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Brain-Machine-Interface in Chronic Stroke Rehabilitation: A Controlled Study

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Abstract

Objective—Chronic stroke patients with severe hand weakness, respond poorly to rehabilitation efforts. Here, we evaluated efficacy of daily brain-machine-interface training to increase the hypothesized beneficial effects of physiotherapy alone in patients with severe paresis in a double blind sham-controlled design proof of concept study.

Methods—32 chronic stroke patients with severe hand weakness, were randomly assigned to two matched groups and participated in 17.8 ± 1.4 days of training rewarding desynchronization of ipsilesional oscillatory sensorimotor rhythms (SMR) with contingent online movements of hand and arm orthoses (experimental group , n=16). In the control group (sham group, n=16) movements of the orthoses occurred randomly. Both groups received identical behavioral physiotherapy immediately following BMI training or the control intervention. Upper limb motor function scores, electromyography from arm and hand muscles, placebo-expectancy effects and functional magnetic resonance imaging (MRI) blood oxygenation level dependent activity were assessed before and after intervention.

Results—A significant group × time interaction in upper limb Fugl-Meyer motor (cFMA) scores was found. cFMA scores improved more in the experimental than in the control group, presenting a significant improvement of cFMA scores (3.41±0.563 points difference, p=0.018) reflecting a clinically meaningful change from no activity to some in paretic muscles. cFMA improvements in the experimental group correlated with changes in functional MRI laterality index and with paretic hand electromyography activity. Placebo-expectancy scores were comparable for both groups.

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Interpretation—The addition of BMI training to behaviorally oriented physiotherapy can be used to induce functional improvements in motor function in chronic stroke patients without residual finger movements and may open a new door in stroke neurorehabilitation.

Introduction

Paralysis after stroke or neurotrauma is among the leading causes of long-term disability in adults. Up to 30% of all stroke survivors experience very limited motor recovery and depend on assistance to manage their daily living activities[1,2]. While recent studies provided evidence that techniques like constraint-induced movement therapy (CIMT) or bilateral arm training represent useful strategies to improve motor function in chronic stroke patients[3-5], such options are not applicable for stroke patients with severe limb weakness since residual active movement is necessary for CIMT[6]. For this patient population BMI may play a crucial role.

However, severely weakened stroke patients are still able to imagine movements of the paretic hand and can attempt to move even in the absence of actual movements[7-11]. These imagery and intent-to-move strategies have been reported useful in patients with mild to moderate motor deficits[12]. In line with this previous information, it was proposed that brain-machine interface (BMI) systems allowing online classification of neuroelectric or metabolic brain activity, e.g. associated with planning and intended execution of grasping movements, and their translation into control of external devices such as orthoses driving motions of an extremely weakened hand/arm might have a beneficial role in neurorehabilitation[13-15].

Previous studies showed that learning to control desynchronization of ipsilesional sensorimotor rolandic brain oscillations (SMR) after stroke can be translated into grasping movements of an orthosis attached to the paralyzed limb[11,16]. Furthermore, simultaneous contingent association between brain oscillations and grasping movements of an orthosis has been proved to elicit motor learning in healthy participants16. In accordance with basic animal single cell experimental evidence[17-21] we hypothesized superior associative learning in severely brain damaged stroke patients if a close contingent connection between the neural correlate of an intention to move and the consequent feedback of the movement (visual and proprioceptive) is established via a BMI. The extent to which this approach is useful adjuvant to behavioral physiotherapy or the generalization of improvements in control of brain oscillatory activity to clinically meaningful improvements in motor function has not been tested. Our proof of concept controlled randomized double-blind study tested this hypothesis in chronic stroke patients without residual finger movements comparing improvements in motor function between an experimental group receiving BMI training adjuvant to behaviorally oriented physiotherapy and a control group receiving sham-BMI adjuvant to behaviorally oriented physiotherapy, comparing the improvement in combined hand and arm scores (motor part) from the modified upper limb Fugl-Meyer-Assessment (cFMA) (excluding coordination, speed and reflexes scores). Furthermore, we tested if BMI training immediately preceding the relevant period of physiotherapy could prime the effects of our rehabilitation treatment as it was demonstrated in healthy participants[16], i.e. we speculated that learning to control oscillatory brain activity through this BMI approach constitutes the necessary therapeutic ingredient and that physiotherapy allows generalization of re-learned motor skills to meaningful real life activities.

