Brain-Machine Interfaces and Plasticity of Brain Function

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Tübingen, 16.04.2018 _____

Date Signature

To my parents, Edilmar and Maura

for the education and love

To my lovely wife, Carla

for the company and supporting my dreams

And to my siblings, Kevin, Gustavo and Luciana

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“Learn from yesterday, live for today, hope for tomorrow.
The important thing is to not stop questioning.”
Albert Einstein

Summary

I – Abstract

Introduction: Brain–machine interfaces (BMI) create a direct communication pathway between the brain and an external device. BMI can be used, beside other possibilities, for selective induction of use-dependent neuroplasticity that might e.g. facilitate motor recovery. *Objectives:* The dissertation pursued four main goals: 1) to investigate the efficacy of BMI technology as a rehabilitation tool for chronic stroke patients suffering complete paralysis of their fingers and from a damaged brain at the same time; 2) to find biomarkers, e.g. the presence of motor evoked potentials (MEP) that can predict recovery related to BMI training; 3) to investigate the neural substrates, e.g. integrity of the cerebral cortex or thalamus to generate event-related desynchronization (ERD) and thus to control the BMI, and 4) to integrate other biosignals to improve BMI control. *Methods:* 39 severely affected chronic stroke patients with no finger extension underwent a 4-week daily BMI training for one and half hour followed by one hour of physiotherapy. Patients were divided according to feedback contingency, and subcategorized according to the integrity of sensorimotor cortex, thalamus and presence of MEP. *Results:* The results show that patients in the experimental group improved functional outcomes significantly compared to the control group. Patients with ipsilesional upper-limb MEP presented better functional outcomes in both treatment groups, but motor recovery was superior in patients with MEP in the experimental group. Besides that, patients with an intact motor cortex showed significantly stronger ERD since their first training day. Moreover integration of electrooculogram (EOG) seems to improve reliability of BMI control. *Interpretation:* The results show that BMI technology is a reliable tool in neurorehabilitation of chronic stroke patients. The success of BMI training can be improved according to the integrity of the motor cortex or the presence of MEP.

Keywords: brain-machine interface (BMI), stroke, rehabilitation, motor evoked potential (MEP).

II – Resumo / Resumé

Introdução: A interface cérebro-máquina (BMI) cria um caminho de comunicação direto entre o cérebro e um aparelho externo. A BMI pode ser utilizada, dentre outras possibilidades, para indução seletiva de neuroplasticidade dependente do uso, o que deve por exemplo facilitar a recuperação motora. *Objetivos:* A tese aspira quarto objetivos principais: 1) investigar a eficácia da tecnologia BMI como uma ferramenta de reabilitação para pacientes crônicos de derrame com paralisia completa dos dedos e um cérebro danificado; 2) encontrar biomarcadores, por exemplo, a presença de potencial motor evocado (MEP) que possa prever recuperação relacionada ao treinamento com BMI; 3) investigar os substratos neurais, por exemplo, a integridade do cortex cerebral ou do tálamo para gerar a desincronização relacionada ao evento (ERD) e com isso controlar a BMI, e 4) integrar outros sinais biológicos para aprimorar o controle da BMI. *Métodos:* 39 pacientes de derrame em estado crônico, e severamente afetados – sem nenhuma extensão dos dedos – submeteram-se a um treinamento diário de BMI por 4 semanas por uma hora e meia seguido por uma hora de fisioterapia. Os pacientes foram divididos de acordo com o tipo de feedback, e subcategorizados de acordo com a integridade do córtex sensoriomotor, tálamo e a presença de MEP. *Resultados:* Os resultados mostram que pacientes no grupo experimental apresentaram melhoras funcionais significativas comparados ao grupo de controle. Pacientes com MEP ipsilesional no membro superior apresentaram melhoras funcionais em ambos os grupos, mas a recuperação motora foi superior nos pacientes com MEP no grupo experimental. Além disso, pacientes com córtex motor preservado mostraram ERD significativamente mais forte desde o primeiro dia de treino. Além disso, a integração de eletrooculografia (EOG) parece aprimorar a confiabilidade do controle da BMI. *Interpretação:* Os resultados mostram que a tecnologia BMI é uma ferramenta confiável na neuroreabilitação de pacientes crônicos de derrame. O sucesso do treinamento com BMI pode ser aperfeiçoado de acordo com a integridade do córtex motor ou a presença de MEP.

Palavras-chave: Interface cérebro-máquina (BMI), derrame, reabilitação, potencial motor evocado (MEP)

1.0 – Introduction

Brain–machine interfaces (BMI) or brain–computer interfaces (BCI) utilize physiological signals originating in the brain to activate or deactivate external devices or computers (Birbaumer and Cohen, 2007). Depending on the aim of BMI/BCI use in neurorehabilitation, two major approaches can be distinguished: assistive and restorative BMI (Soekadar, 2011a). While assistive BMI systems aim e.g. at high dimensional control of robotic limbs or functional electric stimulation (FES) that specifically activate paralyzed muscles to substitute a lost motor function in daily life (Velliste et al, 2008; Hochberg et al, 2006; Pfurtscheller et al, 2003), restorative BMI aim at selective induction of use-dependent neuroplasticity to facilitate motor recovery (Broetz et al, 2010; Caria et al, 2010; Nagaoka et al, 2010).

Hand functions are fundamentally important for daily life independence. The loss of these functions – due to neurotrauma, stroke or amputations – can be devastating and cause severe physical and psychosocial dysfunction. Among the most important causes of neurological disabilities provoking permanent damage and reduction of hand functions are: stroke, multiple sclerosis, spinal cord injury and brachial plexus injury. Stroke is the leading causes of long-term disability and affects approximately 20 million people per year worldwide (Ward & Cohen, 2004; McMahon, 2002) and five million remain severely handicapped and dependent on assistance in daily life (WHO, 2008). Nearly 30% of those who suffer a stroke are under the age of 65 (NIH, 2009). While several publications suggest that motor function can significantly improve in the first months after stroke, further recovery is often slow or non-existent (Krakauer, 2005; Gladstone et al., 2002; Duncan et al, 1992; Royal College of Physicians, 2008).

The last years yielded the development and clinical assessment of various neurorehabilitation approaches, some of them proved to be highly efficient (Langhorne et al., 2011), e.g. constraint-induced movement therapy (CIMT), but these rehabilitation strategies require sufficient residual motor function often not present in severely affected stroke patients.

Currently, there is no accepted and efficient rehabilitation strategy available in patients with chronic stroke and no residual hand movements. BMI systems could be a solution for those who suffered a stroke and need to rehabilitate a completely paralyzed limb and a damaged brain at the same time (Birbaumer et al., 2008). Based on the concept of neurofeedback, Birbaumer & Cohen (2007) suggested that contingent reward of ipsilesional motor related brain activity, e.g. mu-rhythms (8-15Hz), might facilitate motor recovery, even in chronic stroke patients. Insofar, restorative or biofeedback BMI can be considered as "training-tools" to induce use-dependent brain plasticity increasing the patient's capacity for motor learning (Wang et al., 2010; Broetz et al., 2010; Caria et al., 2010; Nagaoka et al., 2010; Soekadar et al., 2011). Many studies in both, human and animal models, have demonstrated that neural plasticity after stroke and rehabilitation is related to changes in structure and/or function of the central nervous system (Chen et al., 2010; Dancause and Nudo, 2011; Hosp and Luft, 2011). Besides motor recovery, the use of BMI as an assistive machine that is independent of the peripheral nervous system's integrity represents a promising and appealing perspective. Particularly, if controlled intuitively and without requiring extensive training for reliable control.

Here four publications are presented: three of them making use of the BMI as a restorative tool and one using the BMI as an assistive tool. The first publication "Brain-Machine-Interface in Chronic Stroke Rehabilitation" aims to compare the efficacy of combining daily BMI training and physiotherapy as a functional motor rehabilitation tool. The second publication "Brain-machine interface training and corticospinal system's integrity in chronic stroke" aims to identify biomarkers that predict BMI training related motor recovery, as the integrity of the ipsilesional corticospinal system (CST), e.g., with the presence of upper-limb motor evoked potentials (MEP). The third publication "The sensorimotor cortex and the event-related desynchronization (ERD)" aims to identify the necessary neural substrates to control the BMI looking at different types of lesions (cortical/subcortical) or integrity of the thalamus (intact/affected). Last but not least, the fourth publication "Controlling assistive machines in paralysis using brain waves and other biosignals" introduce as new conceptual framework

using waves in combination with other biosignals to enhance the ability of people with a compromised motor system to interact with assistive machines, e.g., an exoskeleton attached to the paretic arm.

2.0 – Materials and Methods

The methods session describes the key information further detailed in the four publications in chapter five. Three of these publications (first, second and third) share the same patients and study design. The fourth publication also aims at use the BMI to improve patients' daily life activities, but in the sense of an assistive tool, e.g. to control a hand-exoskeleton or prosthetic device.

2.1 – Patients

Patients were recruited from all over Germany via public information channels (German stroke association, hospitals and rehabilitation centers). A total of 504 were potentially eligible and contacted. From these, 39 (24 male, mean age: 54.6±11.7 years old; range 29 to 73 years; interval since stroke: 61.5±56.3 months; range: 10 to 232 months – Table 1) were selected for the intervention fulfilling the following inclusion criteria: age between 18 and 80 years, complete paralysis of one hand without ability for active finger extension, interval since stroke of at least 8 months, no psychiatric or neurological condition other than stroke, no cerebellar lesion or bilateral motor deficit, no epilepsy, Mini-Mental State (MMS) score beyond 21, no contraindication for TMS assessment, no pregnancy, no claustrophobia, and ability to understand and follow instructions. Patients were subcategorized according to the research question: In the second publication, according to the integrity of the ipsilesional corticospinal system as measured by upper-limb MEP; in the third publication, according to the integrity of the sensorimotor cortex (preserved/affected) and thalamus (preserved/affected) using T1 brain images (for characterization of lesion location see Publication 2 - Table 2).

Table 1. Patients demographics

Patient	Feed-back	Lesion Side	Lesion Type	Gender	Age (years)	Months Since Stroke
1	P	R	S	M	48	45
2	P	L	S	F	53	30
3	P	R	M	F	35	28
4	P	R	S	F	35	60
5	P	R	M	M	29	25
6	P	L	S	F	72	44
7	P	L	M	F	36	16
8	P	L	S	M	60	130
9	P	L	S	M	69	72
10	P	R	M	M	51	139
11	P	R	S	M	65	45
12	P	L	M	F	52	156
13	P	L	S	F	55	45
14	P	R	S	M	47	80
15	P	R	M	M	64	23
16	P	L	M	M	70	23
17	P	R	S	M	57	122
18	S	R	M	M	69	89
19	S	L	S	M	40	46
20	S	R	M	M	40	53
21	S	R	M	M	54	121
22	S	L	S	F	53	20
23	S	L	M	F	54	10
24	S	L	S	M	50	215
25	S	L	M	M	51	16
26	S	R	M	M	66	48
27	S	R	S	M	47	232
28	S	R	M	F	73	23
29	S	R	M	M	58	28
30	S	R	S	M	62	10
31	S	L	M	F	66	23
32	S	R	M	M	59	28
33	S	R	S	F	55	17
34	S	R	M	M	50	10
35	N	R	S	M	65	67
36	N	R	M	F	65	131
37	N	R	S	F	65	99
38	N	R	M	F	31	15
39	N	R	M	M	60	14

Feedback: P = Contingent Positive, S = Sham, N = Contingent Negative
Lesion type: S = Subcortical, M = Mixed (cortical + subcortical)

2.2 – Experimental procedure

A total of 39 severely affected chronic stroke patients participated in this BMI rehabilitation study. Patients were sitting comfortably in an upright position with a robotic arm or a hand orthosis attached on the paretic hand and wearing a 16-channel EEG cap. All patients trained for one and half hour per day over

four consecutive weeks and underwent one hour of physiotherapy after each session. During the training, patients were instructed to try to move the arm or to open and close their paralyzed fingers, respectively. Patients were separated in 3 different groups receiving 3 different feedback contingencies. The first group (n = 17) received contingent positive feedback (i.e. event-related desynchronization (ERD) of the ipsilesional brain side was contingently translated into hand orthosis movements), the second (n = 17) received sham feedback (i.e. the orthosis moved independent of brain activity but participants believed in their control) and the third (n = 5) received contingent negative feedback (i.e. event-related synchronization (ERS) was linked to orthosis movements) (Ramos-Murguialday et al., 2012). The amount of time the orthosis was moving in sham feedback group was kept in the same range as in contingent feedback group (between 55-80% of each trial). Integrity of the ipsilesional corticospinal system was evaluated in all patients prior to the interventions using transcranial magnetic stimulation (TMS). Motor function of the upper-limb was tested two months and one day before (pre1 and pre2), and immediately after (post1) the intervention using a modified version of the upper-limb Fugl-Meyer Motor Assessment (uFMA). All participants gave written informed consent. The study was approved by the University of Tübingen Ethics Committee.

2.3 – Assessments

Functional magnetic resonance (fMRI)

Patients' anatomical images were accessed before and after the intervention. Data were acquired using a 3 Tesla Siemens MRI system (Siemens TIM Trio, Erlangen, Germany). Functional MR images were acquired using a gradient-echo planar imaging (EPI) aligned in axial orientation: TR = 2000 ms; TE = 30 ms; flip angle = 90°; FOV = 210 mm; matrix size = 64; interslice gap = 0•75 mm; slices = 28; slice thickness = 3 mm. A T1-weighted anatomical MR images was acquired using a 1 mm isotropic MPRAGE sequence with the following parameters: TR = 2300 ms; TE = 3•03 ms; TI = 1100ms; flip angle = 8°; FOV =

256 x 256; matrix size = 256 x 256; number of slices = 176; slice thickness = 1 mm, bandwidth = 130 Hz/Px.

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a well-tolerated and safe technique to elicit motor evoked potentials (MEP) reflecting excitability and integrity of the corticospinal system (Perez and Cohen, 2009). The use of the anatomical image of the patients' head, acquired with MRI, allowed neuronavigated stimulation of cortical brain areas. Assessments of corticospinal system integrity was done using single-pulse TMS (Magstim 200® Whitland, UK). A 70mm figure-eight coil was used to elicit upper-limb motor evoked potentials (MEP) recorded bilaterally from the following eight different muscles: first dorsal interosseous (FDI), abductor pollicis brevis (APB), extensor pollicis longus (EPL), extensor digitorum communis (EDC), extensor carpi ulnaris (ECU), flexor carpi radialis (FCR), biceps brachii (BB) and triceps brachii (TB) (see Figure 1). Electromyographic (EMG) activity was recorded using bipolar surface electrodes (Norotrode 20TM, Myotronics Inc., Kent, WA, USA) kept at impedance below 8kΩ. If no MEP could be detected after 10 TMS pulses (MEP-), stimulation intensity was increased by 10% until maximum stimulation output. If a MEP could be elicited (MEP+), the exact position was saved using a neuronavigation system (LOCALITE GmbH, Sankt Augustin, Germany) using patients' brain images acquired with MRI. Detailed description can be found on the methods session of chapter 4.2.

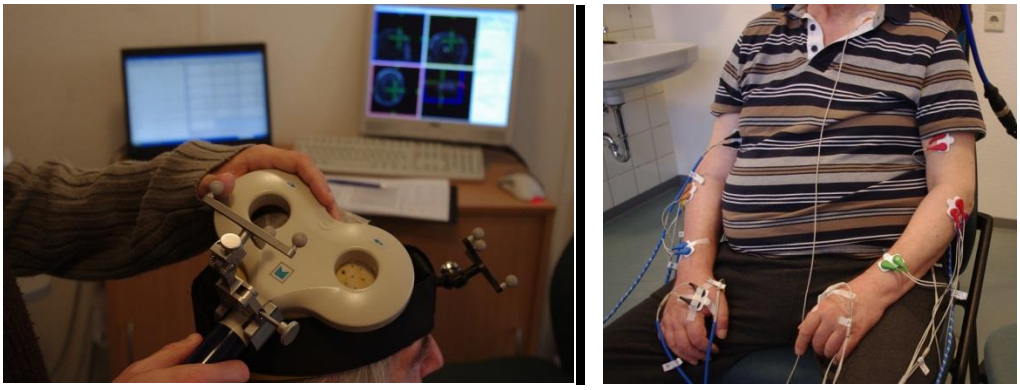


Figure 1 – TMS assessment

Motor function assessment

Motor function of the upper-limb was determined 8 weeks before (pre1) and one day before (pre2), and after intervention (post) using the combined hand and arm motor part of the upper-limb modified Fugl-Meyer Motor Assessment (uFMA) (Fugl-Meyer et al, 1975) a well-established and reliable measure of upper extremity function after stroke (Duncan et al, 1983; Gladstone et al, 2002) excluding sub-scales for coordination speed and reflexes as these measures showed to be unreliable in severe stroke (Crow and Harmeling-van der Wel, 2008). The uFMA, has 2 sub-scores for different functional domains (hand/finger and arm). The achievable maximum score is 54 ($FMA_{hand/finger}$: 24; FMA_{arm}: 30). Detailed description can be found on the methods session and supplementary material of chapter 5.2.

2.4 – Data acquisition

During the training, electric brain activity was recorded by 16-channel EEG (BrainAmp 32-channel amplifier from Brain Products GmbH, Munich German) placed according to the international 10/20 system recording from the following positions: Fp1, Fp2, F3, F4, Fz, T7, T8, C3, C4, Cz, CP3, CP4, P3, P4, Pz, Oz. SMR changes in signal amplitudes recorded from the ipsilesional brain hemisphere during attempted arm or finger motions were translated online (delay 240ms) into reaching motions or hand opening and closing motions, respectively, driven by an robotic arm (ReoGo, Motorika, Israel) or an orthotic device fixed to the patient's paralyzed fingers (see Fig 1) (Buch et al., 2008; Soekadar et al., 2011a). Detailed description can be found on the methods session and supplementary material of chapter 4.4.

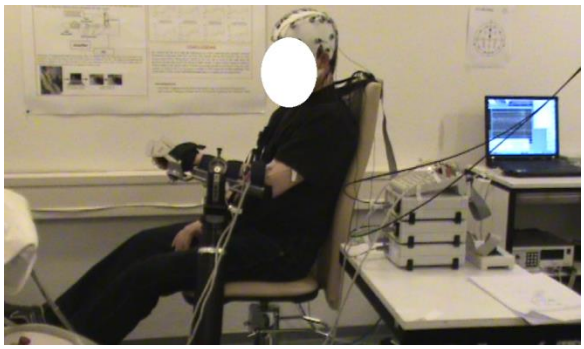
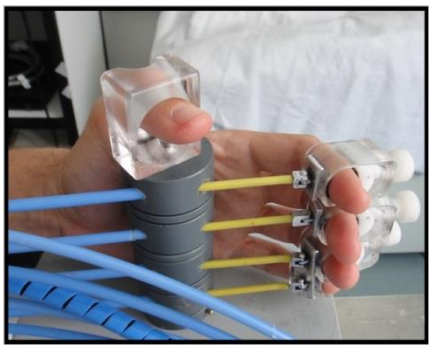
a)  b) 

Figure 2 – BMI training. a) Robot arm, b) Hand orthosis device

2.5 – Interventions

Brain-machine interface (BMI) training

The training was performed according to individual impairment. Patients with FMA_{arm} scores smaller or equal to 10 started the BMI training using the robotic arm (ReoGo, Motorika, Israel) and after two weeks – or according to the physiotherapist's decision, started to use the hand orthosis device (Fig. 2). On the other hand, patients with FMA_{arm} scores higher than 10 started the BMI training directly on the hand orthosis device.

SMR changes in signal amplitudes recorded from the ipsilesional brain hemisphere during attempted arm or finger motions were translated online into reaching motions or hand opening and closing motions respectively, driven by an orthotic device fixed to the patient's paralyzed fingers. For online signal processing and orthosis control during the training the BCI2000 software platform was used (www.BCI2000.org) (Wolpaw et al., 2002; Schalk et al., 2004). BCI2000 is based on a system model that consists of four modules (source, signal processing, user application and operator interface) (Schalk et al., 2004) and incorporates customizable signal filtering as well as extraction of signal features for translation into device control signals (Soekadar et al., 2011b).

Behavioral physiotherapy

After each training session patients received one-hour of behavioral physiotherapy focused on transferring arm reaching and hand movements to real life

situations such as grasping a stick, opening a door, holding a toothbrush, and were systematically rewarded verbally and by tapping the patient's arm or hand (Broetz et al, 2010). During attempted movements with the paralyzed limb, relevant muscles were touched and motions passively assisted. Detailed description can be found on the methods session and supplementary material of chapter 4.4.

2.6 – Data analysis

Transcranial magnetic stimulation (TMS)

A 10-Hz high pass Butterworth filter and notch filter (50Hz) was applied offline to the EMG raw signals using Matlab R2012a (The MathWorks, Natick, MA). TMS-triggered 100ms EMG data epochs were analyzed for MEP presence with peak-to-peak amplitudes of >50mV. All detected MEP were verified through visual inspection to exclude false positive findings. Patients were grouped according to MEP presence (MEP+) or not (MEP-).

Event-related desynchronization (ERD)

ERD were computed based on the power method described by Pfurtscheller (1979) using the following equations:

$$RV = \frac{1}{|T_{ref}|} \sum_{t \in T_{ref}} P_t \qquad (1)$$

$$ERD(t) = \frac{P_t}{RV} - 1, \qquad t \in T_{task} \qquad (2)$$

Where: RV = reference value; Pt is the power estimate in a given frequency band of the t sample block. Detailed description can be found on the methods session of chapter 5.2.

Statistical analyses

To verify reliability of uFMA assessments before intervention, the intra-class correlation coefficient (ICC) of the uFMA and sub-scores was calculated.

Intervention related changes of uFMA were calculated as the mean difference between pre1/pre2 in order to reduce variability (Whitall et al, 2011) and post.

In the first publication uFMA changes were evaluated using a general linear model based repeated-measures ANOVA with factors of feedback contingencies “Contingent positive” and “Sham” as within-group variables and repeated measures on time (pre and post).

