in the patients, which would increase the success of BMI-based rehabilitative or restorative interventions[28]. These interventions, which have shown very promising results even in complete SCI patients[10], might constitute future standardized tools to improve the quality of life of people with complete tetraplegia. However, this single case study can only provide preliminary insights about the feasibility of this tool to be used before a BMI intervention. Further research should be conducted with a larger number of patients to confirm and extend our findings in a larger population, including also different typologies and levels of lesions. A more detailed characterization of the effects of the intervention in different types

of activity (e.g., changes in eyes-closed and eyes-open resting-state activity, or during movement attempts of different limbs) should also be carried out to better understand the underlying principles of this type of NF therapy and as a potential means of discovering new ways to optimize its design.

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Declaration of conflicting interests

The authors declare no conflict of interests.

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