Methods

In this study, two patient groups underwent physiotherapy following BMI or Sham-BMI training sessions. While the control group received BMI training in which online reaching and grasping movements of the orthosis occurred randomly, orthoses movements in the experimental group were contingent with desynchronization of ipsilesional SMR brain oscillations.

Study design

This study involved thirty two chronic stroke patients with combined hand and arm scores (motor part) from the modified upper limb Fugl-Meyer-Assessment (cFMA) of 12.15 ± 8.8 (maximal score is 54 points. See Supp. Information, Section 2.1) unable to extend their fingers. The study was conducted at the University of Tubingen, Germany. Informed consent was obtained from all patients involved. The study was approved by the ethics committee of the Faculty of Medicine of the University of Tübingen (Germany). In the experimental group patients' successful control of ipsilesional SMR brain oscillatory activity was translated concurrently into movement of the orthosis attached to the paralyzed limb, while in the control group patients' movements of the orthosis occurred randomly, unrelated to SMR control. Thus, hypothesized group effects on motor function would reflect the contribution of learning to control SMR oscillatory brain activity immediately preceding physiotherapy. Both groups received continuous assessments of subjective expectancies for treatment success and credibility for differential placebo effects.

Patients

Patients were recruited via public information (German stroke associations, rehabilitation centers, hospitals) all over Germany from December 2007 to March 2011 and a total of 504 were assessed potentially eligible and were contacted and 32 were allocated to intervention.

Exclusion criteria, number of excluded patients and reasons for exclusion are described in the Supporting Information Section 1.1.

All participants fulfilled the following criteria: 1) paralysis of one hand with no active finger extension; 2) time since stroke of at least 10 months; 3) age between 18 and 80 years; 4) no psychiatric or neurological condition other than stroke; 5) no cerebellar lesion or bilateral motor deficit; 6) no pregnancy; 7) no claustrophobia; 8) no epilepsy or medication for epilepsy during the last 6 months; 9) eligibility to undergo magnetic resonance imaging (MRI); 10) ability to understand and follow instructions. A summary of patient group demographic and functional data and individual lesion localization are presented in Table 1 and Supp. Info. Section 1.2, respectively. Patients were randomly assigned to the experimental or the control group. An investigator blind to the study design assigned patients in a pairwise fashion. Groups were matched for age, gender, paretic side, and motor impairment scores (cFMA) at time of inclusion each of them being assigned with a different weight from 1 to 4 respectively. Once the matching was performed, Matlab "random" function was used to randomly assign one patient of each pair of patients to one of the two groups with a 50% probability. Group assignment was blinded for all participants and for the scientific-clinical personnel, none of the patients or therapists were able to identify group assignment reflected in the results of placebo and motor function scales below. None of the patients could elicit active finger or wrist extension. The mean ± SD scores for wrist stability in 15° extension, elbow at 90° and at 0° were 0.27 ± 0.64 and 0.30 ± 0.65 respectively. Only 8 and 7 patients presented scores different from zero before intervention respectively. Two patients of the control group were excluded due to: equipment malfunction during BMI training (n=1); faking functional deficit during baseline measurements in order to be included in the study (n=1)

Assessment

A comprehensive battery of assessment instruments was given twice before (eight weeks and one day before the first training session) and once immediately after treatment (See Fig. 1.A).

Primary behavioral outcome measures

We used the combined hand and arm scores (motor part) from the modified upper limb Fugl-Meyer-Assessment scale (cFMA) (See Supp. Info. Section 2.1, with a maximal score of 54 points) as primary behavioral outcome measures[22]. We excluded upper limb Fugl-Meyer-Assesment scores related to a) coordination and speed and b) reflexes because: a) patients in this study could not touch their noses with the index finger fully extended and had no remaining finger extension (inclusion criteria) and b) reflex scores add uncertainty to the measurement[23]. We used these scores as primary outcome measure because they are related to the two body parts trained during the BMI (hand and arm) and reflect motor recovery and measures motor aspects that may limit but are not related to task accomplishment (e.g. joint motion).