In the second publication uFMA changes were evaluated using a general linear model based repeated-measures ANOVA with factors MEP+ and MEP- as within-group variables.

In the third publication ERD changes were evaluated using a general linear model based repeated-measures ANOVA with feedback factors “Contingent positive”, “Sham” and “Contingent negative” within-group variables and lesion type as covariates.

A one-way analysis of covariance (ANCOVA) with between-subjects factor: feedback; covariates: lesion (cortical, subcortical) and thalamus (affected, preserved) was conducted for ERD and uFMA on the beginning and end of training.

An independent/paired-samples t-test was used as post-hoc test according to the research question.

Statistical tests were performed by SPSS for Windows v.20 (SPSS Inc, Chicago, Illinois, USA). p-values < 0.05 were considered statistically significant.

3.0 – Results

Patients

Patients were subcategorized in the second and third publications:

- In the second one, according to the integrity of the corticospinal system: 12 patients with upper-limb MEP and 18 with no upper-limb MEP.
- In the third one, according to the integrity of the sensorimotor cortex: preserved/affected – 18 subcortical, 21 mixed lesion, respectively; and thalamus: 12 preserved, 27 affected.

Upper-limb Fugl-Meyer Motor Assessment (uFMA)

Intra-class correlation (ICC (3, 1)) of the uFMA assessments before intervention showed good reliability (ICC uFMA=0.94). At the beginning of training an ANCOVA revealed for uFMA no mean effects of feedback, $F(2, 30) = .053$, $p = .948$, $n_p^2 = .004$, nor of lesion, $F(1, 30) = 0.316$, $p = .578$, $n_p^2 = .010$, nor of thalamus, $F(1, 30) = 1.35$, $p = .254$, $n_p^2 = .043$. At the end of training an ANCOVA revealed no significant changes for uFMA, with no mean effect of feedback, $F(2, 30) = .332$, $p = .720$, $n_p^2 = .022$, nor of lesion, $F(1, 30) = .077$, $p = .784$, $n_p^2 = .003$, nor of thalamus, $F(1, 30) = 2.53$, $p = .122$, $n_p^2 = .078$.

Across training GLM repeated measures showed a significant difference for uFMA of feedback $F(2, 30) = 5.52$, $p = .009$, $n_p^2 = .269$ (see Figure 3), but no difference of lesion $F(1, 30) = .657$, $p = .424$, $n_p^2 = .021$, neither of thalamus $F(1, 30) = 2.17$, $p = .151$, $n_p^2 = .067$. Post-hoc paired-samples t-test indicated that uFMA scores were significantly higher for the contingent positive feedback group in the post (M = 14.6, SD = 7.81), than in the pre assessment (M = 11.2, SD = 6.93), $t(15) = -6.09$, $p < .000$.

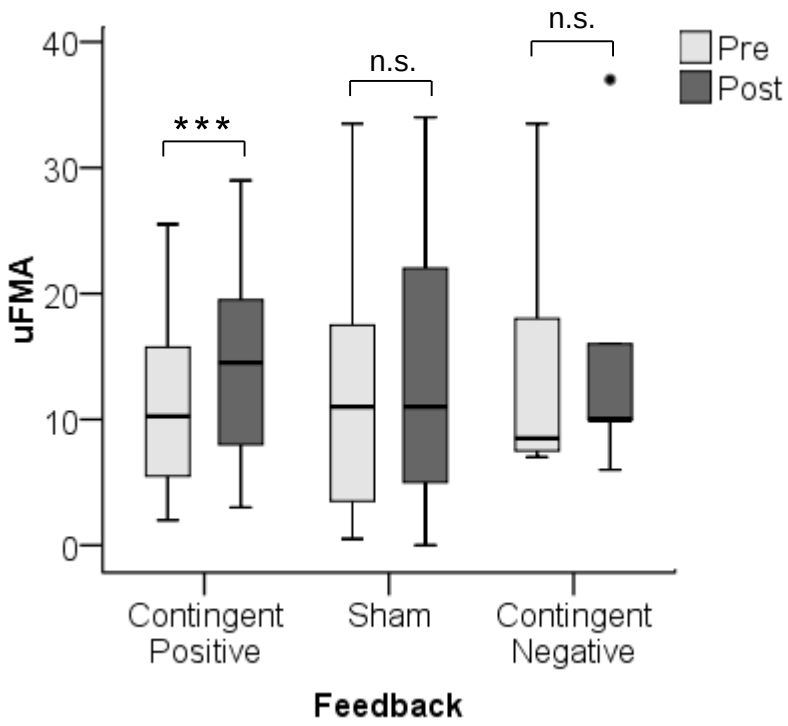


Figure 3. Upper-limb Fugl-Meyer Motor Assessment (uFMA) variation across training. Asterisks denote ***p < .001; n.s. = not significant; • = outlier

Patients with MEP+ in the contingent positive feedback group improved in motor function more than in the sham feedback group ($F(1, 10) = 11.8$, $p = 0.006$). We found that patients in the contingent positive feedback group with MEP+ improved more in uFMA ($t(7) = -7.04$, $p < 0.001$) compared to patients with MEP- ($t(7) = -3.24$, $p= 0.014$), while in the sham feedback group, no MEP related differences in uFMA scores were found (see Figure 4).

When averaging uFMA scores according to MEP presence (MEP+) or absence (MEP-) across groups, patients with MEP+ improved (MEP+: $t(11) = -4.63$, $p < 0.001$), while patients with MEP- did not (MEP-: $t(17) = -1.59$, $p = 0.130$).

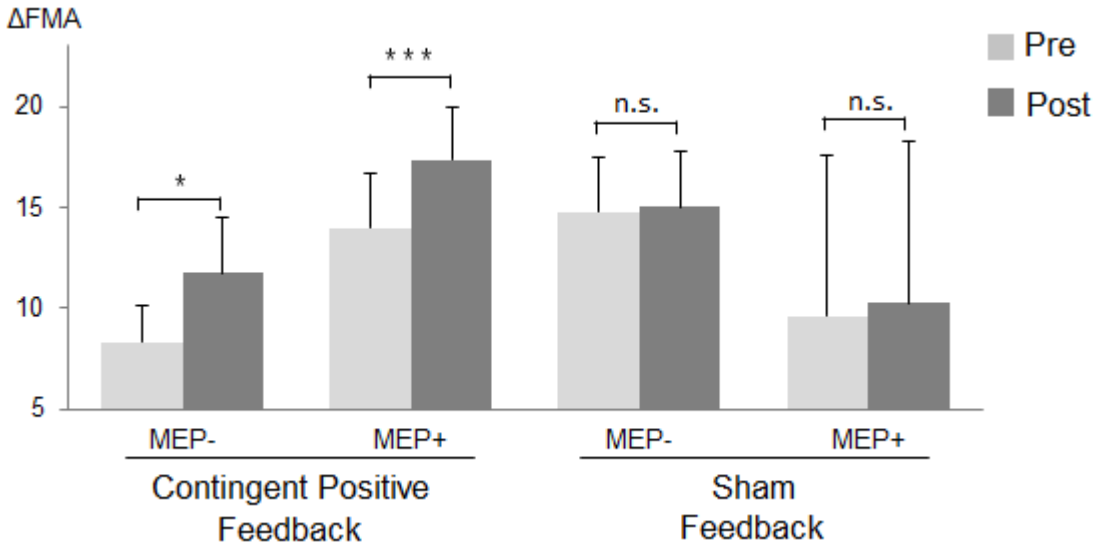


Figure 4 - Upper-limb Fugl-Meyer Motor Assessment improvements according to the presence of upper limb motor-evoked potential (MEP).

Event-related desynchronization (ERD)

Results for ERD showed significant differences since the beginning of training. An ANCOVA revealed for ERD on the ipsilesional channel C does not indicate effects of feedback, $F(2, 34) = 1.81$, $p = .179$, $n_p^2 = .096$, but revealed an effect of lesion, $F(1, 34) = 9.30$, $p = .004$, $n_p^2 = .215$. Post-hoc independent-samples t-test indicated that scores for ERD on the ipsilesional channel C were significantly better for subcortical lesion (M = -17.3, SD = 8.41) than for cortical lesion (M = -11.0, SD = 7.69), $t(37) = 2.43$, $p = .020$.

At the end of training an ANCOVA revealed no significant changes on the ipsilesional channel C, with no mean effect of feedback, $F(2, 33) = 1.32$, $p = .282$, $n_p^2 = .074$, neither of thalamus $F(1, 33) = 0.26$, $p = .612$, $n_p^2 = .008$, but revealed effect of lesion, $F(1, 33) = 9.98$, $p = .003$, $n_p^2 = .232$. Post-hoc independent samples t-test indicated that scores for ERD on the end of training were significantly better for subcortical lesion (M = -17.56, SD = 9.69) than for cortical lesion (M = -7.68, SD = 7.17), $t(36) = 3.60$, $p = .001$ (Figure 5).

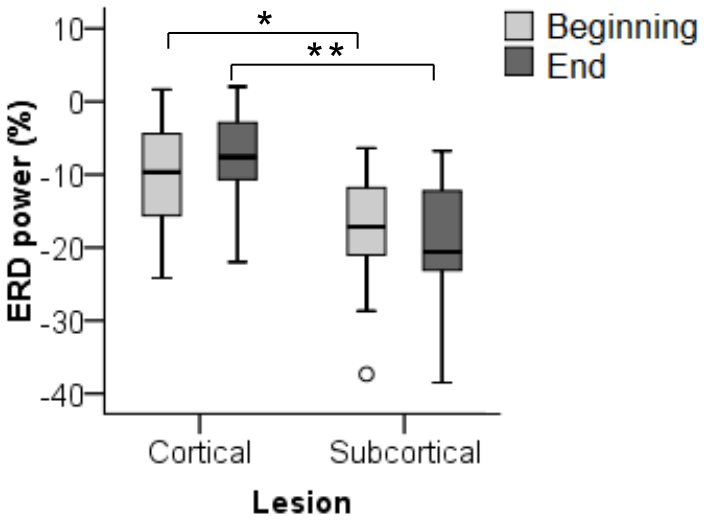


Figure 5 – Boxplot comparing event-related desynchronization (ERD) on the beginning and end of training according to type of lesion (lower values are better) in the ipsilesional channel C. Whiskers bars = standard deviation (SD) and ° = outlier.

4.0 – Conclusion

Sterr and Conforto (2012) believe that despite the incredible advancements in brain imaging, rehabilitation research and the growth of knowledge on brain plasticity over the last 20 years, at present there is little we can offer to patients with minimal recovery at present. Contrary to this opinion, the presented results indicate that the combination of contingent BMI training and physiotherapy is a promising rehabilitation strategy for chronic stroke patients with no residual hand movements. These patients presented improvements in motor function scales after only 4-weeks of daily BMI training and physiotherapy. Other results suggest that intensity and progression are the active ingredients of a rehabilitation program that drive beneficial neural plasticity leading to positive functional outcomes (Bowden et al, 2013). Thus it is reasonable to think that increasing the training intensity used in the here presented studies can lead to higher improvements in functional outcomes. Besides this, the functional outcomes can be improved if: I) patients have pure subcortical lesion, resulting in better control of BMI, and/or II) the corticospinal system is preserved, as indicated by presence of upper limb MEP on the paretic arm for instance.

5.0 – Publications

5.1 – Publication 1 – Brain-Machine-Interface in Chronic Stroke Rehabilitation

Journal: Annals of Neurology

Current status: Under revision (second time)

Personal Contribution:

- Data acquisition: fMRI, BMI training (orthosis and robot using EEG), magnetoencephalography (MEG), electromyography (EMG) and screening.
- Data analysis: part of statistics
- Text: part of methods and editing.
- Figures/Tables: Table 1. Supplementary tables 1 and 2.

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, behavioral physiotherapy. 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 x 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) 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.

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 participants[16]. 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.

[Table 1 about here]

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[17]. 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[18]. 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)[19] and a Goal Attainment Scale (GAS)[20]. (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[21] and BOLD signal functional magnetic resonance imaging (fMRI) to identify possible changes in brain function with the interventions[22].

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 pre-processed 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 [23,24]. In healthy subjects, cortical activity is lateralized to sensorimotor areas contralateral to the moving hand[22]. Activity associated with affected hand motions in well-recovered stroke patients resemble patterns identified in healthy individuals, mainly contralateral during movement and movement preparation[22,25]. 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[26]. 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 x 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[27] 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.

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[28,29]. (See Supp. Info. Section 5.3 and Video2).

[Figure 1 about here]

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.[30] A two-way mixed model ANOVA (with independent measures on group and repeated measures on time) showed a significant time (pre and post) x 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 7). 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[7,16,31].

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 x 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.).

[Figure 2 about here]

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, improves the beneficial effects of physiotherapy on motor function [32]. 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[33-35].

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 BMI training immediately preceding the relevant period of physiotherapy, operates as proposed by cortical stimulation[37-39], priming the effects of customary rehabilitation treatments[40] as shown in healthy participants[16]. We believe a contingent link between brain activity (intention to move) and paretic limb movements (othoses), 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[36] 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[31]. 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[35,38]. 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[41,42].

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[30,39]. The neuroplastic processes that characterize early brain reorganization after stroke change with time[34]. 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[30].

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.

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Figures Legends:

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. 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). * $p < 0.05$.

Table 2. 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).

Supporting Information

1 Patients

1.1 Patients recruitment

Patients were recruited via public information (German stroke associations, rehabilitation centers, hospitals) all over Germany.

Assessed for eligibility N=504.

Excluded N=465. Not meeting the inclusion criteria N=263. Declined to participate N=202. Other Reasons N=9. (See Supp. Fig. 1)

Causes of exclusion:

- fMRI not possible (e.g. pacemaker, metal pieces in the body, claustrophobia) N=36
- Depression N=10 (measured with Beck depression inventory), IQ below 80 (standard progressive matrices), or any psychological impairment (self-rated by patients or relatives, physician information letter e.g. medication or screening) N=18.
- Active finger extension (measured by asking the patient to extend the fingers while gently touching skin areas on top of the involved muscles and to grasp a pen or piece of paper). If any spontaneous finger extension activity was observed patients were excluded N=138
- More than one stroke N=6
- Not motivated to participate after detailed information of the study (mostly geographic distance as a reason) N=202
- Others (e.g. Brain trauma N=3; Aneurysma clipping N=2, Locked in Syndrome N=2; Severe Aphasia N=17; Severe Pain N=4; Neuroprothesis N=1; Leg amputation N=1; Cancer N=1) N=31

Patients could decide to leave the trial at any time for any reason. If the health status of more than 30% of the participants involved in the study is worsened and it cannot be ruled out that such a worsening is conditioned by the participation in the study, this would be considered to be a sufficient reason to stop the trial.

This enrollment process resulted in 32 patients involved in the randomized double blind study allocating 16 patients to each group (16 experimental-contingent positive and 16 sham-control). In the sham group 2 patients did not receive correct allocated intervention because of technical issues to complete BMI intervention (N=1) and because of faking functional deficit to get enrolled in the study (N=1).

The number of patients enrolled in the study was limited by the recruiting and our very strict inclusion criteria, the funding and time to perform the study (we performed 2 BMI and 2 Physotherapy sessions each day and recorded many pre and post EEG, EMG, psychophysiological, clinical and fMRI measurements).

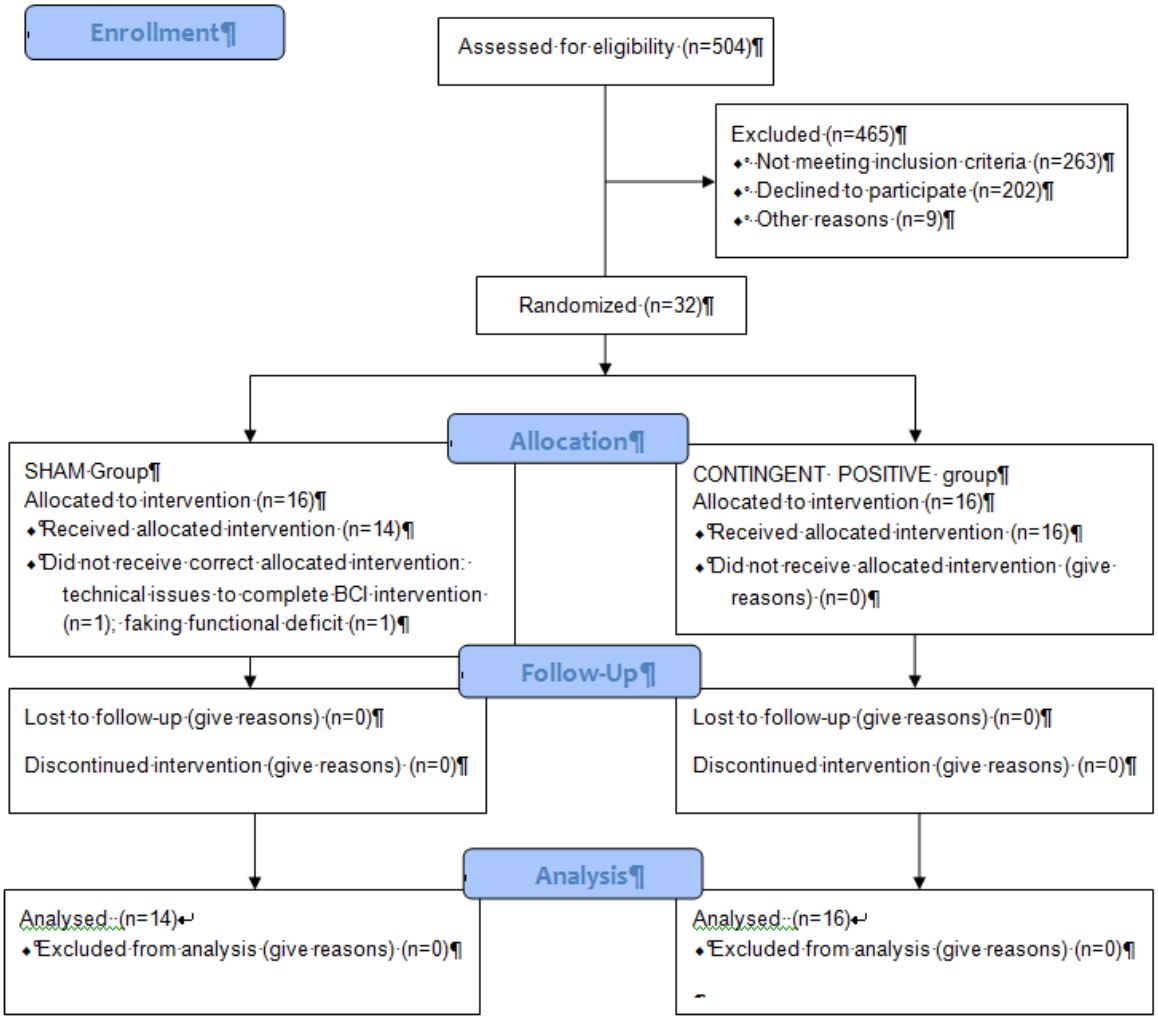

Figure 1. CONSORT flow diagram. Study enrollment diagram. 504 patients were screened to be eligible for the study and 465 were excluded. 32 underwent intervention and were randomly assigned to 2 groups depending on the BMI feedback received: a) contingent positive feedback groups (brain activity was contingently and concurrently linked with orthoses movements) and b) sham feedback group (orthoses movements were random and not associated with brain activity). In the sham group 2 patients did not receive correct allocated intervention.

1.2 Individual demographic, functional data and lesion localization

Experimental– Contingent Positive Group (C+)

ID	Gender	Age	Time Since Stroke (years)	Lesion location	UL-FMA Pre1/Pre2 Post	GAS (hand) Pre/Post	MAL Pre/Post	BMI – runs
48	M	45	4	Subcortical lesion. CI, genu, external capsule, putamen, thalamus, claustrum, head and tail of caudate nucleus, corona radiate, insula.	60/54 59	(0/2)	1/28	281
89	F	51	3	Subcortical lesion. Corona radiata, external capsule, thalamus, putamen, CI, genu.	56/59 57	(0/1)	0/0	242
154	M	62	4	Subcortical lesion. Parietal lobe. White matter of inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus. Corona radiata, thalamus, genu, partially CI, external capsule. Also affection the white matter underlying the right insular cortex.	49/48 51	(0/1)	5.5/5	268
155	F	30	5	Subcortical lesion. Frontal, parietal and temporal lobe. White matter of postcentral gyrus; middle temporal gyrus and angular gyrus. CI, Thalamus, external capsule, genu, tail of caudate nucleus.	80/83 88	(0/3)	8/7	295
258	M	47	10	Subcortical lesion. Corona radiata, external capsule, putamen, posterior CI, thalamus.	72/72 76	(0/3)	16/24	242
261	F	68	4	Subcortical lesion. Frontal and parietal lobe. White matter of inferior frontal gyrus; pre and poscentral gyrus; supramarginal gyrus. Multiple nectrotic vesicles. Trunk of corpus callosum, head of caudate nucleus, corona radiata, putamen, external capsule, CI, genu, thalamus.	57/58 58	(0/1)	0/0	269

ID	Gender	Age	Time Since Stroke (years)	Lesion location	UL-FMA Pre1/Pre2 Post	GAS (hand) Pre/Post	MAL Pre/Post	BMI – runs
263	F	34	1	Mixed lesion. Frontal and parietal lobe. Middle and inferior frontal gyrus; postcentral gyrus. Corona radiata, caudate nucleus, external capsule, CI, genu, thalamus, putamen, insula.	64/62 68	(0/2)	3.5/20	397
363	M	49	11	Subcortical lesion. Parietal lobe. White matter of Precentral gyrus. Corona radiata, anterior CI, putamen, external capsule, thalamus, insula.	55/63 64	(0/1)	6.5/5	312
394	M	63	6	Subcortical lesion. Frontal and parietal lobe. Extensive white matter hypodensity of inferior frontal gyrus and precentral gyrus. Corona radiata, head of caudate nucleus, CI, genu, external capsule, putamen, thalamus, insula.	61/57 67	(0/0)	2.5/2	254
400	M	39	12	Mixed lesion. Frontal and parietal lobe. Encephalomalacia in the frontal and parietal lobe. Middle and inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus.	80/74 80	(0/2)	24.5/27	253
453	F	32	2	Mixed lesion. Frontal, parietal and temporal lobe. Inferior frontal gyrus; pre and postcentral gyrus. Corona radiata, head of caudate nucleus, CI, genu, external capsule, thalamus, putamen, insula.	67/59 68	(0/1)	0/5	302
523	F	39	13	Mixed lesion. Frontal, parietal and temporal lobe. Superior, medial, middle and inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus; angular gyrus; middle and inferior temporal gyrus. Corona radiata, head of caudate nucleus, CI, genu, putamen, thalamus, external capsule, trunk of corpus callosum, insula.	57/59 58	(0/0)	0/4	308

ID	Gender	Age	Time Since Stroke (years)	Lesion location	UL-FMA Pre1/Pre2 Post	GAS (hand) Pre/Post	MAL Pre/Post	BMI – runs
554	F	52	4	Subcortical lesion. Corona radiata, head of caudate nucleus, external capsule, CI, genu, putamen, thalamus, globus pallidus, claustrum.	68/79 84	(0/3)	34/37	282
563	M	40	7	Subcortical lesion. CI, genu, external capsule, claustrum, putamen, head of caudate nucleus, thalamus.	65/68 71	(0,5/3)	4.5/27	305
615	M	26	2	Mixed lesion. Frontal and parietal lobe. Inferior frontal gyrus; precentral gyrus. Insula cortex, external capsule, CI, head of caudate nucleus, genu, putamen, thalamus.	66/68 71	(0/1)	12/15	239
623	M	68	2	Mixed lesion. Frontal and parietal lobe. Inferior frontal gyrus; precentral gyrus. External capsule, putamen, thalamus, CI, genu, insula.	66/63 67	(0/3)	8.5/44	247

Table 1. Demographic description of the experimental the experimental group patients. Pre in GAS and MAL indicates (Pre1+Pre2)/2.