Secondary behavioral outcome measures

Ashworth Scale, Motor Activity Log (MAL)[24] and a Goal Attainment Scale (GAS)[25]. (More information about assessment instruments can be found in Supp. Info. Section 2).

Two expectancy-placebo questionnaires were collected from each patient 1) after each fifth treatment session and 2) at the end of treatment. The first questionnaire contained 15 questions (scale 1 to 6) concerning: professional behavior of the therapists, mood, and expectations of improvement. The second contained 12 questions (scale 1-6) concerning comfortable and proper functioning of the BMI-orthosis system (Examples could be found in Supp. Info. Section 4).

Assessments associated with the primary behavioral outcome measure

We measured EMG to document muscle activity and muscle innervation[26] and BOLD signal functional magnetic resonance imaging (fMRI) to identify possible changes in brain function with the interventions[27].

Electromyography (EMG)

We recorded EMG during performance (trying to perform) of arm movements (opening and closing the hand and arm extension) in order to quantify the patients' ability to generate EMG activity as a function of time and intervention. The EMG data was preprocessed and the cumulative amplitude changes for the relevant frequency bins of the signal were extracted serving as a measure of muscle control. This was quantified by calculating the waveform length providing indicators for EMG signal amplitude and frequency (See Supp. Info. Section 6.1).

Functional magnetic resonance imaging (fMRI)

Inside the scanner, patients were asked to perform three different tasks: (1) to perform (try to perform) hand closing and opening (2), to imagine hand closing and opening and (3) to remain motionless; all conditions were cued by auditory-visual signals every 1.5 sec. A lateralization index (LI) was calculated to assess changes in cortical lateralization between pre and post BMI-training sessions[28,29]. In healthy subjects, cortical activity is lateralized to sensorimotor areas contralateral to the moving hand[27]. Activity associated with affected hand motions in well-recovered stroke patients resemble patterns identified in healthy individuals, mainly contralateral during movement and movement preparation[27,30]. The LI, computed as the normalized difference between the number of all active voxels in the ipsilesional and contralesional areas (anatomically defined regions of interest conforming to MNI-space) was assessed separately for motor and premotor cortices, and for somatosensory cortex for the paretic and healthy hand in the pre- and post-training sessions[31]. All patients underwent fMRI but only those with subcortical lesions (Experimental group, N = 14; Control group, N = 7) not involving sensorimotor and premotor areas were considered for LI assessment (More information about fMRI data acquisition and processing can be found in Supp. Info. Section 6.2). The differences of LI calculated individually were assessed across sessions and groups. A 2 × 2 repeated measures ANOVA with group(experimental and control) as between factor and session (Pre-Post) as within factor was performed on LI values. Subsequently, separate paired-samples t tests were carried out as post-hoc analyses to compare the dependent variables in the Pre- and Post-sessions for each group.

Interventions

Intervention involved daily training for 4 weeks (excluding weekends) and there was no difference in time of training (BMI + Physiotherapy) between groups.

BMI-training

During BMI-training patients were instructed to desynchronize SMR rhythms measured at electroencephalography (EEG) electrodes overlying the ipsilesional motor cortex by intending to move their severely impaired upper limb. Successful SMR control resulted in concurrent movements of the arm and hand orthoses in the experimental group only, while in the control group patients received sham feedback which means random movements of the robotic orthoses not linked to the patient ipsilesional SMR oscillations (See Supp. Info. Video1). The training using the arm orthosis targeted the patient's ability to move the upper arm and reach forward. Upon hearing the corresponding auditory cue, the patient was instructed to try to reach (even if the arm does not follow their intention), grasp, and bring an imaginary apple to their lap, thus involving, finger extension during the reach and grasp movement. This movement was chosen because of its functional value and following Tyc and Boyadjian[32] findings indicating that proximal (upper arm) training induces distal (hand) recovery but distal training does not produce proximal recovery unless it uses coordination movements implying distal and proximal joints control.[9] Concurrently, the reach and grasp attempt supposedly generates brain activity assisting BMI intention detection and influencing not only proximal but also distal muscles. The training using the hand orthosis targeted the patient's ability to open and close the hand.

近端(上臂)训练可诱发远端(手)恢复，但远端训练不能产生近端恢复，除非它使用的是远端和近端关节控制的协调动作

None of the patients in the control or experimental groups reported any perception of inconsistency during training. Patients were instructed to avoid blinking, coughing, chewing, head movement and body compensation movements. They were told that these actions could affect the training. By asking the patients to produce these artifacts before training the credibility of the measurement was enhanced on both groups: The placebo questionnaires showed no differences in perception of the BMI system in both groups. After calibration, (See Supp. Info. Section 5.1) the BMI training began.

Physiotherapy

Immediately following a BMI training session, patients in both groups received one hour of behavioral physiotherapy focused on transferring arm reaching and hand movements to real life situations such as grasping a toothpaste tube, eating, relaxation in case of spasticity, reaching and grasping while standing and with social distractions[33,34]. (See Supp. Info. Section 5.3 and Video2).

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Results

Primary behavioral outcome measure: combined hand and arm scores (motor part) from the modified upper limb Fugl-Meyer Motor Assessment (cFMA)

We performed the statistical analysis on the cFMA scores. For the pre- to post- intervention comparison the average of the two baseline measurements was used as a single pre-measurement reducing test variability effects as used before in other studies for stroke rehabilitation.[35] A two-way mixed model ANOVA (with independent measures on group and repeated measures on time) showed a significant time (pre and post) × group ($F(1,28) = 6.294$, $p=0.018$) interaction and a significant effect of time ($F(1, 28) = 9.588$, $p=0.004$) on cFMA scores. There was no main effect of group ($F(1,28)=0.034$, $p=0.855$).

Post-hoc comparisons using two-tailed paired-samples t-test revealed a significant improvement in cFMA scores for the experimental group comparing pre- and post- BMI training ($t(1,15) = -6.049$, $p<0.001$). Specifically, average cFMA score ± standard error (SE) increased from 11.16±1.73 before training to 14.56±1.95 after training. By contrast, a two-tailed paired-samples t-test comparison did not reveal significant improvement from pre (13.29±2.86) to post (13.64±2.91) BMI training in the control group ($t(1,13) = -0.316$, $p=0.757$) (See Supp. Figure 5). Raw data post-training was significantly different from pre-training in the absence of averaging pre1 and pre2 measurements, i.e. when comparing one of each pre-measurements separately with the post-measurement (See Supp. Info. Section 7.2). Change in the range of 3.4 points on cFMA motor activity related scores reflects a change from no activity to some in muscles involved in i.e. lifting and stretching the arm, turn the forearm, extend the wrist and/or fingers (See Supp. Info. Video3). In the experimental group 11/16 patients and in the control group 7/14 improved their hand FMA scores. In the experimental group 15/16 patients and in the control group 7/14 improved their modified arm FMA scores. In the experimental group 15/16 patients and in the control group 8/14 improved their cFMA scores.

Secondary outcome measures: GAS, MAL, Ashworth, Placebo questionnaires

We found no significant differences in Ashworth values but significant improvements in GAS and MAL in both groups. A two-way mixed model ANOVA (with independent measures on group and repeated measures on time) was conducted to explore the impact of BMI-training and time on hope for improvement, as measured by BMI-Placebo Questionnaire and did not show any significant effect. Furthermore, Mann-Whitney U tests comparing the experimental group and control group for professional competence for every training week did not reach statistical significance either. Placebo scores remained high during and after training with no significant difference between groups (see Supp. Table 7), demonstrating stable positive expectancies, hope for improvement, and no recognition of group assignment, which would have resulted in lower scores for the control group (More information about these analyses and statistics can be found in Supp. Info. Section 7.1).