Control-Sham Group (S)

ID	Gender	Age	Time Since Stroke (years)	Lesion location	UL-FMA Pre1/Pre2 Post	GAS (hand) Pre/Post	MAL Pre/Post	BMI – runs
35	M	61	7	Mixed lesion. Frontal, parietal and temporal lobe. Middle and inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus; middle and inferior temporal gyrus. Corona radiata, head of caudate nucleus, CI, genu, external capsule, claustrum, putamen, truck of corpus callosum, insula, thalamus.	80/83 75	(0/2)	5/6	273
207	M	36	4	Subcortical lesion. Head of caudate nucleus, CI, genu, external capsule, putamen, claustrum, corona radiata.	91/88 88	(0/3)	12/24	287
241	M	36	4	Mixed lesion. Frontal, parietal and temporal lobe. Inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus. Corona radiata, head of caudate nucleus, CI, genu, putamen, posterior part of external capsule, thalamus, claustrum, Gl. Palidus, trunk of corpus callosum, insula.	49/48 51	(0/0)	4/4	258
510	M	44	10	Mixed lesion. Frontal and parietal lobe and the adjacent white matter. Superior, medial, middle and inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus. Corona radiata, head of caudate nucleus.	73/75 85	(0/3)	17.5/23	323
516	F	51	2	Subcortical lesion. Head of caudate nucleus, CI, genu, putamen, thalamus, corona radiata, external capsule, claustrum.	73/75 72	(0/2)	0/2	314
533	M	32	18	Subcortical lesion. Corona radiata, CI, genu, thalamus, external capsule, putamen, claustrum, insula and	91/91 93	(0/3)	42/32	262

536	M	50	1	Mixed lesion. Frontal and parietal lobe and adjacent white matter with multiple necrotic. Middle and inferior frontal gyrus; pre and postcentral gyrus; middle temporal gyrus.	59/51 55	(0/2)	13/17	292
551	M	62	4	Mixed lesion. Frontal, parietal and temporal lobe. Middle and inferior frontal gyrus; pre and postcentral gyrus. Corona radiata, external capsule, claustrum, putamen, insula.	59/61 61	(0/1)	10.5/15	304
578	M	28	19	Mixed lesion. Frontal and parietal lobe. Precentral gyrus. Corona radiata, thalamus, putamen, posterior CI, claustrum, external capsule, insula.	67/66 63	(0/1)	4/7	293
593	F	71	2	Mixed lesion. Frontal, parietal and temporal lobe. Superior, medial, middle and inferior frontal gyrus; pre and postcentral gyrus. Corona radiata,thalamus, putamen, posterior CI partially, genu, external capsule, trunk of corpus callosum.	48/45 40	(0/2)	0/0	297
610	M	56	2	Mixed lesion. Frontal, parietal and temporal lobe. Middle and inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus; angular gyrus. Trunk of corpus callosum, corona radiata, caudate nucleus, claustrum, putamen, CI, genu, thalamus, external capsule, insula.	57/56 56	(0/1)	7.5/6	308
612	F	53	1	Mixed lesion. Frontal, parietal and temporal lobe. Inferior frontal gyrus; pre and postcentral gyrus; middle temporal gyrus. Corona radiata, CI, genu, external capsule, putamen, thalamus.	61/60 64	(0/2)	0.5/20	271

ID	Gender	Age	Time Since Stroke (years)	Lesion location	UL-FMA Pre1/Pre2 Post	GAS (hand) Pre/Post	MAL Pre/Post	BMI – runs
613	F	64	2	Mixed lesion. Frontal and parietal lobe. Superior, medial, middle and inferior frontal gyrus; pre and postcentral gyrus.	72/68 77	(0/1)	9/18	285
622	F	54	1	Subcortical lesion. Corona radiata, body of caudate nucleus, external capsule, putamen, genu, anterior CI, insula cortex.	50/48 49	(0/1)	4.5/18	297

Table 2. Demographic description of the control group patients. Pre in GAS and MAL indicates (Pre1+Pre2)/2.

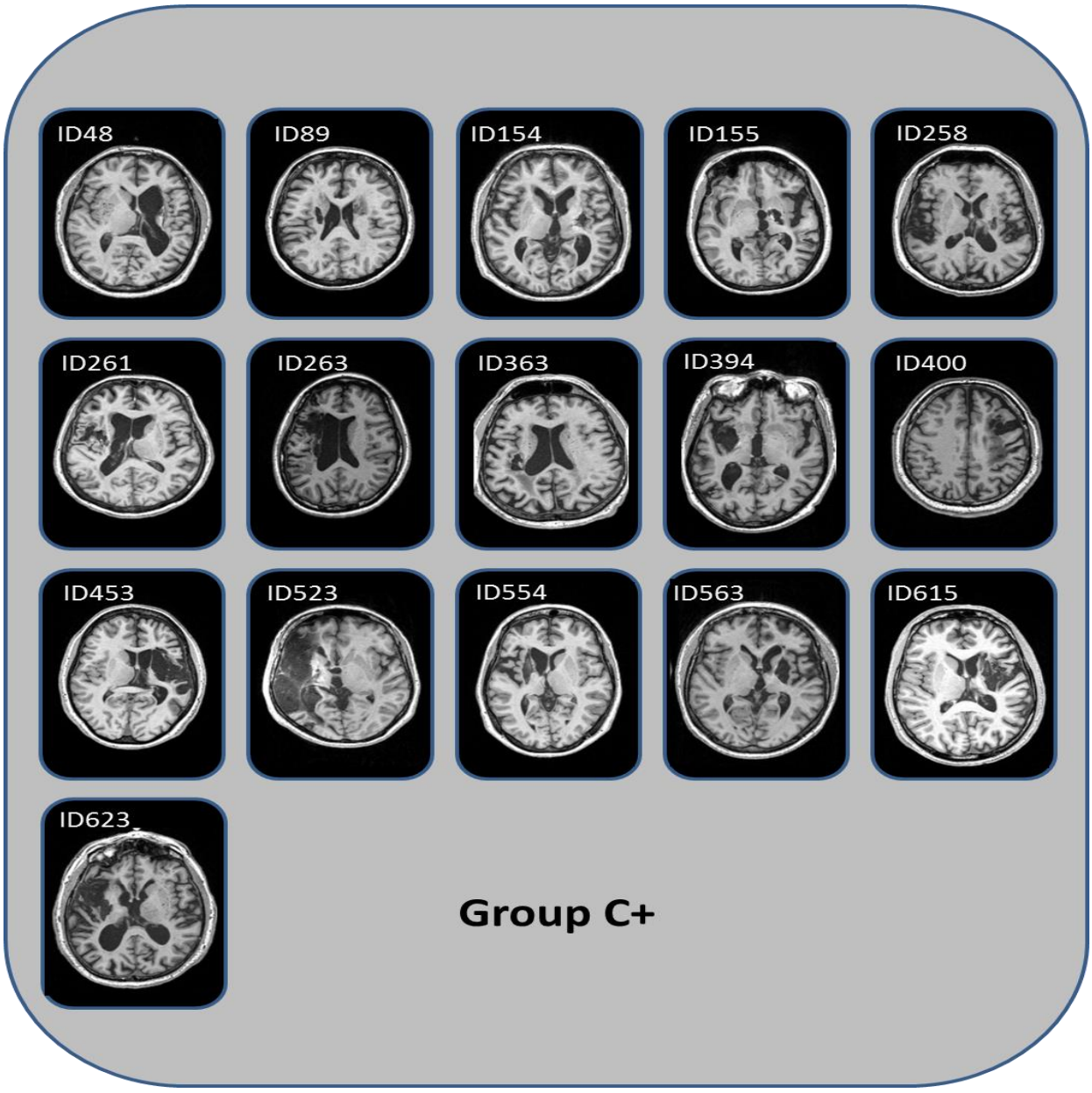

Figure 2. MRI showing lesion location of the patients from the experimental or contingent positive group (Group C+).

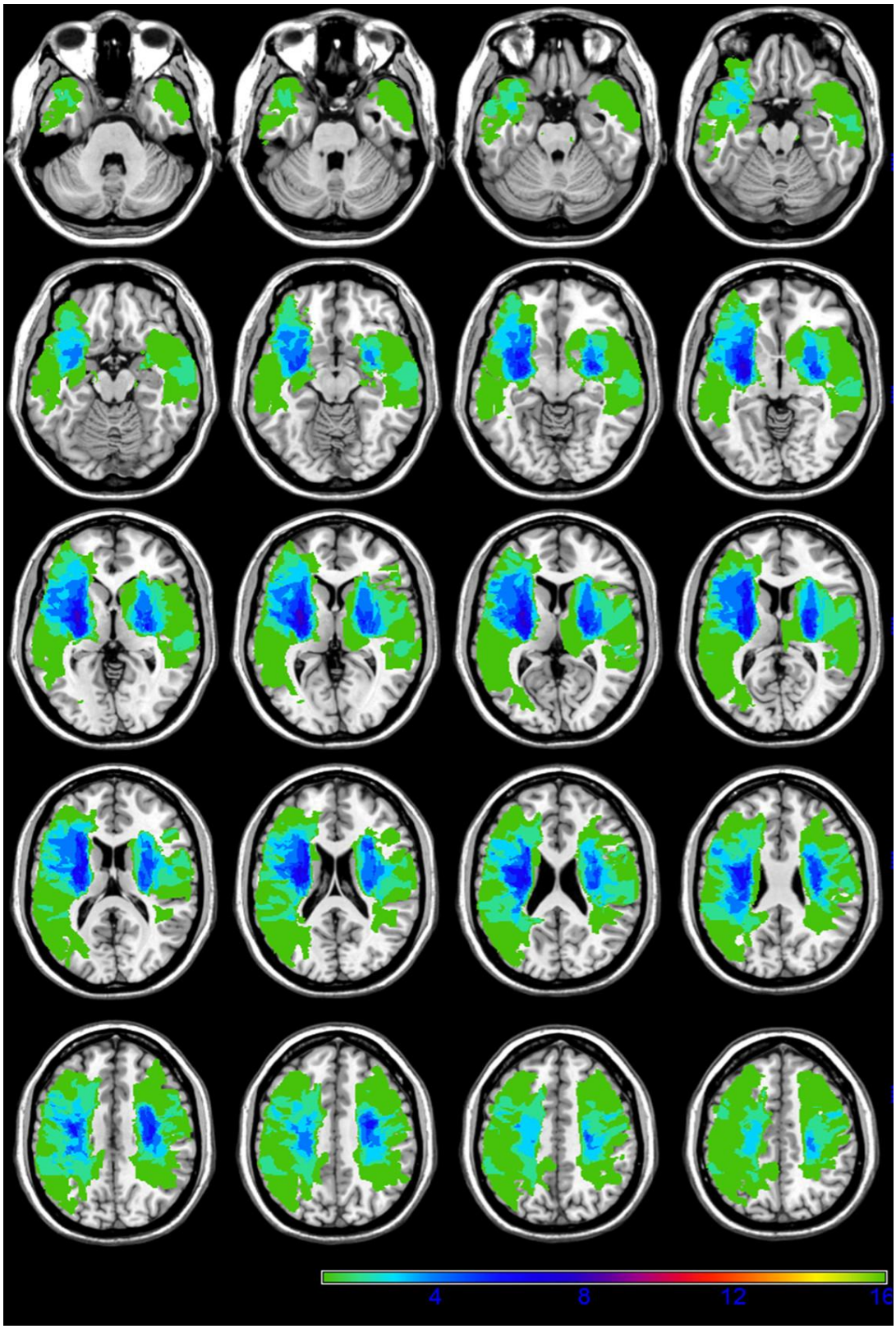

Figure 3. MRI lesion mask showing lesion location of the patients from the experimental or contingent positive group (Group C+).

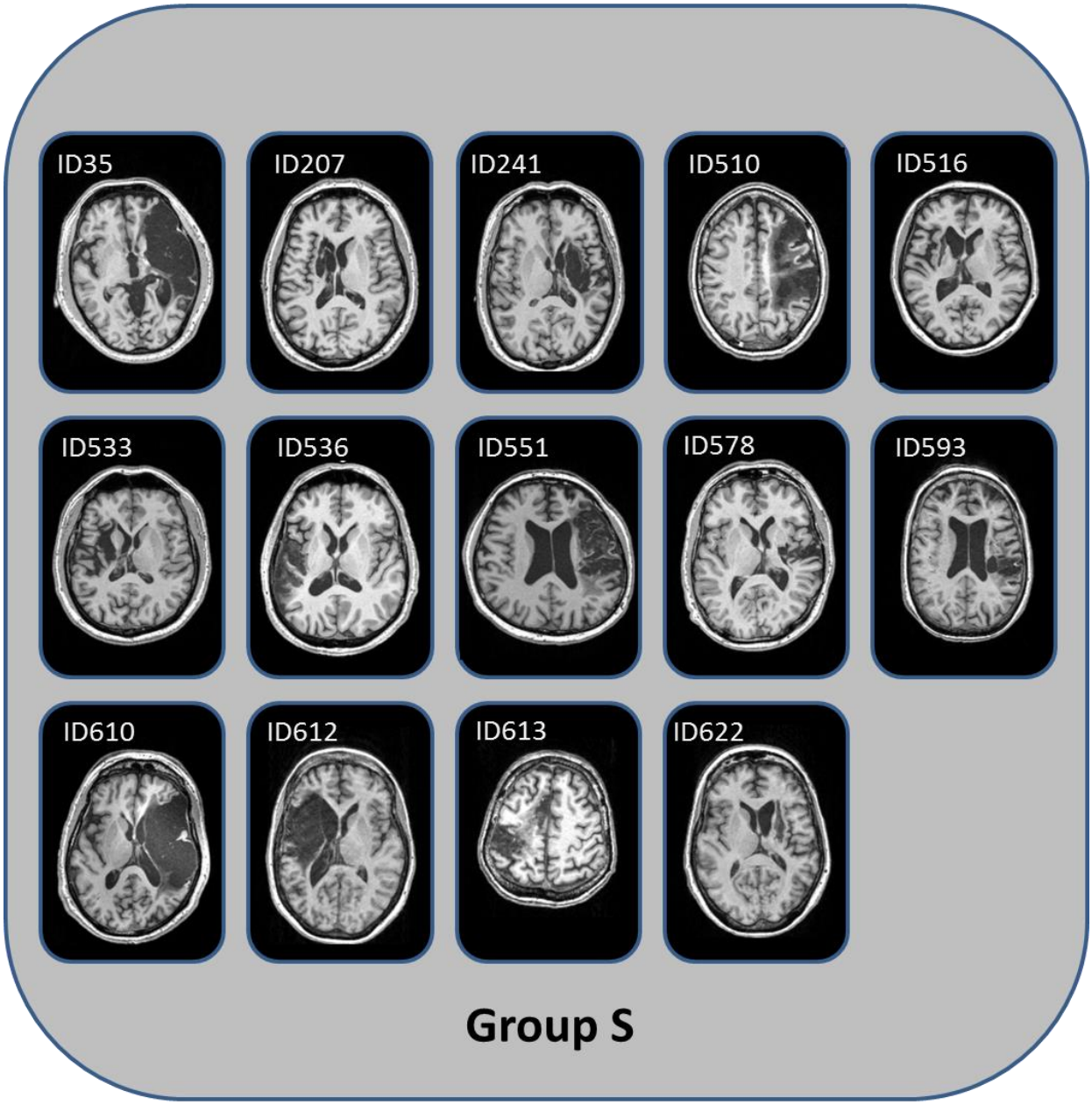

Figure 4. MRI showing lesion location of the patients from the control or sham group (Group S)

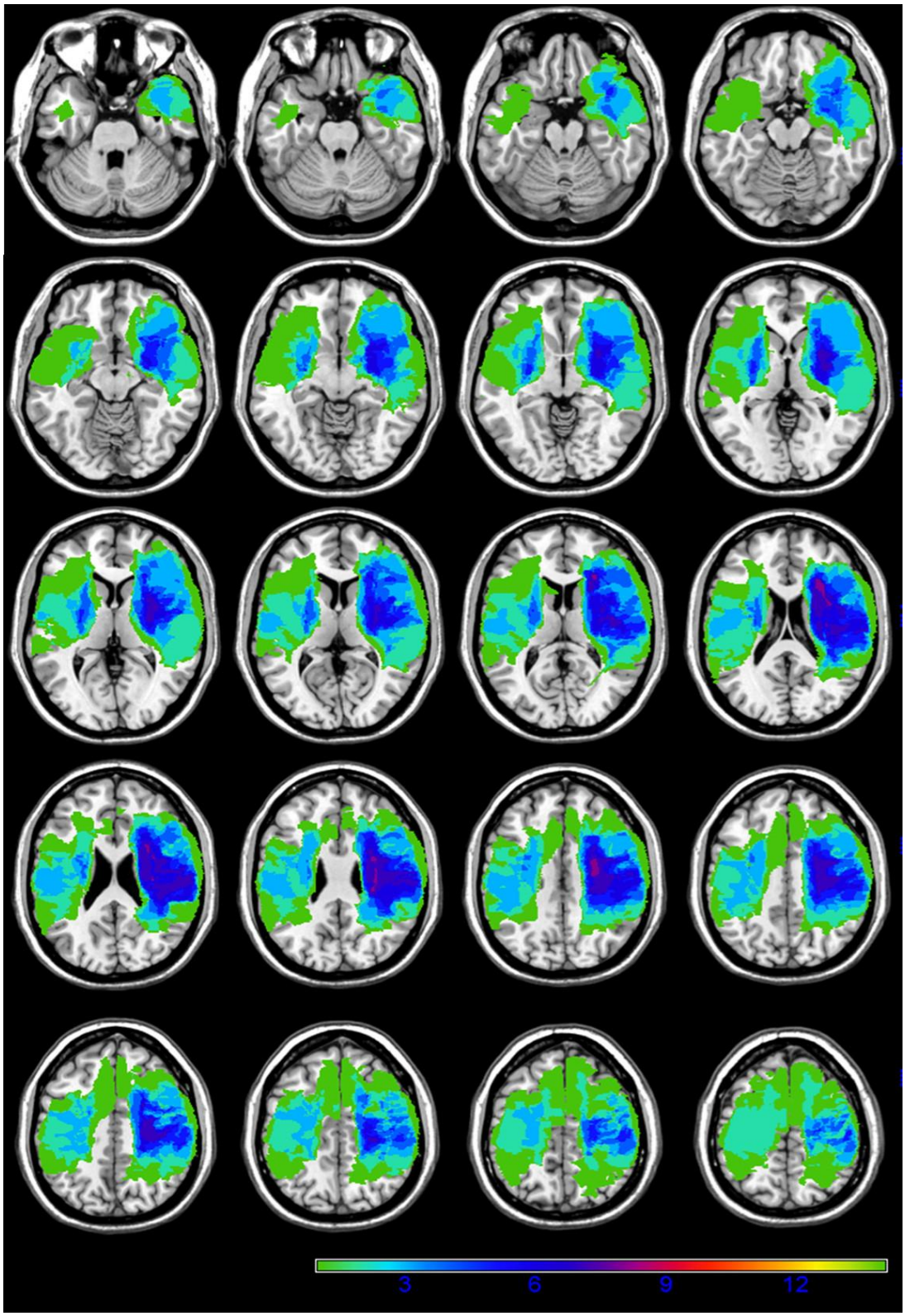

Figure 5. MRI lesion mask showing lesion location of the patients from the control or sham group (Group S)

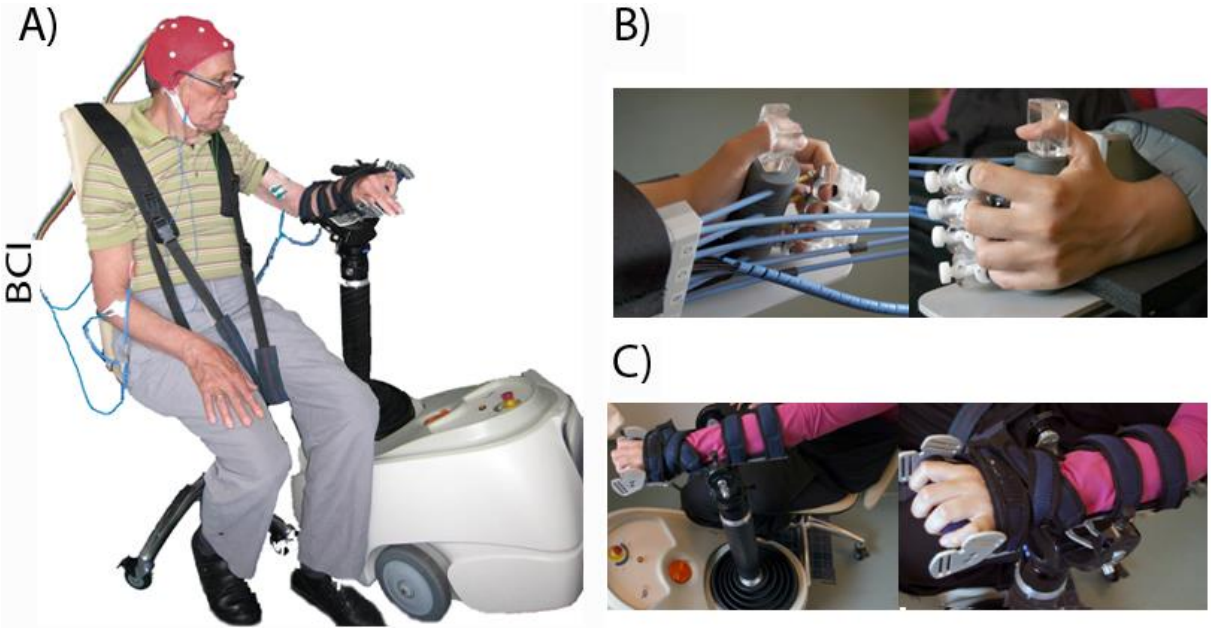

Figure 6. Robot/Orthosis BMI configuration. Procedure of the online BMI for paralyzed chronic stroke patient rehabilitation. A) User wearing the 16-channel EEG system with his arm and hand attached to the ReoGo robotic arm from Motorika, Israel. B) Anterior and posterior view of the hand of a user attached to the robotic hand orthosis. C) Arm of a user gently strapped to the motorika “ReoGo” robot arm handle.