BMI control, EMG and fMRI

BMI control—The movements of the arm/hand were directly dependent upon sensorimotor oscillations of 8-13 Hz recorded over the ipsilesional sensorimotor cortex and were used as a measure of BMI performance. The patients observed and felt their arm/hand moving during a successful trial in BMI-training. The statistical analysis performed on BMI performance (moving the arm/hand with brain oscillations) showed that the experimental group only was able to improve BMI control significantly. (More information about the BMI performance measures, results and analysis can be found in the Supp. Info. Section 7.3.3). Learning self-regulation of BMI control follows a monotonic positive course over time in the experimental group similar to other reports of BMI learning indicating procedural memory mechanisms for training periods as used here[7,16,36].

EMG—We analyzed the muscle activity related to grasping movements before and after training. A Wilcoxon Signed Ranks Test (EMG data was not normally distributed) on the amplitude and frequency of the muscle activity as reflected by the waveform length of the extensor digitorum EMG signal (Supp. Info. Section 6.1) during opening and closing of the hand elicited a statistically significant change in the experimental group ($z = -2.327$, $p = 0.020$). EMG waveform length (± standard error (SE)) increased from 2.42±0.46 before training to 3.69±0.71 after treatment in the experimental group, while in the control group values increased from 1.95±0.45 to 3.58±0.97 although not significantly ($z = -1.601$, $p = 0.109$). Overall the results suggest an improvement in the ability to voluntarily engage muscle activity in the paretic hand. Mann-Whitney U tests comparing experimental and control group EMG waveform length delta (Pre-Post difference) did not reach statistical significance ($U = 107$, $P = 0.835$).

To control for changes in muscle activation in the upper arm, EMG data were analyzed using paired t-test between pre and post. The experimental group showed a significant increase in paretic side activity during upper arm and elbow extension at location deltoid from 1.35±0.08 to 1.47±0.1 ($t = 2.246$, $p = 0.040$) and triceps from 1.17±0.08 to 1.38±0.13 ($t = 2.253$, $p = 0.040$) towards normal EMG activity, while the control group did not show any significant EMG waveform length change at deltoid from 1.53±0.14 to 1.84±1.03 ($t = 1.739$, $p = 0.106$) and triceps from 1.66±1.18 to 1.51±0.76 ($t = 0.667$, $p = 0.517$).

Independent-sample t-test comparing experimental and control group EMG waveform length delta (Pre-Post difference) during upper arm and elbow extension did not reach statistical significance at location deltoid ($t(1,28) = -1.014$, $p=0.319$) And at location triceps ($t(1,28) = 1.589$, $p=0.123$) did not reach statistical significance.

No significant paretic side EMG activity change during supination and wrist extension was found in any of the groups (See Supp. Info. Section 7.3.1). None of the two groups of patients showed significant changes in EMG at the electrodes placed over the healthy side.

fMRI—The repeated measures ANOVA of group × session (pre post) on LI of activity in the motor and premotor cortices during the 'actual' movement condition revealed a significant interaction effect, $F(1,19) = 10.22$, $p = 0.005$ (Experimental group, pre = -0.04±0.37 mean ±SD, post = -0.27±0.48; S, pre = -0.12±0.39, post = 0.27±0.42). After training, a significant difference of the LI in the motor and premotor cortices only during the 'actual' movement condition was measured in the experimental group for all 14 patients ($t(13) = 2.61$ $p = 0.02$ paired sampled t-test), whereas the control group showed no significant changes neither for motor and premotor cortices nor for somatosensory cortex during executed (attempt to) and imagined hand movements (Figure 2 and Supp. Info. Section 7.3.2.). 11 patients out of 14 and 0 out of 7 of the experimental and control group respectively, showed a shift of motor and premotor activity from the contralesional hemisphere towards the ipsilesional hemisphere, i.e. towards normal activity, when movements were performed with the paretic hand. Moreover a significant correlation between the difference of lateralization of brain activity (LI_{pre}-LI_{post}) for motor and premotor cortices during executed (attempt to) hand movements and cFMA scores after training was found in patients with subcortical lesions of the experimental group (Pearson $r(12) = 0.55$ $p =0.05$ two-tailed). (More information regarding fMRI statistical analysis can be found in Supp. Info. Section 7.3.2.).

Discussion

The results of this study indicate that contingent online orthosis-BMI- training adjuvant to physioteraphy results in more prominent improvement in cFMA in chronic stroke without residual movement capacity of the affected hand than control BMI+physiotherapy. They show that BMI training, involving proprioceptive positive feedback and reward that is time-contingent upon control of ipsilesional sensorimotor brain oscillations may prime and thus improves the beneficial effects of physiotherapy on motor function[37]. Significant improvement on cFMA motor activity related scores reflected a clinically meaningful change from no activity to some in muscles involved in e.g. lifting and stretching the arm, turn the forearm, extend the wrist and/or fingers. Immediate and correct feedback and reward in the framework of reinforcement learning of control of brain oscillatory activity translated in a reaching and grasping movement of the paretic limb constitutes the critical ingredient[38-40].

The finding of significant differences between the experimental group and the control group receiving random feedback indicates that this contingency is critical to improve a physiotherapy-based neurorehabilitative intervention. Placebo effects could not explain the results. It is conceivable that the random non-contingent feedback in the sham group resulted in a diminished positive effect of physiotherapy or motor learning. Thus contingent BMI may produce a better outcome as it avoids this negative effect. A cross-over design trial could possibly help sort out this issue but cross-over designs produce difficult to separate sequence effects. Furthermore, the questionnaires used to uncover placebo effects may not be sensitive enough to reflect such non-conscious deleterious effects. Because of the subconscious nature of such an effect it is difficult if not impossible to rule out such unconscious placebos. However, if such a non-conscious learning impairment occurred in the control group it should surface in a more negative attitude and treatment evaluation in the controls which was not the case: controls rated their treatment and therapists as equally efficient and competent.

It is conceivable that BMI training immediately preceding the relevant period of physiotherapy, operates as proposed by cortical stimulation[41-43], priming the effects of customary rehabilitation treatments[44] as shown in healthy participants[16]. We believe a contingent link between brain activity (intention to move) and paretic limb movements (orthoses), influences the specific neural network activity of the visuomotor loop involved in a motor task. This contingency could be interpreted as an instrumental motor learning task strengthening the associative (and neural) connection between movement attempt and the consequence consisting of an actual arm/hand movement[45] following principles of Hebbian plasticity. The neuronal consequence of such a plastic procedure may consist in an incremental excitability of motor pools that represent these movements to the level that this neuronal activity is high enough to produce a voluntary action potential in latently functional, spared descending corticospinal fibers. It remains to be determined the best timing between BMI training and physiotherapy to elicit the beneficial effects on cFMA scores.

We proved that altering a brain signal (increase in SMR desynchronization), which is linked to prosthesis movements in time leads to motor learning and induces neural plasticity or neural compensation and that induces motor function improvement[36]. On the other hand, a difference of BMI training with cortical stimulation is that BMI training engages a group of ecologically relevant brain regions related to the intention to perform a movement that these patients could not execute (e.g. paretic finger motions) while cortical stimulation is commonly applied over one target region like the primary motor cortex (but as well the vicinity structures depending on the invasiveness of the stimulation) and is not related to volitional brain signals. It is conceivable that BMI training engaging a crucial network of brain regions related to intent of the lost function could have contributed to improve the effects of physiotherapy, evidenced in cFMA scores and EMG activity. The use of ipsilesional brain oscillations only could be a limitation in our study since after stroke there is a shift of activity towards the contralesional hemisphere and engagement of activity in these regions could have improved BMI performance. However, as presented in previous work, functional improvements were associated with changes in LI towards ipsilesional motor regions, i.e. towards normal LI in healthy individuals[40,43]. This effect is in line with the view that training results in increased recruitment of brain networks located in the vicinity of the lesion accompanied by a decrease of contralesional activity in the healthy hemisphere[46,47].