2. Behavioral/clinical observation level assessments:

2.1 Modified upper limb Fugl-Meyer Assessment (FMA)

(Maximal score is 114 points; values 0-2, 0 = no activity, 1= partly activity; 2= perfect activity)

A higher score means better functional state. The FMA was used in a modified but widely accepted version of the regular Fugl-Meyer scale previously used in other studies.[18] The only modification from the regular upper limb FMA scale is the exclusion of scores related to a) coordination and speed and b) reflexes. We excluded these scores because: a) the patients in this study could not touch their noses with the index finger fully extended because they had no remaining finger extension (inclusion criteria) and b) reflex scores have been proved to introduce unreliability into the measurement.[18] These two sections of the scale were disregarded because if included would reduce sensitivity of the measurement. The FMA uses an ordinal scale for the quantification of motor impairment.

2.1.1 Modified upper limb Fugl-Meyer Assessment

scores are composed of the subscores:

- passive joint movement (12 movements; max 24points)
- pain during joint movements (12 movements; max 24points)
- sensibility (6 items; max 12points)
- motor skills upper arm and forearm
- motor skills hand and fingers

2.1.2 Modified FMA arm is based on motor skills of upper arm and forearm (15 items; maximal score is 30 points) from which reflexes scores are not included to avoid unreliability of testing reflexes;[18] the movements are:

1- 6. “flexorsynergies” touch the ipsilateral ear - assessed movements: Elevation, shoulder retraction, abduction, external rotation, forearm supination.

7-9. “extensorsynergies” touch the contralateral knee – assessed movements: shoulder adduction/internal rotation, elbow extension, forearm pronation.

10. hand to lumbar spine
11. shoulder flexion 0-90°
12. pro-supination elbow in flexion
13. shoulder abduction 0-90°
14. shoulder flexion 90-180°
15. pro-supination elbow in extension.

2.1.3 FMA hand is based on motor skills of hand and fingers (12 items; maximal score is 24 points); the movements are:

1. wrist stability in 15° extension, elbow at 90°
2. wrist flexion/extension elbow at 90°
3. wrist stability in 15° extension, elbow at 0°
4. wrist flexion/extension elbow at 0°
5. wrist circumduction
6. finger flexion
7. finger extension
8. grasp against resistance with metacarpophalangeal joints of digit 2and flex the proximal interphalangeal joints
9. grasp of a scrap of paper
10. grasp a pencil
11. grasp a cylinder

12. grasp a tennis ball

Only the motor part of the "classic" Fugl Meyer Score (ranging from 0 to 66) has shown to be reliable and valid[43] and therefore we used the motor part of the upper limb FMA leaving out the scores for reflexes as primary outcome measure. The modified upper limb FMA we used comprising the somatosensory, sensibility, pain and motor parts. Again, we used as primary outcome measure the motor section of the upper limb FMA without reflexes scores (combined arm and hand modified FMA) and therefore no other modalities such passive joint movement part of the FMA could influence our primary outcome measure result. Furthermore we want to emphasize that we eliminated variance and increased reliability of our primary outcome measure ignoring reflexes scores from the upper limb motor part of the FMA[18].

2.1.4 Primary outcome measure: Combined hand and arm modified upper limb Fugl-Meyer-Assessment scale (cFMA) scores (maximal score is 54 points)

This is the combination of 2.1.2 and 2.1.3 scores and was used as primary outcome measure because of its direct relation with the intervention training based on arm and hand grasping movements.

2.2 Ashworth Scale

Assesses: resistance against passive joint movements (spasticity)

Maximal value: 56 (14 movements, 0-4)

A low score indicates a good outcome

	Maximal score	Minimal score	Group	Pre Max. Score	Pre Min. Score	Mean ± SD Pre.	Mean ± SD Pre-Post Delta
Modified upper limb FMA (mupFMA)	114	0	C+	81·5	48·5	64·03±8·6	3·91±2·8 *
			S	89·5	46·5	65·89±14·7	0·46±4·7
cFMA	54	0	C+	25·5	2	11·15±6·9	3·4±2·2 *
			S	33·5	0·5	13·28±10·7	0·36±4·2
Hand part	24	0	C+	7·5	0	3·25±2·4	0·81±1·1 *
			S	11	0	3·32±3·3	0·39±1·8
Arm part	30	0	C+	18·5	1·5	7·91±5·1	2·59±2·1 *
			S	24	0·5	9·96±8·2	0·03±3·1

Table 3. Modified FMA scale. We used the upper limb part of the FMA test and removed the scores related to reflexes, speed and coordination (modified upper limb FMA) comprising 114 points. As primary outcome measure we used the motor part of the modified upper limb FMA (cFMA) comprising 54 points combining hand (24 points) and arm (30 points) parts. In this table we present maximal and minimal values of baseline scores. Pre scores stands for the average between 2 different baseline measurements. Mean ± SD for pre-post differences in scores (Delta) are presented. Asterisks represent statistically significant pre-post delta difference. C+ contingent group (experimental). S sham group (control)

2.3 Goal attainment scale (GAS)

Assesses: attainment of a personalized functional goal concerning control of the paralyzed hand and arm or performance of a specific daily life activity. Two important meaningful and realistic goals are selected in agreement between patient and therapist concerning the use of the hand (e.g. to hold and release a toothpaste tube). Scaling ranged from 0 (baseline; no change) to 4 (much better than expected).

Maximal value: 4

A high score indicates a good outcome

2.4 Modified Motor Activity Log (MAL)

Assesses: the patient's use of the paralyzed hand in daily life activities (patient's point of view)

Maximal value: 65 (13 items, value 0-5)
A high score indicates a good outcome

We decided to measure the MAL scores and other functional measures despite of being subjectively reported by the participants and weakly associated with real changes in outcome because they can serve to bolster the importance of a small gain in cFMA scores in the experimental group. Despite of their subjective nature we decided to include them because of the importance of self-rating correlated to quality of life and motivation and because of their frequent use in the literature.
GAS is not a questionnaire but a custom made scale on the basis of individual and realistic functional goals important for the patient. Furthermore the examiner assesses if the patient is able to perform the task defined as relevant goal for the patient. There is no “objective” assessment at activity level that can measures hand and arm function, which was the aim of our training. Assessments at activity level like the FIM and Barthel Index are independent of motor recovery[44] and thus do not meet the aim of the study.
We indeed used Stroke Functional Rating Scale (SFR), the NIH stroke scale and quality of life scale (Seiqol). SFR and NIH scales did not present any variation in our patients (data available if requested).
Arm Motor Assessment Test was not performed because its similarity to Fugl Meyer.
We decided not to perform the scored Functional Independence Measure subscale for upper limb function test because there is no “objective” assessment at activity level in the test measuring hand and arm function, which was the aim of our training.

3 Behavioral/clinical observation level statistical analysis of baseline scores between groups:
(Baseline experimental group) VS (Baseline control group): where baseline is □Pre = (Pre1+Pre2)/2

3.1 Combined hand and arm modified upper limb Fugl-Meyer-Assessment scale (cFMA) scores (cFMA)
Independent-sample t-test comparing the experimental group and the control group for pre-FM total scores (t(1,28) = -0•430, p=0•671) did not reach statistical significance.
3.2 Ashworth

Mann-Whitney U tests comparing the experimentalC+ group and Sthe control group for pre-Ashworth scores (U = 69•5, P = 0•077) did not reach statistical significance.

3.3 MAL

Mann-Whitney U tests comparing the experimentalC+ group and Sthe control group for pre-MAL scores (U = 67•5, P = 0•82) did not reach statistical significance.

3.4 GAS Hand

Mann-Whitney U tests comparing the experimentalC+ group and Sthe control group for pre-GAS Hand scores (U = 105, P = 0•79) did not reach statistical significance.

4. Placebo

Two expectancy-placebo questionnaires were filled out: 1) after each fifth treatment session and 2) at the end of the treatment. One questionnaire contained 15 questions (scored on Likert scale from 1 to 6) concerning: A) Therapeutic staff: professional behavior of the therapists, well-being during training, expectations of improvement. B) Functioning of BMI-robot/orthosis system: The second contained 12 questions (scored 1-6) concerning, comfortable and proper functioning of BMI-robot/orthosis system.

Examples of the two questionnaires

A. Therapeutic staff

I noticed that my therapists are very capable.

I believe I would be much better at the end of the therapy.

B. Functioning of BMI-robot/orthosis system

I brought the hand and arm movements properly to my mind

The robot/orthosis resembles my movement intention and moved accordingly.

5. Intervention

5.1 BMI Calibration

One EEG-screening was performed the day before the first training session and was used as a calibration session to identify the best features (electrodes and frequency bins) to be used by the BMI classifier. In this screening session the subjects were randomly presented with visual and auditory cues corresponding to three different

tasks indicating to either relax (task 1), actively open and close the healthy hand (task 2) or try to open and close the paretic hand upon his/her capacity (task 3). After a 5 second period of performing the tasks, a rest cue was presented indicating patients to stop. The inter-trial-interval was randomized between 5 and 7 seconds. The patients underwent 4 to 5 runs of 25 trials each. The features to be used by the BMI platform were defined through a visual inspection of the R-square values[45] obtained when comparing EEG activity during rest versus intention to move (hand open and close). The power in the ipsilesional electrodes and frequency bins with highest R-square values were identified as customized sensorimotor rhythm (SMR) features and used as input for the classifier. In the online application, a center-surround local spatial filtering approach, in which a radial difference-of-Gaussians function was used to weight the electrodes at each spatial location, was applied to the EEG activity from each electrode. The spatial filtered EEG was modeled as an autoregressive (AR) process[46] over a normalized sliding temporal window 500 msec in duration shifting every 40 msec, and power spectral density of the AR-model for each electrode was computed to calculate the mean SMR-band power in each chosen frequency bin.

The BMI software maintained a history of the mean neural rhythm amplitude estimate from each trial and assigned this to a distribution representing observations for the two classes (rest or motor intention). The classification threshold, defined as the zero mean distance to the two distributions, was adaptive to account for changes in the shapes of these distributions over the course of training.

5.2 BMI Training

While assistive or biomimetic BMI systems aim for continuous high-dimensional control of robotic devices or functional electric stimulation (FES) of paralyzed muscles to substitute for lost motor functions[47,48], restorative or biofeedback BMI systems aim at normalization of neurophysiological activity that might facilitate motor recovery. Therefore, sensorimotor rhythm (SMR) desynchronization at the EEG electrodes over the ipsilesional motor cortex was used to move the robot and to re-train reaching movements of the paralyzed arm. The duration of the intervention was chosen based on a previous study that used a similar technique in patients with relatively similar impairment[7]. Power was similarly based in that study.

A warning auditory cue was presented to the patient and 2 seconds afterwards an auditory trigger signal (”GO”) initiated the trial which lasted for 5 sec. If the patient produced a desynchronization of his/her pre-identified sensorimotor rhythm (SMR) during this period his arm was moved along a predefined trajectory adjusted to the patient’s range of motion. The BMI2000 two-class classifier (motor intention versus rest) sends an output every 40 msec to the robot/orthosis. Five consecutive classifier outputs for the same condition, i.e. detecting either intention to move or rest five consecutive times, were needed in order to send the orthosis a no-move (zero velocity value) or a move (positive velocity) command. This was performed to avoid false positives and false negatives that could arise due to EEG signal noise. During the sham feedback condition the output of the BMI classifier changed with a probability of 10 %, i.e. when the output indicates moving there is a probability of 10 % that next BMI output will be to stop and vice versa, asking again for 5 consecutive outputs of the same sign to change the movement status of the orthosis. When the patient was able to extend the arm correctly (with gravity compensation), or the 8th training session was reached, BMI-training was switched from the arm to the hand orthosis.

In the control group the patients received sham feedback which means random movements of the robotic orthosis not linked to the patient ipsilesional sensorimotor rhythm (SMR) oscillations. The percent of time the orthosis moved during the training resembled the mean percent of time the orthosis moved during a training session of patients in the experimental group in which the patients SMR oscillations are directly linked with the orthosis movements. In the experimental group the BMI classifier uses ipsilesional SMR oscillations to decode whether the patient is trying to move the affected limb or not. On the other hand, the outputs of the BMI classifier (trying to move - resting) were randomly adjusted for the sham feedback group. In both groups the BMI sends its output, i.e. classification every 40 msec. To avoid EEG noise contribution to the output of the BMI classifier and therefore to avoid confusion in the feedback for both groups, a time filter was used. This time filter limited the speed of change in status of the orthosis (status A: movement – status B: stop) to 200 msec because 5 consecutive outputs of the brain machine interface (BMI) classification (move or stop) of the same class were needed to change the previous orthosis status. This time filter made the system more robust and resistant against noise in the EEG signals and produced a slow and harmonic appearance of the feedback signal in both groups. By chance the

patients in the sham group were presented sometimes with positive and negative feedback because their brain state (decrease/increase in SMR power) occasionally matches the orthosis status (movement/stop) and at some other moments their brain state (decrease/increase in SMR power) will be negatively correlated with the orthosis status (stop/movement). This occasionally correct feedback assists patients of the sham group to perceive the BMI feedback as veridical. To verify the identical perception of the BMI in both groups standardized questionnaires were answered after every week of treatment requiring a judgment of the subjective perception of the correctness of and attitudes toward the BMI treatment (the questionnaires could be provided if needed).

At no point in time a significant difference between the subjective perception of the veridical character of the BMI functioning between groups appeared (See Suppl. Fig. 7) confirming the compatibility and credibility of both groups independent of the timing of feedback. None of the patients in the sham group reported any confusion of any perception of inconsistency throughout the whole treatment. All patients wanted to receive more sessions at the end and therefore patients motivation and energy stayed intact or was even increased. Furthermore, patients were instructed to avoid blinking, coughing, swallowing, chewing, head movement and body compensation movements and were warned explained that these actions could bias the BMI movement intention classification. The exact instructions to the patients were warned and explained:

1. Please sit relaxed in a comfortable position, look at your hand and listen to the auditory cues
2. When you hear the auditory cue “Left Hand” get ready and concentrate on your affected arm and wait for the “GO” cue
3. Only after the “GO” cue try to move your paretic arm/hand (reaching and grasping during arm orthosis and hand opening and closing during hand orthosis training). After the “GO” the orthosis will be ready to support your movements.
4. Avoid blinking, head movements, chewing, swallowing, coughing and compensatory movements with the body during the run. We understand you cannot perform the movement as we ask you but please try to do so as without extra compensatory movements. We will “read” the brain activity with some delay and will move the hand/arm for you with the orthosis. It is very important that you try to move your hand/arm naturally without extra effort since we want to train the natural connections between the brain and the affected muscles.

5. The computer will tell you with an “END” auditory cue the moment in which you can relax and wait for the next “Left Hand” and “GO” cues after which you will have to try to move your affected hand/arm again. Please be aware that it is very important to stay still during these little breaks after the “END” auditory cues. Only when you try to perform the movement correctly without compensatory movements and you rest correctly without movements you interaction between yourself and the system will be successful.

6. The movement starts from the position you stopped after the last “END” cue. This means that if you were extending at that point in time you will have to continue extending or flexing otherwise. At the maximal extension and flexion point a “beep” will help you understand that you need to flex if you were extending and vice versa.

7. Every run takes 2 minutes and 10 seconds and then we will have a brief break of 30 seconds in which you can move blink, cough, drink water and do whatever is necessary to feel comfortable and start with the next run again. We will make from 16 to 20 runs in todays’ session and you can have as many breaks as you need and can stop the training if you want so too.

8. For the success it is of vital importance that you look at your hand/arm. This will make the system identify the movement intention easier. Please be aware that movements of the other arm or your feet can influence negatively the system. Please try to avoid all training unrelated movements and reflexes that we discussed before.

Our placebo questionnaires certified no differences in functionality perception of the BMI system in both patient groups. Still, an unconscious “mismatch” –effect between the actual EEG and the orthosis movement could generate a deterioration of learning in the control group. While such an unconscious “conflict” cannot be excluded completely usually it manifests itself at the conscious level as a more negative experience and negative emotional valence comparable to “loss of control”- experimental procedures. The questionnaires used here carefully evaluated such “loss-of-control” effect and could not detect any indicators in that direction.

During the first intervention part (arm training), 6•5±3•8 (experimental group) and 5•1±3•9 (control group) training sessions (days), an arm orthotic device (Motorika, Israel) for upper arm rehabilitation (See Supp. Fig 6) was used and connected to the BMI platform, which transformed successful SMR desynchronization into arm movements in the experimental group and random movements not related to brain activity

in the control group. The patients arm was strapped gently to the arm orthosis (See Supp. Fig 6.A and 6.C).

The second part of the BMI training (hand orthosis) had the same time sequence but instead of the arm the fingers of the paralyzed hand were inserted in the slings of an orthosis (see Supp. Fig.6.B). During the second intervention part (hand training) resulted in 11 ± 3•8 and 13•1 ± 3•9 sessions performed in the experimental and control group respectively. Patients were instructed to try to open their hand after the auditory trigger signal (”GO”) for 5 sec even if the fingers do not actually follow their intention. Again, event- related- desynchronization (ERD) of the ipsilesional SMR of a certain threshold opened the hand in the orthotic device for the experimental group and a randomization algorithm for the sham group. Algorithm and functioning of the EEG-BMI are described in E information part.

5.3 Physiotherapy

Immediately following the BMI session, patients received one hour of behavioral physiotherapy targeted at training and 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. This treatment mode was selected following positive results of several groups with goal-directed training,[28,29] and de-emphasizing explicit explanations of the muscles or muscle groups that should be activated.[49] The aim of the physiotherapy was to attain relevant goals where motor control of the paralyzed hand is necessary and to coach the patient to use newly learned skills during BMI-training in daily life. Exercises selected followed a standardized treatment manual.[29] In addition to verbal information the physiotherapist stimulated the somatosensory system by touching the skin covering the main muscles involved in each movement and supporting movements passively if necessary, so that the patient was successful in achieving the task. The application of somatosensory stimulation to the paretic hand results in performance improvements in the paretic limb and a normalization of activity-dependent modulation of interhemispheric inhibitory interactions accompanies these functional improvements.[50,51] When a visible movement or muscle contraction was initiated by the patient, this movement was verbally rewarded and positively reinforced. Treatments in both groups were identical. This new physiotherapy approach is different from other physiotherapy and exercise therapies.

It is daily life oriented, goal directed, based on active involvement and uses the principles of motor learning. The patient is coached (more than treated) to achieve autonomy in exercises. Patients are encouraged to adapt behavior and to use new learned skills in daily life.

6. Measures associated to the primary behavioral outcome measure

6.1 EMG

Electromyography was acquired 8 weeks before intervention, immediately before and after intervention.

6.1.2 EMG-EEG Screening (grasping movements: opening and closing the hand)

During the pre- and post- EEG assessment measurements (explained above) ipsilateral and contralateral electromyographic recordings (EMG) from four locations at each arm were collected using 8 bipolar Ag/AgCl electrodes from Myotronics-Noromed (Tukwila, WA, USA) and placed on antagonistic muscle pairs: 1) extensor carpi ulnaris 2) extensor digitorum 3) on the long head (laterally) head of the biceps 4) the external head of the triceps. To keep the EMG electrodes position identical at every recording session a permanent marker was used to re-draw every day the exact position of the electrodes (contour) avoiding variation of electrode placement and therefore signal changes due to different electrode placement.