Unbalanced bilateral brain activity towards the non-lesioned hemisphere in the chronic stage might indicate a failure of compensatory mechanisms to restore normal, predominantly lateralized motor activation. Therefore, although the redundancy of an unaffected cortex and the potential functional role of ipsilateral pathways seem advantageous and might help during the acute phase, in the chronic phase the abnormally increased inhibitory influence of the healthy hemisphere upon the ipsilesional hemisphere may play a maladaptive role[35,43]. The neuroplastic processes that characterize early brain reorganization after stroke change with time[44]. The direct physiological regulation of these networks using behavioral principles of reinforcement learning and procedural memory for skill acquisition may be responsible for such a lasting and widespread cortical reorganization accompanied by the positive clinical modifications[35].

In summary and despite of the limited number of patients involved, our proof of concept study demonstrates that BMI training can successfully prime behaviorally oriented physiotherapy to induce more clinically significant improvements in motor function in chronic stroke patients with substantially restricted residual finger movements and that these improvements are accompanied by a pattern of cortical reorganization previously associated with spontaneous recovery of function and by an increase in EMG activity in muscles of the paretic hand.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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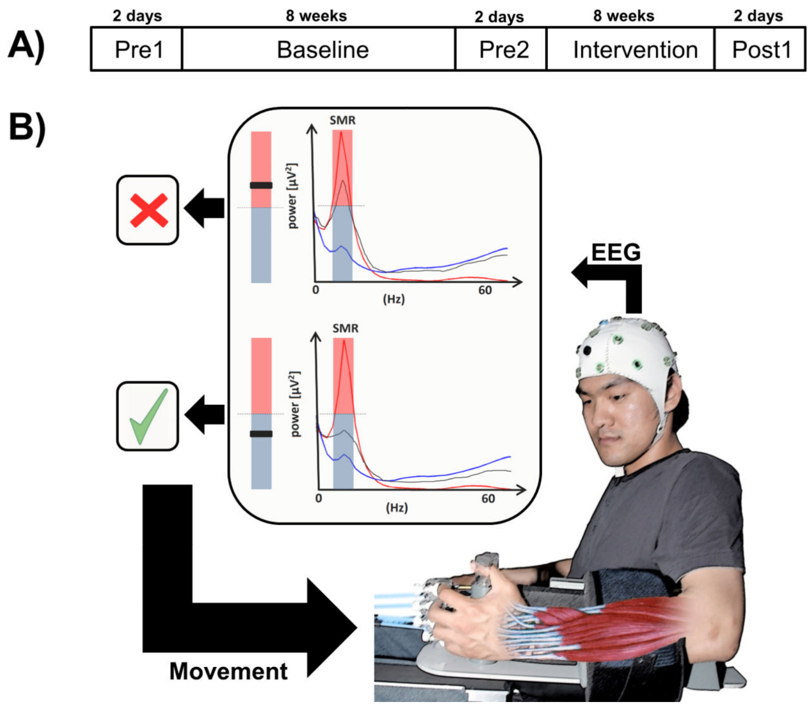

Figure 1. Brain-Machine-Interface in stroke

A) Experimental time course of the online-BMI for paralyzed chronic stroke patients' rehabilitation. B) User wearing the 16-channel EEG system with the hand attached to the orthosis to drive extending fingers (hand opening) motions muscles as indicated by the illustration during the second part of the BMI training. The sensorimotor rhythm (SMR) power recorded from the ipsilesional electrodes (gray line) is translated into movement of the orthosis. A threshold (dashed line) calculated as the point of equal distance to the mean of the power distribution during rest (red line) and motor intention (blue line) calculated over the last 15 seconds defines rest (red shading) and motor intention (blue shading) classification areas. If the SMR power is continuously in the motor intention classification area (blue shading) for 200 msec the orthosis moves, stops if it returns to the rest classification area (red shading) for 200 msec, or maintains the previous state otherwise. The same BMI principle was applied when training reaching movements with the arm orthosis (See Supp. Info. Supp. Fig. 6). Finger extension and flexion when using hand orthosis (grasping) and upper arm extension when using arm orthosis (reaching) were part of the training task while the wrist was immobilized and fixed to the orthoses.