6.1.2 EMG-bilateral movements

The patients were placed on a comfortable chair about 1 meter distance from a 17 inches laptop screen. Six different auditory and visual cues were presented corresponding to six different arm and hand movements: 1) flexion, 2) abduction of the upper arm, 3) extension of the elbow, 4) supination, 5) wrist extension and 6) finger extension. An instruction period of 3 sec in which the patients were presented with three pictures of the movement they had to perform (beginning, middle and end of the movement), having the movement name on top of the pictures indicated the task to the patients. After the instruction period, two “ready” and one final “Go” cues were presented for 1 sec each. Right after the “GO” cue the patients had 6 sec to perform the movement, reach the final position and maintain before a “Relax” cue was presented to them. During each movement, the subjects were presented with a correspondent classical music piece increasing the volume during the entire 12 sec of each trial (instructions + ready + movement). This was used as a motivation and concentration tool. A silent inter-trial period between 4 and 7 sec was used to allow the patients to return to the resting and

start position (hands resting on their lap). Patients were instructed to perform each movement with both arms simultaneously after the Go cue maintaining their gaze on the screen to avoid neglecting the non-affected hand due to a concentration shift towards the paretic arm. The patients had to try to perform these movements with the paretic hand and the healthy arm. Compensatory movements were discouraged. EMG data was acquired and placed on antagonistic muscle pairs in the same manner as for the EEG Screening experiment but recordings involved four more recording locations having a total of 8 electrodes on each arm: 1) extensor carpi ulnaris, 2) extensor digitorum, 3) on the flexor carpi radialis, palmaris longus, flexor carpi ulnaris (flexion), 4) on the long head of the biceps (flexion), 5) the external head of the triceps, 6) anterior portion of the deltoid muscle, 7) lateral portion of the deltoid muscle, and 8) posterior portion of the deltoid muscle over the teres minor and infraspinatus muscles. Every session consisted of 4 to 5 runs of 60 trials (10 per movement).

The EMG data was filtered using a 10 Hz high pass and a 50 Hz notch filter, bipolarized, rectified and epoched from +0•5 to +5 sec with respect to the “GO” cue during the EEG screening session and from +3•5 to +5•5 sec with respect to the “GO” cue during the “EMG-Bilateral Movements” measurements. A sliding window of 200 msec with an overlap of 20 msec was used to calculate the waveform length of the signal from each location serving as a measure of motor innervations.[45] This time domain feature was averaged in a time window and used in the posterior statistical analysis (See below).

Waveform Length (WL): estimates the complexity of the EMG waveform. The calculation is defined as

$$WL = \sum_{k=1}^{L} |\Delta x_k| \quad \Delta x_k = x_k - x_{k-1}$$

L being the length of the window use in the estimation of the waveform length and Xk being the amplitude of the filtered and rectified EMG signal at time point k. The waveform length of the signal provides indicators for signal amplitude and frequency. We used this time domain feature (Waveform length) because it has been largely used and accepted in EMG decoding and estimation[52]. This parameterization has been used in EMG decoding of individual finger movements and proved to be one of the most sensitive indexes of EMG activity[53].

EMG waveform length from the electrode placed on the main muscle involved in each movement was considered for the statistical analysis.

- Hand open-close (wrist extension and finger extension) →electrode placed over the extensor digitorum
- Upper arm flexion (deltoid)
- Upper arm abduction (deltoid)
- Elbow extension (triceps)
- Supination (biceps)

6.2 fMRI

The patients were asked to a) try to perform, b) imagine hand closing and opening and c) rest. The trial starts with a random resting time between 2 and 3•6 seconds. Immediately after that period, there is a 10 sec instructions time, where the subjects have to attend to the instructions related to the task they are going to perform next (a, b or c). After those 10 sec a “ready” followed by a “GO” auditory and a visual cue indicates when to start the task. During the actual task, rhythmic auditory and visual cues helped the patients to maintain a comfortable movement pace of 1•5 seconds (time from open to close). The auditory cues were “Close” and “Open” for imagery or active movement and “tic” “tac” for rest condition while the visual cues (circle blinking) were the same for all conditions.

Data were acquired using a 3 Tesla Siemens MRI system (Siemens TIM Trio, Erlangen, Germany). Functional MR images were acquired using a gradient-echo planar imaging (EPI) aligned in axial orientation: TR = 2000 ms; TE = 30 ms; flip angle = 90°; FOV = 210 mm; matrix size = 64; interslice gap = 0•75 mm; slices = 28; slice thickness = 3 mm. A T1-weighted anatomical MR images was acquired using a 1 mm isotropic MPRAGE sequence with the following parameters: TR = 2300 ms; TE = 3•03 ms; TI = 1100ms; flip angle = 8°; FOV = 256 x 256; matrix size = 256 x 256; number of slices = 176; slice thickness = 1 mm, bandwidth = 130 Hz/Px.

Each fMRI session (190 volumes) consisted of four runs (30 trials x condition volumes) of visually- and auditory–cued executed and imagined flexion–extension of the fingers (12sec), with either the affected or the unaffected hand, alternating with rest (12sec). fMRI data analysis was performed using SPM8. EPI volumes of the pre- post- training fMRI sessions were realigned, slice-time corrected, anatomically coregistered, spatially normalized to the Montreal Neurological Institute (MNI) reference space and

smoothed (9 mm FWHM). Hemodynamic response amplitudes were estimated using standard regressors, constructed by convolving a boxcar function, for each of the three different conditions (actual movement, imagined movement and rest), with a canonical hemodynamic response function using standard SPM8 parameters. The time series in each voxel were high-pass filtered at 1/128 Khz to remove low frequency drifts. Movement parameters were also included into the general linear model (GLM) as covariates to account for head motion artifacts.

Previous studies demonstrated the validity of the laterality index to assess cerebral cortical lateralization in healthy subjects and stroke patients[23,24]. Cortical activity is almost completely lateralized to sensorimotor areas contralateral to the moving hand in healthy people[19]. Moreover, activity in well-recovered patients tends to resemble that of healthy individuals, mainly contralateral during movement and movement preparation[54] and therefore we performed an LI analysis to quantify recovery. A lateralization index (LI) expressed as the normalized difference between the number of active voxels in the ipsilesional and contralesional hemisphere[55] was calculated for the paretic and healthy hand before and after BMI-training sessions. Only patients with subcortical lesions (Experimental group, n = 14; S, n = 7) were considered for LI assessment. Voxels were identified as significant if they surpassed a threshold of p < 0•001 uncorrected. LI was calculated by selecting separately an inclusive mask of motor and premotor regions (M1, PMC and SMA), and an inclusive mask of primary and secondary somatosensory regions, both masking out the midline (+/-5mm), and using a combination of clustering (smoothing = 3 x voxel size) and variance weighting approaches to determine reliability of activations and remove outliers[47]. LI yields a value of 1 or -1 when the activity was respectively purely contralesional or ipsilesional. The differences of LI calculated individually were assessed across sessions and groups. A two x two repeated measures ANOVA with group (experimental, 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.

7. Results: Statistical analysis

We analyzed statistically our primary behavioral outcome measure (combined hand and arm scores from the modified Fugl-Meyer-Assessment scale cFMA) and collected the rest of the data as secondary behavioral outcome measures and associate

measures for descriptive purposes in order to prove the efficacy and specificity of the intervention. Same analysis design was applied to all primary and secondary behavioral measures and software SPSS version 19.0 was used for statistical analysis. Two-way- mixed model ANOVAs (with independent measures of group and repeated measures of pre- and post- BMI training) and t-tests comparisons were applied if the data were normally distributed (cFMA scores, BMI-Placebo scores, upper arm EMG) to analyze pre- and post -treatment effects. If the data were not normally distributed Wilcoxon Tests (Ashworth, GAS hand, MAL and Therapy-Placebo scores, hand EMG and BMI performance) and Mann-Whitney-U-Tests (Physiotherapy-Placebo) between and within groups were applied. Post-hoc comparisons using two-tailed paired-samples t-test were performed to control for pre to post improvement in every group. For the analysis of the fMRI data, A 2 x 2 repeated measures analysis of variance (ANOVA) with group(experimental, control) as between factor and session (pre-post) as within factor was performed on LI values. Subsequently, separated paired-samples t tests were carried out as post-hoc analyses to compare the dependent variables (cFMA, GAS, MAL, Ashworth, Placebo, BMI, EMG) pre- post- sessions effect within each group. For these tests, the two pre-measurements of the baseline (pre1 and pre2) of all measures were collapsed to enhance robustness in the comparison as shown before[30]. Furthermore, to emphasize the intervention results of the primary and secondary behavioral outcome measures, we performed pre to post post-hoc statistical comparisons without averaging, i.e. when comparing one of each pre-measurements separately with the post-measurement. Two-tailed paired-samples t-test were used when data was normally distributed (cFMA) and Wilcoxon Signed Rank Test when not normally distributed (Ashworth, MAL, GAS).

High variance in cFMA scores was present and this could be explained because, “nothing”, “something” and “perfect” are the 3 possible rating scores for FMA, which makes the scale less sensitive to small changes and the variance larger. If the patient presented few and weak activity in the paretic hand it could happen that he/she accomplishes the task once and next time he/she cannot, introducing high variance in the scores. Therefore, these severely impaired patients with “higher” scores presented higher variance in the scores and this appears as outliers in our data distribution. In general, the variance of the distribution of the FMA scores in the control group is higher than in the experimental group. In the hand FMA scores the maximum score in the control group is 11 and 2 patients presented this score while in the experimental group

the maximum score is 8 and 2 patients presented this score. In the arm FMA scores the maximum score in the control group is 21 and three patients presented scores above 20 points, while in the experimental group the maximum score was 21 and only one patient presented scores above 20. These differences in outliers in the control group produced the non significant difference in variance between groups. However the pre- to post-delta presented a homogenous variance within groups and therefore did not influence the pre- to post- statistical analysis (See Supp. Fig. 7). In the experimental group 11/16 patients and in the control group 7/14 improved their hand FMA scores, which means that no overall negative effect was created by the sham BMI. However, very few patients could “grasp” after the training – i.e.extend the fingers, reach for an object and/or hold the object.

In the experimental group 15/16 patients and in the control group 7/14 improved their modified arm FMA scores.

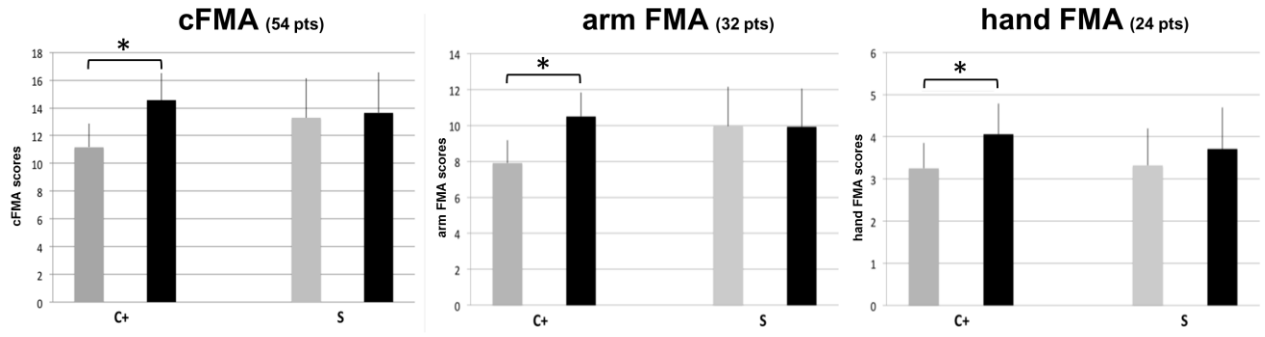

Figure 7. Hand, arm and the combination of both scores (motor part) from the modified upper limb Fugl-Meyer-Assessment (hFMA, aFMA and cFMA respectively) (maximal score 24, 32 and 54 points respectively). The combined Fugl-Meyer Assessment scores from a modified arm section (section total score 30 points. No reflexes scores included) and hand (section total score 24 points) (cFMA) was used as primary outcome measure (total score 54 points). Scores obtained in each group (Experimental or contingent group (C+) and control or sham (S)). The bars indicate the means and standard errors. An asterisk indicates statistically significant change between the mean of the two measurements before training (pre -grey bars-) and the measurements after training (Post -black bars-). cFMA scores showed significant group x time interaction.

In the experimental group 15/16 patients and in the control group 8/14 improved their combined hand and arm scores in the modified upper limb motor part of the FMA test.

Our patients changed more from zero to partial than from partial to full capability (if any). We did not analyze subsections of each motor part of the upper limb FMA because of the tests variance in these severely impaired patients. It has been proven that FMA scores a few days post-stroke were strongest predictor of motor recovery [56-58] and in chronic stroke[59]. Furthermore, the study of Lambercy and colleagues in chronic stroke patients showed a larger increase in functional assessment scores during therapy in patients initially with moderate impairment (FM > 35) and suggested that patients already having some motor function of the arm and hand benefit from the functional hand therapy[60]. In our study case, although cFMA scores were not significantly different between the experimental and the control group before intervention, if one group should have more possibilities of recovery should be the control since their cFMA scores previous to intervention are slightly better (not significant) than the experimental group. However, the experimental group only showed significant improvement in cFMA scores.

		H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	SUM
C+	Mean	0.07	0.03	0.1333	0	0	0	0.07	0.43	0.03	0.067	-0.03	-0.067	0.73
	SD	0.32	0.3	0.3994	0	0	0.38	0.26	0.56	0.58	0.258	0.129	0.258	1.76
S	Mean	0.11	0.11	-0.1071	0	0	0.36	0	0.04	-0.04	0	0	-0.071	0.39
	SD	0.4	0.4	0.2129	0.34	0	0.57	0	0.66	0.5	0	0.392	0.267	1.16

Table 4. Change in scores (Pre-Post) for each of the movements in the hand FMA subsection. This table depicts means, standard deviations (SD) for both patients groups and three assessment time points (assessments before training were collapsed for clarity and because no significant differences emerged between time point one and two). H1 to H12 represent the 12 movements within the hand and fingers motor skills FMA scores as described in 2.1.3. SUM stands for the sum of all hand and fingers related score change. C+ contingent group (experimental). S sham group (control).

		A1	A2	A3	A4	A5	A6	A7	A8	SUM
C+	Mean	1.2	0.2	0.43	0.1	0.37	0.2	0	-0.07	2.43
	SD	1.92	0.77	0.56	0.34	0.52	0.46	0	0.18	3.28
S	Mean	-0.11	0.29	-0.14	0	0.04	0.11	-0.04	-0.11	0.035
	SD	1.82	1.05	0.36	0.2	0.5	0.4	0.41	0.29	3.25

Table 5. Change in scores (Pre-Post) for each of the movements in the arm FMA sub-section. This table depicts means, standard deviations (SD) for both patients groups and three assessment time points (assessments before training were collapsed for clarity and because no significant differences emerged between time point one and two). A1 to A8 represent the 8 movements within the upper arm and forearm motor skills FMA scores as described in 2.1.2. SUM stands for the sum of all hand and fingers related score change. C+ contingent group (experimental). S sham group (control).

No available treatment could prove so far improvement in this type of patients. BMI-orthosis training combined with behavioral physiotherapy offers these patients a change from very severe impairment to severe impairment. Our results reflect a change from no activity to some in specific movements, i.e. lifting and stretching the arm, turn the forearm, extend the wrist and/or fingers, allowing the patient to get enroll in other motor rehabilitation therapies. However, we believe contingency between brain signals and movement of the limb even in medium and severely impaired patients could possibly improve motor rehabilitation outcomes and speed up the recovery. In recent work[61,62] 2 different statistical analysis were used to calculate the minimal change in the FMA to be considered significant motor recovery and therefore clinical improvement. These two studies do not apply to our patient sample for several reasons:

patients used in both studies were not severely impaired (Upper Limb motor part of the FMA scores were substantially lower in our patients)

Reflex scores were included in the upper limb motor part of the FMA, which reduce reliability and increase variance in the upper limb motor part of the FMA[18].

Months since stroke of their patients was significantly lower than in our more chronic group

However, the methods used in both cited studies (Z scores and receiver operating characteristic (ROC) curve) used a 2 baselines method for a completely different number of patients (14 and 146; we used 32) to generate a threshold using a 95% confidence interval. We believe this methods are equivalent to the statistical methods we used in this work to identify significant changes (two-way mixed model ANOVA). We performed a mean of the 2 baselines measurement and compared it to post-scores and performed statistical comparisons between each baseline (Pre1 and Pre2) and post-scores independently (See Supp. Info 7.2) obtaining significant results in all the comparisons between pre- and post-scores in the experimental group only.

7.1 Secondary behavioral outcome measures: Ashworth, MAL, GAS, placebo

7.1.1 Ashworth: No significant difference was observed in the average Ashworth score between pre and post BMI training in the experimental group (z = -1•426, p = 0•154, Wilcoxon signed rank test) and in the control group (z = -0•237, p = 0•813, Wilcoxon signed rank test) respectively.

7.1.2 MAL

A Wilcoxon Signed Ranks Test showed that the BMI training elicited a statistically significant change in MAL scores in the experimental group (z = -1•958, p = 0•05). Average MAL scores (SE) increased from 10•22±2•19 before training to 15•63±3•53 after treatment (See Supp. Table5). Moreover, a significant difference was observed in the average MAL scores between pre (9•31±2•88) and post (12•44±2•15) BMI training in the sham feedback group (z = -2•599, p = 0•009,) (See Supp. Table5).

7.1.3 GAS Hand

A Wilcoxon Signed Ranks Test showed that BMI training elicited a statistically significant change in GAS-Hand scores in the experimental group (z = -3•336, p = 0•001). Average GAS-Hand score (SE) increased from 0•03±0•03 before training to 1•69±0•27 after treatment (See Supp. Table5). Moreover, a significant difference was observed

in the average GAS-Hand scores between pre (0) and post (1•71±0•24) BMI training in the sham feedback group (z = -3•106, p = 0•002, Wilcoxon signed rank test).

		Ashworth		GAS "Hand"		MAL	
		Pre	Post	Pre	Post	Pre	Post
C+	Mean SD SE	**10.28** 7.41 1.85	**9.13** 7.32 1.83	**0.03*** 0.13 0.03	**1.69*** 1.08 0.27	**10.41*** 10.72 3.23	**15.63*** 14.11 3.53
S	Mean SD SE	**6.46** 5.04 1.35	**6.36** 5.54 1.48	**0*** 0 0	**1.71*** 0.91 0.24	**9.72*** 11.22 3.11	**13.71*** 9.60 2.56

Table 6. Results of BMI training. Functional scales. This table depicts means, standard deviations (SD) and standard errors (SE) for both patients groups and three assessment time points (assessments before training were collapsed for clarity and because no significant differences emerged between time point one and two). Ashworth scale, goal attainment scale (GAS) for hand and Placebo scores are presented. Asterisks represent statistically significant differences between pre and post training measurements. C+ contingent group (experimental). S sham group (control).

The results in the GAS and MAL scales showing a significant increase in both groups supports the suggestion by Levin and colleagues[63] to discriminate between clinical scales measuring specific motor aspects that may limit but are not directly related to task accomplishment (EMG, motion, FMA…) and function measures indicating the level of a task success (key turning, GAS, MAL…). Compensation, i.e., using healthy muscles combined with specific postures, can help achieve a specific functional task and can be trained. This improvement will be reflected in scales like GAS and MAL but does not imply any kind of physiological recovery as remarked by Levin and colleagues[63] , i.e. functional recovery can occur even in the absence of motor recovery (e.g. lost motor patterns have not returned). Therefore, our results indicate that the use of behavioral physiotherapy after moving the affected limb while the patient intends that precise movement achieves functional recovery in BMI-training as shown by the GAS and MAL scales using compensatory strategies and that the BMI plays a key role in achieving functional and physiological recovery (motor recovery), as shown by the cFMA (health condition level; Impairment scale), EMG (Body function level) and well

controlled fMRI results. All these results together allowed us to distinguish between recovery and compensation.

7.1.4 Placebo Effects:

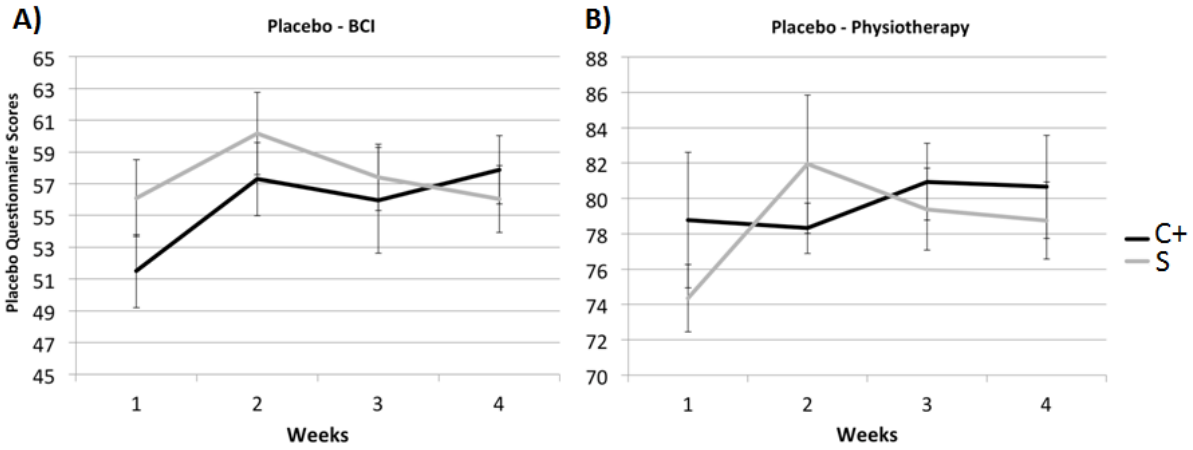

Figure 8. Placebo Scores during 4 weeks of training. A) Placebo scores during the BMI training.. B) scores during the goal oriented physiotherapy after the BMI training. Black and gray lines represent contingent positive or experimental (C+) and sham or control (S) feedback groups. Error bars correspond to standard errors.

Placebo questioners were analyzed separately for the BMI-training situation and therapists behavior during the BMI training and during physiotherapy.

7.1.4.1. Placebo effects for BMI training and Therapists

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. The main effect for time ($F(1,26)=2•553$, $p=0•077$) and the main effect for group ($F(1,28)=0•374$, $p=0•546$) did not reach statistical significance. Also the interaction effect ($F(1,26)=1•898$, $p=0•155$) did not reach statistical significance (See Supp. Fig.8).

		Placebo - BMI				Placebo - Physiotherapy			
		Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 1**	**Week 2**	**Week 3**	**Week 4**
C+	**Mean**	**51.5**	**57.29**	**55.96**	**57.88**	**78.77**	**78.32**	**80.95**	**80.66**
	SD	9.69	10.41	8.35	8.46	7.59	15.68	9.24	8.71
	SE	2.42	2.6	2.09	2.11	1.9	3.92	2.31	2.18
S	**Mean**	**56.1**	**60.16**	**57.4**	**56.04**	**74.35**	**81.94**	**79.39**	**78.75**
	SD	8.62	8.6	12.46	8.04	14.36	5.34	8.17	10.92
	SE	2.3	2.3	3.33	2.15	3.84	1.43	2.18	2.92

Table 7. Placebo questionnaires' scores: (mean, standard deviation (SD) and error (SE)) for the BMI and physiotherapy sessions during training for the 2 groups: experimental or contingent group (C+) and sham or control (S).

7.1.4.2. BMI- Physiotherapy professional competence

Mann-Whitney U tests comparing the experimental group and control group for Week 1 (U = 99•5, P = 0•602), Week 2 (U = 110, P = 0•934), Week 3 (U = 94•5, P = 0•466) and Week 4 (U = 106, P = 0•822) did not reach statistical significance (See Supp. Fig.7). Placebo scores remained high during and after training with no significant difference between groups (see Supp. Table7) demonstrating stabile positive expectancies, hope for improvement and no recognition of group assignment, which would have resulted in lower placebo scores for the control group.

7.2 Analysis comparing Pre1 and Pre2 data with Post data independently

This was performed in order to emphasize the intervention results (See Supp. Table8).

7.2.1 Pre 1 versus Post

7.2.1.1 Combined hand and arm from the modified FMA (cFMA) (54 points)

A two-tailed paired-samples t-test comparison revealed significant improvement from pre 1 (10•44±1•68) to post (14•56±1•95) BMI training in the experimental group (t(1,15) = -5•293, p=0•000)

A two-tailed paired-samples t-test comparison did not revealed significant improvement from pre 1 (13•50±2•87) to post (13•64±2•91) BMI training in the S group (t(1,13) = -0•119, p=0•907)

7.2.1.2 Ashworth

No significant difference was observed in the average Ashworth score between pre 1 and post BMI training in the experimental group (z = -1•542, p = 0•123, Wilcoxon signed

rank test) and in the control group (z = -0•051, p = 0•959, Wilcoxon signed rank test) respectively.

7.2.1.3 MAL

A Wilcoxon Signed Ranks Test showed that the BMI training elicited a statistically significant change in MAL scores in the experimental group (z = -2•482, p = 0•013). Average MAL scores (SE) increased from 7•44±2•07 before training (Pre 1) to 15•63±3•53 after treatment.

Moreover, a significant difference was observed in the average MAL scores between pre 1 (8•29±2•6) and post (12•31±2•32) BMI training in the sham feedback group (z = -2•358, p = 0•018,).

7.2.1.4 GAS

It is not possible to compare the variables Pre 1 (hand) and Post GAS since Pre score is a constant.

7.2.2 Pre 2 versus Post

7.2.2.1 Combined hand and arm modified FMA (cFMA) (54 points)

A two-tailed paired-samples t-test comparison revealed significant improvement from pre 2 (11•88±1•88) to post (14•56±1•95) BMI training in the experimental group (t(1,15) = -4•175, p=0•001).

A two-tailed paired-samples t-test comparison did not revealed significant improvement from pre 2 (13•07±2•89) to post (13•64±2•91) BMI training in the S group (t(1,13) = -0•496, p=0•628).

7.2.2.2 Ashworth

No significant difference was observed in the average Ashworth score between pre 2 and post BMI training in the experimental group (z = -1•105, p = 0•269, Wilcoxon signed rank test) and in the control group (z = -0•079, p = 0•937, Wilcoxon signed rank test) respectively.

7.2.2.3 MAL

		cFMA		Ashworth		GAS "Hand"		MAL	
		Pre1	**Post**	**Pre1**	**Post**	**Pre1**	**Post**	**Pre1**	**Post**
C+	**Mean**	10.44*	14.56*	10.28	9.13	0.03*	1.69*	7.44*	15.63*
	SD	6.72	7.81	7.41	7.32	0.13	1.08	8.76	14.11
	SE	1.68	1.95	1.85	1.83	0.03	0.27	2.07	3.53
S	**Mean**	13.50	13.64	6.46	6.36	0*	1.71*	8.29*	12.31*
	SD	10.75	10.88	5.04	5.54	0	0.91	10.78	8.05
	SE	2.87	2.91	1.35	1.48	0	0.24	2.6	2.32
		Pre2	**Post**	**Pre2**	**Post**	**Pre2**	**Post**	**Pre2**	**Post**
C+	**Mean**	11.88*	14.56*	10.28	9.13	0.03*	1.69*	8.38*	15.63*
	SD	7.54	7.81	7.41	7.32	0.13	1.08	8.76	14.11
	SE	1.88	1.95	1.85	1.83	0.03	0.27	2.99	3.53
S	**Mean**	13.07	13.64	6.46	6.36	0*	1.71*	10.21*	12.31*
	SD	10.81	10.88	5.04	5.54	0	0.91	10.78	8.05
	SE	2.89	2.91	1.35	1.48	0	0.24	3.37	2.32

Table 8. Functional scales. This table depicts mean, standard deviation (SD) and standard error (SE) for both patients groups and three assessment time points (8 weeks before intervention Pre1, immediately before intervention Pre2 and immediately after intervention Post1). Combined hand and arm modified Fugl-Meyer Assessment scores (cFMA), Ashworth, goal attainment scale (GAS) for hand and Placebo scores are presented. Asterisks represent statistically significant differences between pre and post training measurements

A Wilcoxon Signed Ranks Test showed that the BMI training elicited a statistically significant change in MAL scores in the experimental group (z = -2•232, p = 0•026). Average MAL scores (SE) increased from 8•38±2•99 before training (Pre 2) to 15•63±3•53 after treatment.

Moreover, a significant difference was observed in the average MAL scores between pre 2 (10•21±3•37) and post (12•31±2•32) BMI training in the sham feedback group (z = -2•606, p = 0•018,).

7.3 Results: EMG, fMRI, BMI control

7.3.1 EMG:

We analyzed the hand activity before and after training. A Wilcoxon Signed Ranks Test of the amplitude and frequency as reflected by the waveform length of the extensor digitorum EMG signal during the EEG screening session showed that BMI training elic-

ited a statistically significant change using EMG mean scores during opening and closing the hand in the experimental group (z = -2•327, p = 0•020). Average EMG score ± standard error (SE) increased from 2•42±0•46 before training to 3•69±0•71 wave, form length values after treatment. The average EMG score scores between pre (1•95±0•45) and post (3•58±0•97) BMI training in the control group (z = -1•601, p = 0•109) were not statistically significant. We performed the same statistical test using the median of the EMG activity. Test showed that BMI training elicited a statistically significant change in EMG median scores in the experimental group (z = -2•017, p = 0•044). Average EMG score (±SE) increased from 2•09±0•42 before training to 2•83±0•54 after treatment. No significant difference was observed in the average EMG score scores between pre (1•7±0•41) and post (3 ±0•8) BMI training in the control group (z = -1•601, p = 0•109).

To control for changes in muscle activation in the upper arm, several movements involved in the Fugl Meyer were analyzed for significant changes using paired t-test between pre and post. Neither of the two groups of patients showed significant changes at the electrodes placed over the healthy side. The experimental group showed a significant increase in activity during upper arm and elbow extension at location deltoid (1.35±0.08 to 1.47±0.1 (t = 2.246, p = 0.040) and triceps (1.17±0.08 to 1.38±0.13) (t = 2.253, p = 0.040), while the sham group did not show any significant EMG change (See Supp. Fig.9). Wrist extension, supination and pronation did not show any significant change in either group. The BMI training did not generalize to increase strength and control in the main muscles involved during supination and wrist extension as opposed to finger extensors, shoulder or triceps during finger extension, abduction of the upper arm and extension of the elbow respectively. However, the BMI training did not train for supination or wrist extension and it did train elbow extension (triceps), arm extension (shoulder-deltoid) using the arm orthosis and hand open/close (finger extensors) using the hand orthosis. A very similar forearm extensors activity pattern is recruited during wrist extension and we expected to generalize the EMG recovery to these movements too. We decided to record EMG activity from the main movements related to the cFMA scores and supination/pronation and wrist extension are some of them (See Suppl. Section 2.1).

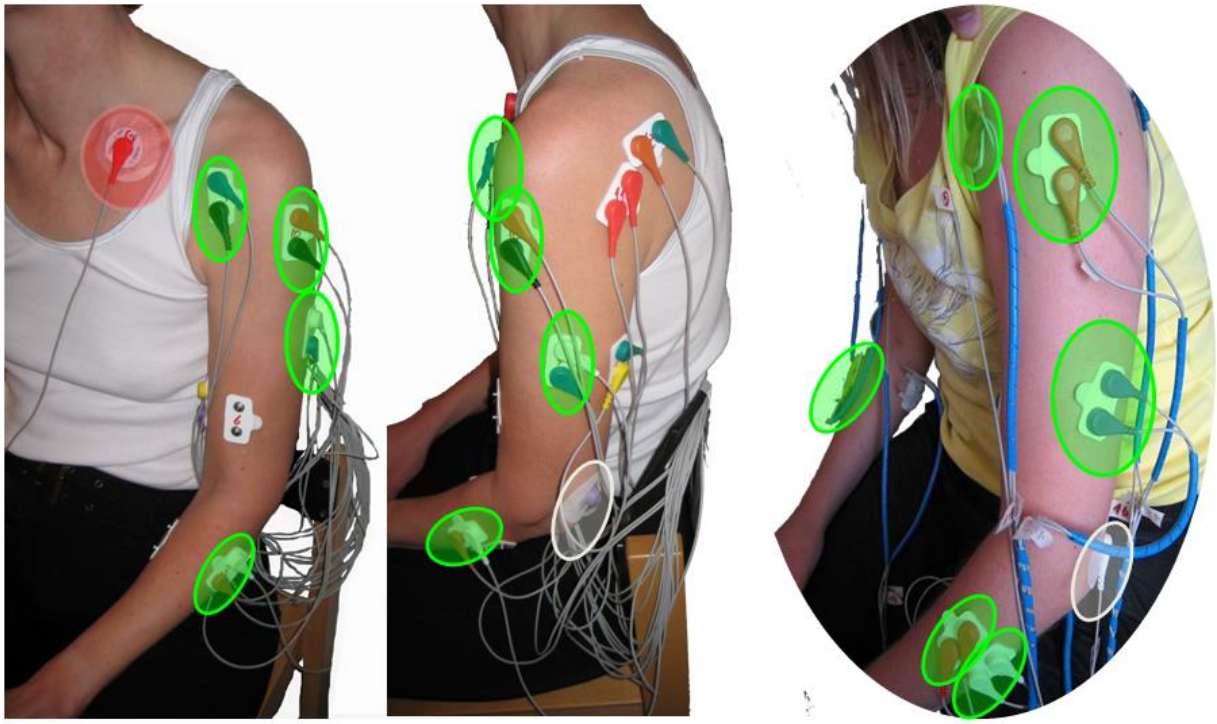

Figure 9. EMG electrodes placement. Electrodes were placed on both arms over the muscles affected by stroke: 1) extensor carpi ulnaris, 2) extensor digitorum, 3) on the flexor carpi radialis, palmaris longus, flexor carpi ulnaris (flexion), 4) on the long head (laterally) of the biceps (flexion), 5) the external head of the triceps, 6) anterior portion of deltoid muscle, 7) lateral portion of deltoid muscle, and 8) posterior portion of deltoid muscle over the teres minor and infraspinatus muscles. The ground and reference electrodes were placed on the clavicle (red circle) and the olecranon (white circle) respectively. After intervention on the electrodes surrounded by a green circle a significant increase of EMG activity was found in the the experimental group only.

7.3.2 fMRI

Lateralitzation index analysis of the number of all active voxels in the ipsilesional and contralesional areas (MI, PMC, SMA, SI, SII, anatomically defined regions of interest conforming to MNI-space) revealed that 11 out of 14 patients of the experimental group howed a shift of activity from motor and premotor regions of the contralesional hemisphere towards the ipsilesional hemisphere when movements were performed with the paretic hand. After training, a significant difference of the LI in the motor and premotor cortices only was measured between pre- and post-training session during paretic hand movements (pre = -0•04±0•37 mean±SD, post = -0•27±0•48; t(13) = 2•61 p = 0•02 paired sampled t-test) in the experimental group (all 14 patients) (Figure 2). The control group did not show a significant change of the LI in the motor and premotor

cortices between pre- and post-training session during paretic hand movements (pre = -0•12±0•39, post = 0•27±0•42; t(6) = -1•81 p = 0•11) (Figure 2). Both patient groups showed contralesional activity in the motor and premotor cortices with no significant differences between pre- (Experimental group, LI = 0•78, SEM = 0•07; Control group, LI = 0•81, SEM = 0•06) and post-BMI training (Experimental group, LI = 0•80, SEM = 0•05; Control group, LI = 0•86, SEM = 0•03) sessions when movements were performed with the healthy hand (Figure 2).). No significant changes in LI were observed during imagined hand movements' condition in both experimental (pre = 0.30±0.28 mean±SD, post = 0.32±0.29; p = 0.86) and control (pre = 0.20±0.52, post = 0.39±0.20; p = 0.27) groups (Supp. Figure 10).

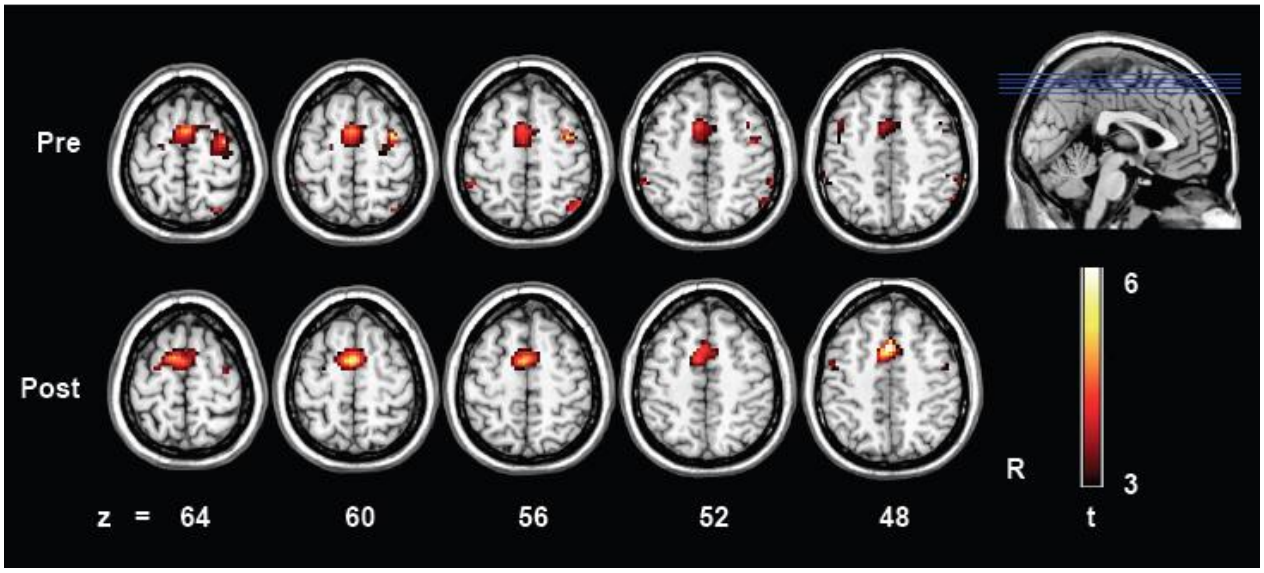

Figure 10. Brain activations during paretic imagined hand movements vs. rest before and after BMI training ($p < 0.001$ uncorrected). No significant changes result from direct comparison of pre vs post BMI training fMRI session.

Moreover a significant correlation between the change of lateralization of brain activity in the motor and premotor cortices (LIpre-LIpost) and upper limb modified FMA scores after training was found in patients with subcortical lesion of the experimental group (Pearson r = 0•55; df =134 ; p = 0•035 two-tailed). It is worth mentioning that the results of the Pearson correlation (2-tailed) between LI changes and hand FMA are r(12) = 0•54, p = 0•05. There was no correlation with modified arm FMA.

7.3.3 BMI control

The movement of the arm/hand was directly linked to the brain through an online BMI and was used as BMI performance indicator. Nevertheless, several other performance

measures indicating different phenomena of SMR modulation were calculated off-line to indentify which of the hand/arm movement parameters was used by the patients to improve the ability to control the robot and orthosis:

a) Percent of time the robot and orthosis was (experimental group) moved or would have been moved (sham group) during a trial. This performance measure reflects the ability of the subject to decrease or maintain the decrease of SMR power during a trial.

b) Maximum consecutive time the robot or orthosis was moving per trial. This measure represents the longest period of time the patient was able to decrease or continuously maintain SMR desynchronization within a trial.

c) Number of robot or orthosis moving onsets switching from not moving to moving per trial. This measure reflects how many times the patient loses and regains control within a trial.

d) Latency to the first onset of robot or orthosis movement per trial. This measure represents the reaction time of the patient in producing a robot or orthosis movement (SMR desynchronization).

The feedback presented to the patients during the BMI-training was visual and proprioceptive only (observing and feeling their arm/hand moving). We separated the performance analysis during robot and orthosis training because the reaction time of the robot was twice as fast as the orthosis. Furthermore, there were a different number of patients in each robot session since, as explained above, once patients were able to extend the arm with the support of the robot actively the patient was transferred to the orthosis training. We performed a Wilcoxon Signed Rank Test (Bonferroni corrected) comparing the first versus each of the other training sessions (days) median scores for all BMI performance scores. Significant increases in the percent of time and maximum consecutive time moving the hand (See Supp. Fig.11) and significant decreases in the number of hand movement onsets (session 7) were present in the experimental group only without moving it through the whole trial. No significant changes were obtained for the latency to the first orthosis movement. We identified percent of time moving the orthosis and the maximum consecutive time moving the orthosis as indicators of BMI control. On average the patients learned to control the BMI after the 7th session (regardless of controlling arm/hand orthosis) as indicated by a reduction in the number of movement onsets and an increase in maximum consecutive time moving the arm/hand. 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.[7,16,31,64,65]

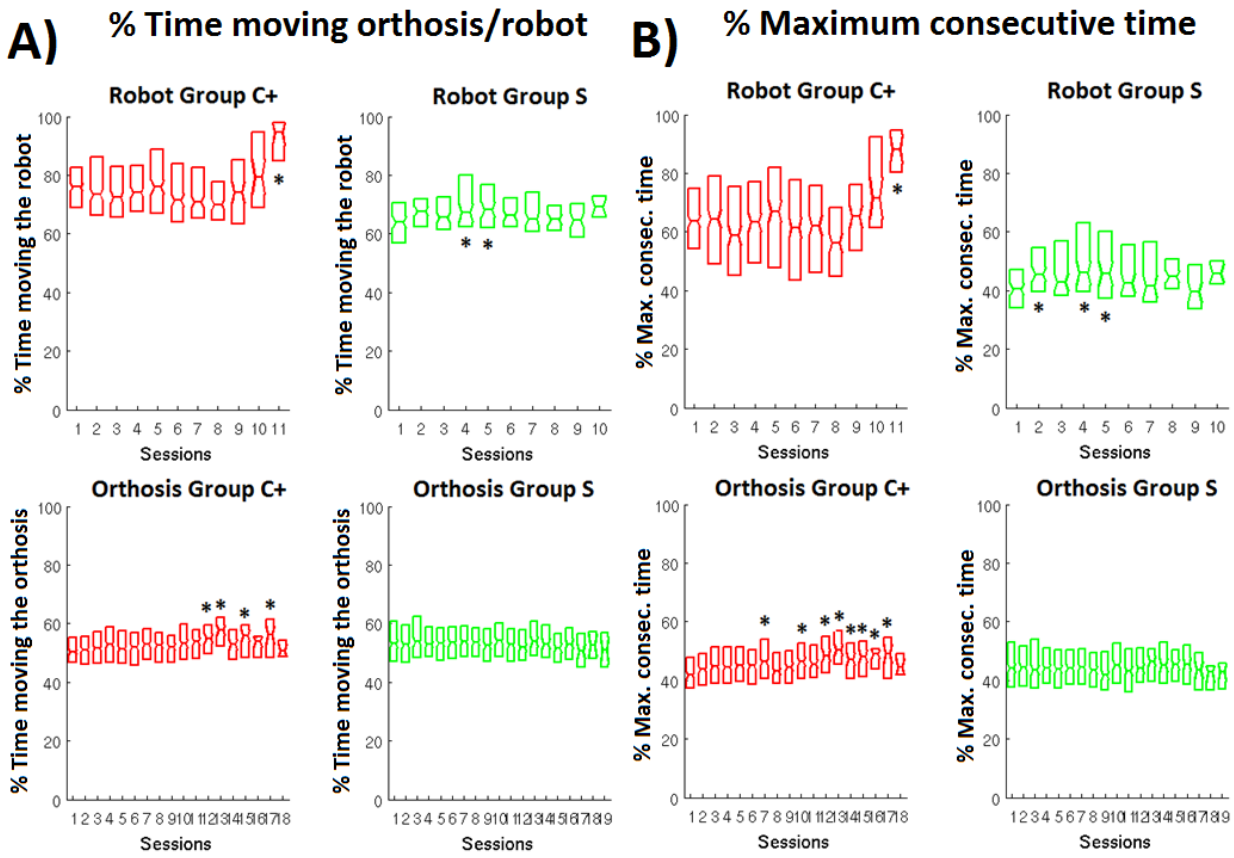

Figure 11. BMI performance scores. On the left the percent of time moving the A) arm (robot) and B) hand (orthosis) over sessions. On the right the maximum consecutive time moving the C) arm (robot) and D) hand (orthosis) in percent. Asterisks indicate significant change in performance compared to the first session. The abscissa represents the training sessions (days). The center horizontal line of each box represents the median while the upper and lower part of a box represents the 25 and 75 percentiles. C+ corresponds to contingent positive or experimental group and S corresponds to shan or control group.