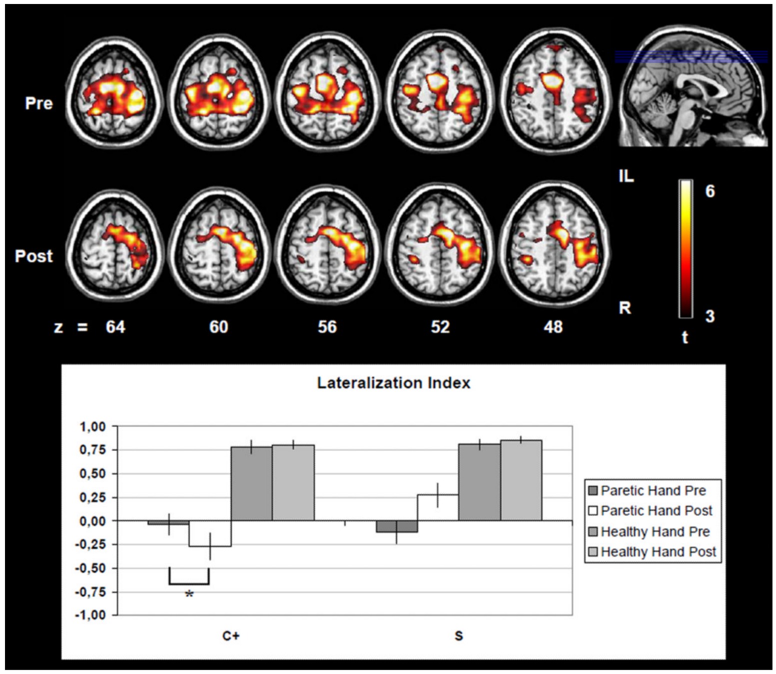

Figure 2. Lateralization index of BOLD activity

1 entirely contralesional; -1 entirely ipsilesional, was calculated for pre and post-training fMRI sessions during hand-opening attempt of patients with the paretic and with the healthy hand in the experimental or contingent positive group (C+) and control or sham group (S). Top: Brain activations during paretic hand movements vs. rest before and after BMI training ($p < 0.001$ uncorrected for visualization). fMRI maps were obtained from mixed effect analysis on the experimental group with subcortical lesion only (N=14; maps of patients with lesion on the left hemisphere were flipped to the right hemisphere). The data for the control group are not shown as no significant changes were observed between pre and post training sessions. Bottom: Lateralization index of active voxels in the ipsilesional and contralesional motor and premotor areas during ‘actual movement’ condition for the paretic and healthy hand in the experimental and control group before and after BMI training (only for patients with subcortical lesions).* p < 0.0.5.

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Table 1

Means and standard deviations of demographic data and functional scores for the two patient groups at the time of enrollment in the study.

	Gender	Age (years)	Months since stroke	Lesion side	cFMA scores	GAS	Training Duration
C+	9M/7F	49.3 ± 12.5	66 ± 45	8 R/8 L	11.15 ± 6.92	0.88 ± 0.67	275 ± 25 (runs)
S	9M/5F	50.3 ± 12.2	71 ± 72	8 R/6L	13.28 ± 10.71	0.63 ± 0.51	291 ± 17 (runs)

In the experimental group (C+) brain activity moved the orthoses and in the control group (S) received random orthosis movements not linked to control of oscillatory brain activity. Lesion side indicates damaged hemisphere being R right and L left. Motor part of the modified upper limb Fugl Meyer Assessment (cFMA) (Hand and arm parts combined having a maximum score of 54 points), i.e. primary outcome measure and Goal attainment Scale (ΔGAS) total scores are presented for both groups. Training duration indicates the amount of runs during the training. One run contains 11 trials of 5 seconds in which the patients were able to move the orthosis using the BMI system. None of the differences of baseline measures between the experimental and control groups were significant (See Supp. Info. Section 3).