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5.2 – Publication 2 – Brain-machine interface training and cortico-spinal system's integrity in chronic stroke

Journal: The Lancet Neurology

Current status: Waiting for acceptance of the first publication to be submitted.

Personal Contribution:

- Data acquisition: fMRI, BMI training (orthosis and robot using EEG), transcranial magnetic stimulation (TMS), electromyography (EMG) and screening.
- Data analysis: motor evoked potentials (MEP) detection/analysis, statistics.
- Text: all sessions.
- Figures/Tables: all figures and tables.

Brain-machine interface training and corticospinal system's integrity in chronic stroke

Running head title: Corticospinal function and BMI training in stroke

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Abstract

Objective: Brain-machine interface (BMI) training contributes to motor recovery after stroke. However, improvements are heterogeneous across stroke patients. Thus, it would be important to identify biomarkers that predict BMI training related motor recovery. Here we tested whether upper limb motor recovery caused by daily ipsilesional BMI training relates to integrity of the ipsilesional corticospinal system as measured by upper limb motor evoked potentials (MEP). **Methods:** 30 chronic stroke patients (20 male, mean age: 53.6±11.9 years; interval since stroke 67.8±57.6 months) without residual finger extension underwent assessment of upper limb MEP and were randomly assigned to two different treatment groups. In group I (n=16), ipsilesional brain activity during intended finger movements resulted in robot induced hand opening- and closing motions, while in group II (n=14) fingers were randomly moved. All patients trained for one and half hour per day over four weeks and underwent one hour of physiotherapy after each session. Motor function of the upper limb was tested before and after the intervention using the upper-limb Fugl-Meyer Motor Assessment (uFMA). **Results:** Before treatment, uFMA scores were not different between groups. Further analysis revealed that patients with upper limb MEP improved more than patients without, regardless treatment group, and patients with MEP in group I improved more than in group II. Taken together, uFMA scores improved only in group I, but not in group II. **Interpretation:** Assessment of the corticospinal system's integrity based on upper-limb MEP might be a useful biomarker for BMI related motor recovery.

Introduction

Injuries of the corticospinal system, e.g. due to stroke, belong to the leading causes of long-term disability[1]. Each year approximately 20 million people suffer a stroke worldwide.[2] Of those who survive, five million remain severely handicapped and dependent on assistance in daily life. While motor function can significantly improve in the first months after stroke, further recovery is often slow or non-existent.[3-6] The last years yielded the development and clinical assessment of various neurorehabilitation approaches, some of them proven to be highly efficient,[7] e.g. constraint-induced movement therapy (CIMT), but these rehabilitation strategies require sufficient residual motor function often not present in stroke patients. For these patients, no standardized and accepted treatment strategy exists, but recent studies suggest that application of brain-machine interface (BMI) systems might constitute a treatment option for patients with severe paralysis.[8-13] Based on the concept of neurofeedback, Birbaumer & Cohen suggested that contingent reward of ipsilesional motor related brain activity, e.g. mu-rhythms (8-15Hz), might facilitate motor recovery, even in chronic stroke patients.[14] The rational of this idea derived from previous studies that showed that modulation of ipsilesional mu-rhythm during movement intentions in the first few months after stroke correlates with long-term clinical motor outcome[15] irrespective the degree of previous motor paralysis. This finding is consistent with neurophysiologic and neuroimaging data suggesting an association of ipsilesional brain activity and functional motor recovery while increased contralesional activation was associated with poor recovery.[16,17]
In a first pilot study, it was shown that chronic stroke patients unable to grasp can learn to control an orthotic device opening and closing their hands and fingers through purposeful modulation of mu-rhythms[13] and that such training if combined with behavioral physiotherapy to support generalization of the newly acquired skill can result in significant recovery in individual patients.[18] This finding suggested that translation of ipsilesional motor related brain activity into control signals of external devices or machines through a brain-machine interface (BMI) delivering contingent sensory feedback might induce use-dependent sensorimotor plasticity facilitating restoration of normal motor control, potentially through rewiring and synaptic strengthening of weakened or previously inhibited ipsilesional motor networks.[19-21] Larger clinical studies indicated that BMI training reinforcing ipsilesional brain activity of chronic stroke patients with severe motor deficits during intended movements of the paralyzed upper limb can improve motor function, but individual improvements varied substantially.[22,23] Thus, identifying

biomarkers correlating with motor recovery would be of great importance. Biomarkers or surrogate markers are defined as laboratory measurements used as substitutes for clinically meaningful endpoints.[24] As such biomarkers might be useful to predict clinical outcome in individual patients. Transcranial magnetic stimulation (TMS) is a well-tolerated and safe technique to elicit motor evoked potentials (MEP) reflecting excitability and integrity of the corticospinal system.[25] While evaluation of MEP in acute and subacute stroke patients is well established allowing some prediction of motor recovery in the early stage of stroke[26-28] there is only limited data available for chronic stroke patients with severe motor impairment.[29]

Here we investigated whether BMI related motor recovery is correlated with the integrity of the ipsilesional corticospinal system as measured by upper limb MEP.

Patients and Methods

Design

Integrity of the ipsilesional corticospinal system was tested in two age, gender and disability matched chronic stroke groups. While group I (n=16) received daily ipsilesional BMI training translating ipsilesional mu-rhythm modulation into contingent hand opening motions, in group II (n=14) hand opening motions occurred randomly. Both interventions were followed by one hour of behavioral physiotherapy. This regime was applied over four weeks. Before the first and after the last training day, upper limb motor function was assessed using a modified version of the upper-limb Fugl-Meyer Motor Assessment ((uFMA) for a detailed description of the tested functions in each sub-score please see Supplementary Table 1) completed on two different days (pre1/pre2 and post) to improve reliability of the evaluation. Integrity of the ipsilesional corticospinal system was evaluated in all patients prior to the interventions using transcranial magnetic stimulation (TMS).

Stroke Patients

30 participants with chronic stroke (18 male, mean age: 53.7±11.9 years; range 29 to 73 years; Table 1, for characterization of lesion location see Supplementary Table 2 and Supplementary Figure 1), interval since stroke: 66.7±59 months; range: 10 to 232 months) who met the inclusion criteria of this study were recruited through the University Hospital of Tübingen. The criteria included: age between 18 and 80 years, complete paralysis of one hand without ability for active finger extension, interval since

stroke of at least 8 months, no psychiatric or neurological condition other than stroke, no cerebellar lesion or bilateral motor deficit, no epilepsy, Mini-Mental State (MMS) score beyond 21, no contraindication for TMS assessment. All participants gave written informed consent. The study was approved by the University of Tübingen Ethics Committee.

Insert Table 1 here

Assessments

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a well-tolerated and safe technique to elicit motor evoked potentials (MEP) reflecting excitability and integrity of the corticospinal system. Before TMS assessment, magnetic resonance imaging (MRI) was used to acquire an anatomical image of the participant's head allowing neuronavigated stimulation of cortical brain areas. For evaluation of corticospinal system integrity, single-pulse TMS (Magstim 200® Whitland, UK) with a 70mm figure-eight coil was used to elicit upper-limb MEP recorded from the following eight different muscles: first dorsal interosseous (FDI), abductor pollicis brevis (APB), extensor pollicis longus (EPL), extensor digitorum communis (EDC), extensor carpi ulnaris (ECU), flexor carpi radialis (FCR), biceps brachii (BB) and triceps brachii (TB). Electromyographic (EMG) activity was recorded using bipolar surface electrodes (Norotrode 20TM, Myotronics Inc., Kent, WA, USA) kept at impedance below 8kΩ. For stimulation, the coil was held tangentially to the skull and rotated by 45 degrees relative to the midline.[30] The patients sat upright and were instructed to keep their eyes open during the stimulation. During assessment of upper-limb MEP (Fig 1), participants attempted to execute a motion against a steady resistance that involved contraction of muscle to be examined. 0.5 sec. before application of each TMS pulse an auditory signal indicated the participant to execute the motion. Single pulse TMS was applied in ascending stimulation intensities starting at 50% of maximum stimulator output (MSO). If no MEP could be detected after 10 TMS pulses (MEP-), stimulation intensity was increased by 10% until maximum stimulation output. If a MEP could be elicited (MEP+), the exact position was saved using a neuronavigation system (LOCALITE GmbH, Sankt Augustin, Germany). The required stimulation intensity to elicit a MEP (motor threshold) was evaluated by adapting the

stimulation intensity so that 5 out of 10 TMS pulses resulted in detection of an upper limb MEP.[31]

Insert Figure 1 here

Motor function assessment

Motor function of the upper limb was repeatedly determined 8 weeks, one day before (pre1/pre2), and after intervention (post) using the combined hand and arm motor part of the upper limb modified uFMA,[32] a well-established and reliable measure of upper extremity function after stroke[33,4] excluding sub-scales for coordination speed and reflexes as these measures showed to be unreliable in severe stroke.[34] The uFMA, showed on the Supplementary Table 1, has 2 sub-scores for different functional domains (hand/finger and arm). The achievable maximum score is 54 ($FMA_{hand/finger}$: 24; FMA_{arm}: 30). Motor function tests were video-taped and rated by two independent physiotherapists.

Interventions

Brain-machine interface (BMI) training

During the training, electric brain activity was recorded by 16-channel electroencephalography (EEG) placed according to the international 10/20 system. Sensorimotor system related changes in signal amplitudes of the mu-rhythm recorded from the ipsilesional brain hemisphere during attempted arm or finger motions were translated online (delay 240ms) into reaching motions or hand opening and closing motions, respectively, driven by an orthotic device fixed to the patient's paralyzed fingers (see Fig 2).[13,35] For online signal processing and orthosis control during the training the BCI2000 software platform was used (www.BCI2000.org).[36,37] Online electromyography (EMG) recordings were obtained from both arms using surface bipolar Ag/AgCl EMG electrodes (Norotrode®, 20TM, Myotronics Inc., Kent WA, USA). In group II, the same setup was used, but orthosis-dependent hand motions were random. The amount of time the orthosis was moving in group II was kept in the same range as in group I (between 55-80% of each trial).

Insert Figure 2 here

Behavioral physiotherapy

Each training session was followed by one-hour of behavioral physiotherapy in which improvements in execution of daily life relevant activities, e.g. grasping a stick, opening a door, holding a toothbrush, were systematically rewarded verbally and by tapping the patient's arm or hand.[18] During attempted movements with the paralyzed limb, relevant muscles were touched and motions passively assisted.

Data Analysis

TMS

A 10-Hz high pass butterworth filter and notch filter (50Hz) was applied offline to the EMG raw signals using Matlab R2011a (The MathWorks, Natick, MA). TMS-triggered 100ms EMG data epochs were analyzed for MEP with peak-to-peak amplitudes of >50mV. An experienced neurophysiologist verified all detected MEP through visual inspection to exclude false positive findings.

Statistical analyses

To verify reliability of uFMA assessments before intervention, the intra-class correlation coefficient (ICC) of the uFMA and sub-scores was calculated. Intervention related changes of uFMA were calculated as the mean difference between pre1/pre2 and post. An independent samples t-test was used to compare uFMA values between groups before intervention. uFMA changes were evaluated using a general linear model based repeated-measures ANOVA with factors MEP+ and MEP- as within-group variables. A paired-sample student's t-test was used to evaluate differences of within-group uFMA changes after the interventions in the total score (uFMA) and each sub-score ($FMA_{hand/finger}$; FMA_{arm}). Statistical tests were performed by SPSS for Windows v.20 (SPSS Inc, Chicago, Illinois, USA). p-values < 0.05 were considered statistically significant.

Results

Motor function assessment

Intra-class correlation (ICC (3,1)) of the uFMA assessments before intervention showed good reliability (ICC_{uFMA}=0.94; Table 2). Before the first training day, groups

were not different in motor function (group I: *M* = 11.16, *SD* = 6.93, group II: *M* = 13.29, *SD* = 10.71; t(28) = -0.66, p = 0.52). While group I improved after intervention (group I: *t*(15) = -6.049, *p* < 0.001), group II did not (*t*(13) = -0.316, *p* = 0.76).

Insert Table 2 here

TMS

Upper limb MEP could be elicited in 12 patients (MEP+), while no MEP were detected in the remaining 18 patients (MEP-). 8 of these 12 patients belonged to group I, while 4 belonged to group II. For detailed information on individual MEP see Supplementary Table 3.

Patients with MEP+ in group I improved more than in group II (*F*(1, 10) = 11.8, *p* = 0.006).

We found that patients in group I with MEP+ improved more in uFMA (t(7) = -7.04, p < 0.001) compared to patients with MEP- (t(7) = -3.24, p= 0.014), while in group II, no MEP related differences in uFMA scores were found (Fig 3, Table 3).

When averaging uFMA scores according to MEP presence (MEP+) or absence (MEP-) across groups, patients with MEP+ improved (MEP+: *t*(11) = -4.63, *p* < 0.001), while patients with MEP- did not (MEP-: *t*(17) = -1.59, *p* = 0.130) (Table 4).

Insert Figure 3 here

Insert Table 3 here

Further analysis of the upper-limb uFMA sub-scores revealed that in group I, patients with MEP+ showed changes for FMA_{arm} (*t*(7) = -3.74, *p* = 0.007) and a trend for improvement in $FMA_{hand/finger}$ (*t*(7) = -2.28, *p* = 0.057), while patients with MEP- showed changes in FMA_{arm} (*t*(7) = 3.11 *p* = 0.017) but not $FMA_{hand/finger}$ (*t*(7) = -1.76, *p* = 0.122). Group II did not change in any uFMA sub-score. Independent of group, patients without detectable MEP did not show any changes in any of the uFMA sub-scores, while MEP+

was associated with changes of uFMA in the subscores for hand/finger ($FMA_{hand/finger}$: t(11) = -2.46, p = 0.032) and arm (FMA_{arm}: t(11) = -3.22, p = 0.008) (Table 4).

Insert Table 4 here

Discussion

We found that ipsilesional corticospinal system's integrity reflected by upper-limb MEP was associated with better motor improvement in both treatment groups, but motor recovery was superior in patients with MEP+ of group I in which ipsilesional brain activity during intended movements of the paralyzed upper limb was rewarded by contingent feedback compared to patients with MEP+ of group II receiving random feedback. Across groups, patients with MEP+ improved while patients with MEP- did not. Furthermore, only patients with MEP+ showed a trend for improvement in hand and finger function ($FMA_{hand/finger}$).

Interestingly, we did not find an association between upper limb motor function and MEP presence before the interventions. This implies that MEP was unspecific for motor function before treatment, but specific for intervention-related recovery. Both interventions, ipsilesional BMI training and behavioral physiotherapy, aimed at strengthening of the sensorimotor loop. While both interventions were combined in group I, sensory feedback during BMI training of group II was random and, thus, participants in group II received less contingent training of the ipsilesional sensorimotor system, but identical training time. These findings are in line with previous reports in acute and sub-acute patients.[38-41]

Of note, patients with MEP- showed improvement in group I. This indicates that in individual cases absence of upper-limb MEP does not exclude motor recovery associated with ipsilesional brain training. However, in absence of MEP, random BMI feedback and conventional behavioral physiotherapy did not result in any measurable improvements in motor function.

Our data suggest that irrespective the severity of motor deficits or chronicity of stroke, upper limb MEP might be a reliable biomarker for ipsilesional BMI training related motor recovery and potentially for any motor recovery in chronic stroke.

While previous studies indicated that MEP can be a predictor of motor outcome in acute and sub-acute stroke[26,39-42] our data complement these studies and provide evidence that this might be also valid for chronic stroke patients with severe motor deficits. Furthermore, they improve our understanding of the structural and functional prerequisites[43] for the development of effective neurorehabilitation strategies in chronic stroke patients with limited residual motor function.

Conclusion

Physiological integrity of corticospinal function in severe chronic stroke predicts response to ipsilesional brain training.

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Potential Conflicts of Interest

The authors have no Conflicts of Interest.

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Figure Legends:

FIGURE 1: Assessment of motor evoked potentials reflecting corticospinal system's integrity.

(A) Above threshold transcranial magnetic stimulation of the ipsilesional hemisphere results in detectable motor evoked potentials in the affected upper limb. (B) Transcranial magnetic stimulation does not result in detectable upper-limb motor evoked potentials reflecting significant damage of the corticospinal system.

FIGURE 2: Principle of ipsilesional brain-machine interface training. Ipsilesional brain activity as measured by sensorimotor rhythm (SMR) desynchronization recorded by electroencephalography associated with attempted finger movements results in contingent passive hand opening motions driven by an orthotic device attached to the patient's paralyzed hand.

FIGURE 3: Change of Motor Function Across Groups. Changes were measured as difference in Fugl-Meyer Assessment (uFMA) scores assessed before first training day and after the last training day. Whiskers indicate standard error (SE) of the mean. * $p<0.05$; *** $p<0.001$; n.s. = not significant.

Tables

TABLE 1

TABLE 1: Epidemiologic Data of The Study Participants

Patient Number	Group	MEP	Sex	Age (Years)	Months Since Stroke	Lesion Side	ΔFMA
1	I – Contingent	MEP+	M	69	72	L	3,5
2			M	51	139	R	2
3			F	35	60	R	3,5
4			M	48	45	R	6,5
5			M	70	23	L	3
6			M	57	122	R	3
7			M	29	25	R	3
8			M	60	130	L	2,5
9		MEP-	F	35	28	R	4
10			F	53	30	L	0
11			F	36	16	L	8
12			F	72	44	L	1
13			F	55	45	L	7,5
14			M	65	45	R	1,5
15			M	47	80	R	4
16			F	52	156	L	1,5
17	II – Random	MEP+	F	73	23	R	-1
18			M	51	16	L	1,5
19			M	50	215	L	0,5
20			F	55	17	R	1,5
21		MEP-	M	54	121	R	10
22			F	66	23	L	4,5
23			F	54	10	L	5
24			M	69	89	R	-4
25			M	40	53	R	1,5
26			M	47	232	R	-3,5
27			M	66	48	R	0,5
28			M	58	28	R	-4,5
29			M	40	46	L	-1,5
30			F	53	20	L	-5,5

Abbreviations: MEP = Motor Evoked Potential;
MEP+ = Patients with detectable upper limb MEP;
MEP- = Patients witn undetectable upper limb MEP;
FMA = Fugl-Meyer Motor Assessment

TABLE 2

TABLE 2: Intraclass Correlation Coefficients (ICC) of Pre-Intervention

FMA Sub-Score	Hand/ Finger	Arm	Total
Range	0 to 24	0 to 30	0 to 54
ICC	0,82	0,94	0,94

TABLE 3

TABLE 3: Within-Group Comparisons of Intervention Related Changes of Fugl-Meyer Assessment (FMA) Scores

	MEP	N	Pre		Post		Paired samples t-test		
			Mean FMA	SD	Mean FMA	SD	T	P	
Group I	MEP+	8	14,00	7,68	17,38	7,25	-7,04	0,000	***
	MEP-	8	8,31	5,03	11,75	7,76	-3,24	0,014	*
Group II	MEP+	4	9,63	15,97	10,25	15,97	-1,06	0,368	
	MEP-	10	14,75	8,51	15,00	8,88	-0,16	0,880	

MEP = motor evoked potential; MEP+ = patients with detectable upper limb MEP; MEP- = patients wit undetectable upper limb MEP; N = number of patients; FMA = Fugl-Meyer Assessment; SD = standard deviation; * $p<0.05$; *** $p<0.001$.

TABLE 4

TABLE 4 : Within- and Across Group Comparisons of Intervention Related Changes of Fugl-Meyer Assessment (FMA) Sub-Scores

Group	MEP	FMA	t	P-value	
I - Contingent	MEP+	Hand / Finger	-2,27462	0,0571	t
		Arm	-3,73484	0,0073	**
		Total	-7,03873	0,0002	***
	MEP-	Hand / Finger	-1,76022	0,1218	
		Arm	-3,10941	0,0171	*
		Total	-3,23529	0,0143	*
II - Random	MEP+	Hand / Finger	-1	0,3910	
		Arm	-1	0,3910	
		Total	-1,05802	0,3677	
	MEP-	Hand / Finger	-0,57937	0,5766	
		Arm	0,12778	0,9011	
		Total	-0,15703	0,8787	
Across Groups	MEP+	Hand / Finger	-2,45845	0,0318	*
		Arm	-3,22265	0,0081	**
		Total	-4,62899	0,0007	***
	MEP-	Hand / Finger	-1,18326	0,2530	
		Arm	-1,4331	0,1700	
		Total	-1,58934	0,1304	

Abbreviations: MEP = Motor Evoked Potential;
MEP+ = Patients with detectable upper limb MEP;
MEP- = Patients witn undetectable upper limb MEP;
FMA = Fugl-Meyer Motor Assessment; * p<0.05; **p<0.01;*** p<0.001, t=trend.

Figures

FIGURE 1

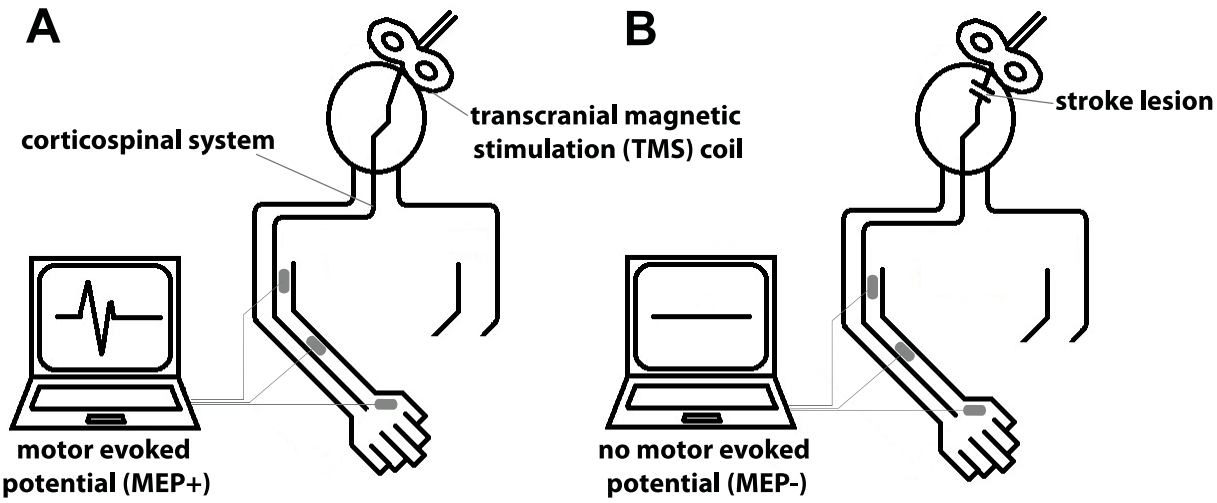


FIGURE 2

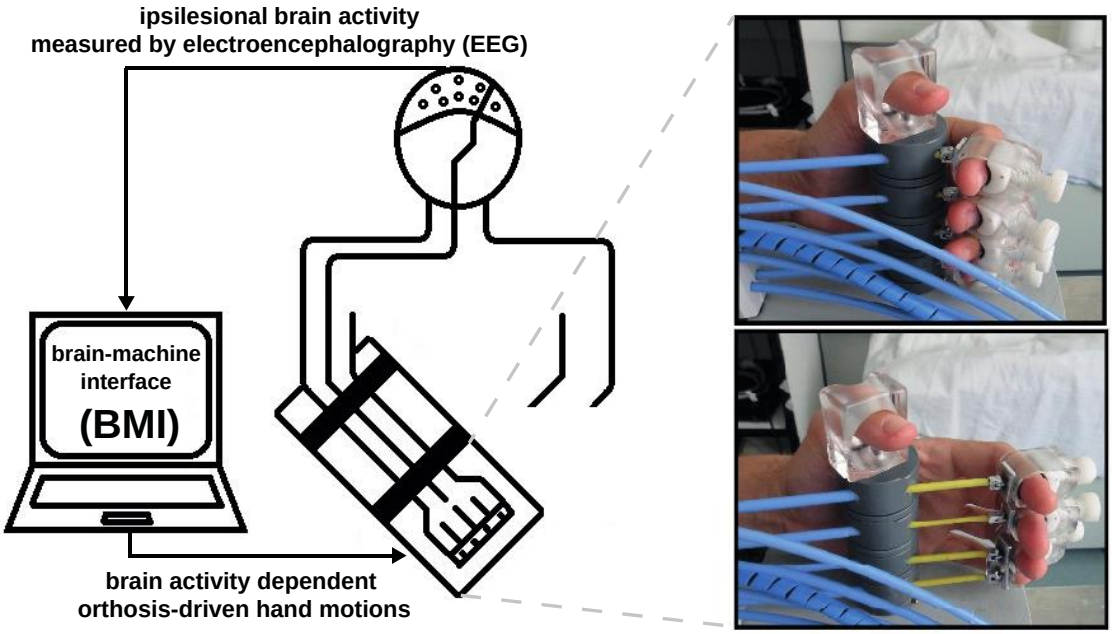
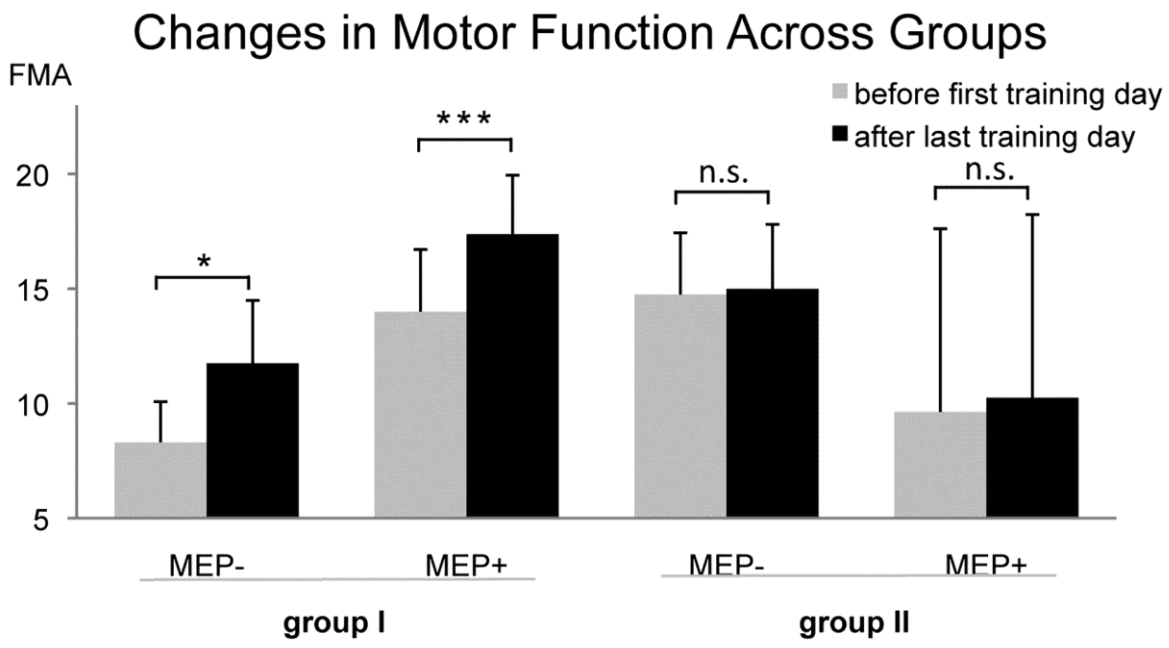


FIGURE 3


Changes in Motor Function Across Groups
FMA
before first training day
after last training day
20
15
10
5
*
***
n.s.
n.s.
MEP-
MEP+
MEP-
MEP+
group I
group II

Additional Supporting Information

SUPPLEMENTARY TABLES

SUPPLEMENTARY TABLE 1:

Fugl-Meyer Assessment Sub-Score	Functional Domain	Tested Function	Maximum Score
$FMA_{hand/finger}$	Motor skills hand and finger	wrist stability in 15° extension, elbow at 90°	2 points
		wrist flexion/extension elbow at 90°	2 points
		wrist stability in 15° extension, elbow at 0°	2 points
		wrist flexion/extension elbow at 0°	2 points
		wrist circumduction	2 points
		finger flexion	2 points
		finger extension	2 points
		grasp against resistance with metacarpophalangeal joints of digit 2and flex the proximal interphalangeal joints	2 points
		grasp of a scrap of paper	2 points
		grasp a pencil	2 points
		grasp a cylinder	2 points
		grasp a tennis ball	2 points
FMA_{arm}	Motor skills upper arm and forearm	“Touching the ipsilateral ear”: elevation, shoulder retraction, abduction, external rotation, forearm supination	12 points
		“Touching the contralateral knee”: shoulder adduction/internal rotation, elbow extension, forearm pronation	6 points
		Hand to lumbar spine	2 points
		Shoulder flexion 0-90°	2 points
		Pro-supination while elbow in flexion	2 points
		Shoulder abduction 0-90°	2 points
		Shoulder flexion 0-90°	2 points
		Pro-supination while elbow in extension	2 points

SUPPLEMENTARY TABLE 2. Lesion Locations of Study Participants

Patient Number	Lesion location
1	Subcortical lesion. Frontal and parietal lobe. Extensive white matter hypodensity of inferior frontal gyrus and precentral gyrus. Corona radiata, head of caudate nucleus, CI, genu, external capsule, putamen, thalamus, insula.
2	Mixedl lesion. Frontal and parietal lobe. Encephalomalacia in the frontal and parietal lobe. Midle and inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus.
3	Subcortical lesion. Frontal, parietal and temporal lobe. White matter of postcentral gyrus; midle temporal gyrus and angular gyrus. CI, Thalamus, external capsule, genu, tail of caudata nucleus.
4	Subcortical lesion. CI, genu, external capsule, putamen, thalamus, claustrum, head and tail of caudate nucleus, corona radiate, insula.
5	Mixed lesion. Frontal and parietal lobe. Inferior frontal gyrus; precentral gryus. External capsule, putamen, thalamus, CI, genu, insula.
6	Subcortical lesion. Corona radiata, external capsule, putamen, posterior CI, thalamus.
7	Mixed lesion. Frontal and parietal lobe. Inferior frontal gyrus; precentral gyrus. Insula cortex, external capsule, CI, head of caudate nucleus, genu, putame, thalamus.
8	Subcortical lesion. Parietal lobe. White matter of Precentral gyrus. Corona radiata, anterior CI, putamen, external capsule, thalamus, insula.
9	Mixed lesion. Frontal, parietal and temporal lobe. Inferior frontal gyrus; pre and postcentral gyrus. Corona radiata, head of caudata nucleus, CI, genu, external capsule, thalamus, putamen, insula.
10	Subcortical lesion. Corona radiata, external capsule, thalamus, putamen, CI, genu.
11	Mixed lesion. Frontal and parietal lobe. Midle and inferior frontal gyrus; postcentral gyrus. Corona radiata, caudata nucleus, external capsule, CI, genu, thalamus, putamen, insula.
12	Subcortical lesion. Frontal and parietal lobe. White matter of inferior frontal gyrus; pre and poscentral gyrus; supramarginal gyrus. Multiple nectrotic vesicles. Trunk of corpus callosum, head of caudata nucleus, corona radiata, putamen, external capsule
13	Subcortical lesion. Corona radiata, head of caudata nucleus, external capsule, CI, genu, putamen, thalamus, globus pallidus, claustrum.
14	Subcortical lesion. Parietal lobe. White matter of inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus. Corona radiata, thalamus, genu, partially CI, external capsule. Also affection the white matter underlying the right insular cortex.
15	Subcortical lesion. CI, genu, external capsule, claustrum, putamen, head of caudata nucleus, thalamus.
16	Mixed lesion. Frontal, parietal and temporal lobe. Superior, medial, midle and inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus; angular gyrus; midle and inferior temporal gyrus. Corona radiata, head of caudata nucleus, CI, genu, put
17	Mixed lesion. Frontal, parietal and temporal lobe. Superior, medial, midle and inferior fronta gyrus; pre and postcentral gyrus. Corota radiata,thalamus, putamen, posterior CI partialy, genu, external capsule, trunk of corpus callosum.
18	Mixed lesion. Frontal and parietal lobe and adjacent white matter with multiple necrotic. Middle and inferior frontal gyrus; pre and postcentral gyrus; middle temporal gyrus.
19	Subcortical lesion. Corona radiata, CI, genu, thalamus, external capsule, putamen, claustrum, insula and adjacent white matter.
20	Subcortical lesion. Corona radiata, body of caudate nucleus, external capsule, putamen, genu, anterior CI, insula cortex.
21	Mixed lesion. Frontal and parietal lobe and the adjacant white matter. Superior, medial, middle and inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus. Corona radiata, head of caudata nucleus.

SUPPLEMENTARY TABLE 2 (continued)

SUPPLEMENTARY TABLE 2 (continued). Lesion Locations of Study Participants

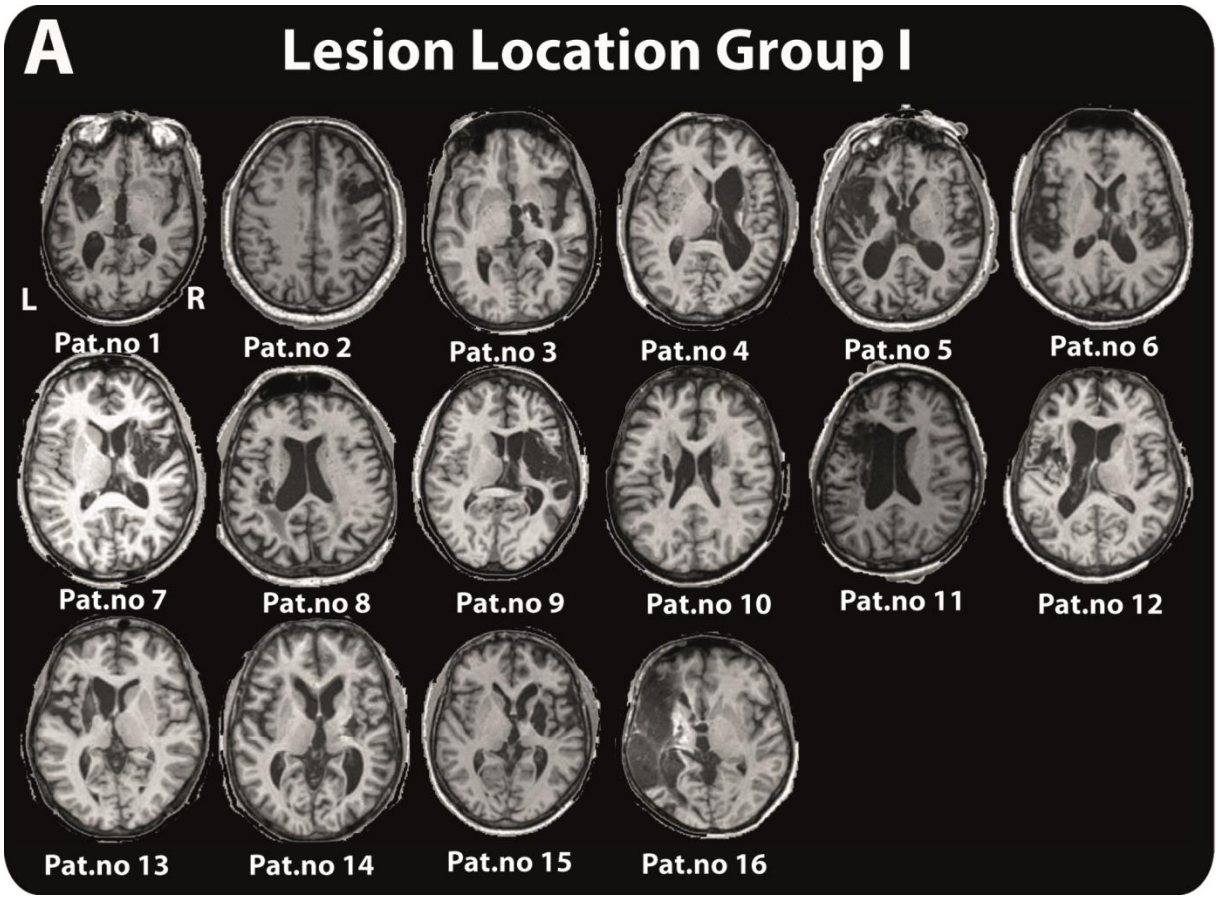
Patient Number	Lesion location
22	Mixed lesion. Frontal and parietal lobe. Superior, medial, midle and inferior frontal gyrus; pre and postcentral gyrus.
23	Mixed lesion. Frontal, parietal and temporal lobe. Inferior frontal gyrus; pre and postcentral gyrus; midle temporal gyrus. Corona radiata, CI, genu, external capsule, putamen, thalamus.
24	Mixed lesion. Frontal, parietal and temporal lobe. Middle and infeior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus; middle and inferior temporal gyrus. Corona radiata, head of caudate nucleous, CI, genu, external capsule, claustrum, putam
25	Mixed lesion. Frontal, parietal and temporal lobe. Inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus. Corona radiata, head of caudata nucleus, CI, genu, putamen, posterior part of external capsule, thalamus, claustrum, Gl. Palidus, tr
26	Mixed lesion. Frontal and parietal lobe. Precentral gyrus. Corona radiata, thalamus, putamen, posterior CI, claustrum, external capsule, insula.
27	Mixed lesion. Frontal, parietal and temporal lobe. Midle and inferior frontal gyrus; pre and postcentral gyrus. Corona radiata, external capsule, claustrum, putamen, insula.
28	Mixed lesion. Frontal, parietal and temporal lobe. Midle and inferior frontal gyrus; pre and postcentral gyrus; supramarginal gyrus; angular gyrus. Trunk of corpus callosum, corona radiata, caudata nucleus, claustrum, putamen, CI, genu, thalamus, external
29	Subcortical lesion. Head of caudate nucleous, CI, genu, external capsule, putamen, claustrum, corona radiata.
30	Subcortical lesion. Head of caudata nucelus, CI, genu, putamen, thalamus, corona radiata, external capsule, claustrum.

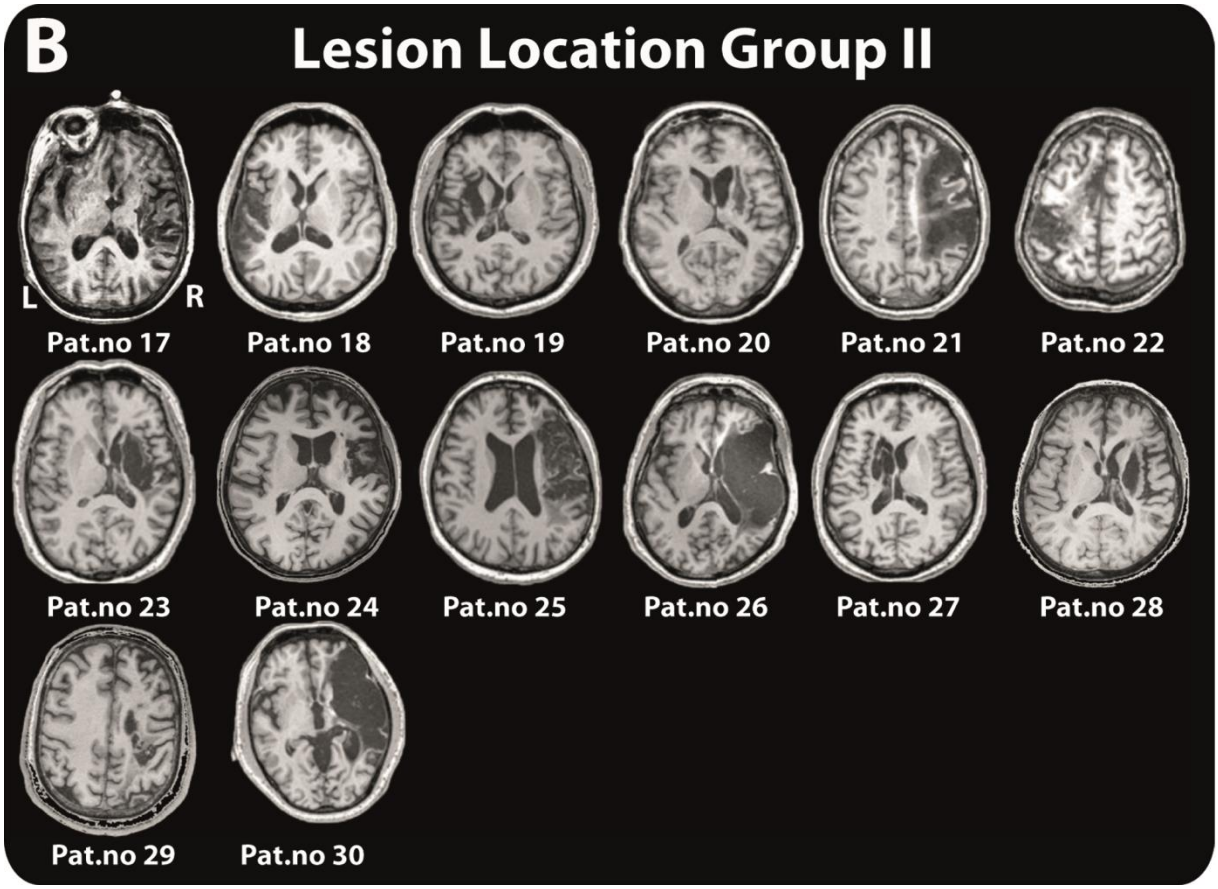
SUPPLEMENTARY TABLE 3

SUPPLEMENTARY TABLE 3 - Motor Evoked Potential (MEP) Location

Patient Number	FDI	APB	EPL	EDC	ECU	FCR	BB	TB
1				x	x		x	
2	x	x	x	x	x	x	x	x
3	x	x	x	x	x	x	x	x
4	x	x	x		x	x	x	
5	x	x	x					
6	x	x	x	x	x	x		
7		x	x	x	x	x	x	x
8	x	x						
9								
10								
11								
12								
13								
14								
15								
16								
17		x						
18	x	x	x				x	
19		x	x	x	x		x	x
20			x	x	x	x	x	x
21								
22								
23								
24								
25								
26								
27								
28								
29								
30								

Abbreviations: FDI = first dorsal interosseous; APB = abductor pollicis brevis; EPL = extensor pollicis longus; EDC = extensor digitorum communis; ECU = extensor carpi ulnaris; FCR = flexor carpi radialis; BB = biceps brachii and TB = triceps brachii


A
Lesion Location Group I
L
R
Pat.no 1
Pat.no 2
Pat.no 3
Pat.no 4
Pat.no 5
Pat.no 6
Pat.no 7
Pat.no 8
Pat.no 9
Pat.no 10
Pat.no 11
Pat.no 12
Pat.no 13
Pat.no 14
Pat.no 15
Pat.no 16


B
Lesion Location Group II
L
R
Pat.no 17
Pat.no 18
Pat.no 19
Pat.no 20
Pat.no 21
Pat.no 22
Pat.no 23
Pat.no 24
Pat.no 25
Pat.no 26
Pat.no 27
Pat.no 28
Pat.no 29
Pat.no 30

SUPPLEMENTARY FIGURE 1: Anatomical Images of Lesion Location in (A) Group I and (B) Group II.

5.3 – Publication 3 – The sensorimotor cortex and the event-related desynchronization (ERD)

Journal: The Journal of Neuroscience

Current status: Waiting for acceptance of the first publication to be submitted.

Personal Contribution:

- Data acquisition: fMRI, BMI training (orthosis and robot using EEG).
- Data analysis: event-related desynchronization (ERD), statistics.
- Text: all sessions.
- Figures/Tables: all figures and tables.

The sensorimotor cortex and the event-related desynchronization (ERD)

Abbreviated title: The sensorimotor cortex and the ERD

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Abstract

Brain-machine interface (BMI) has been used as an alternative rehabilitation strategy on chronic stroke patients to improve motor recovery. A better understanding of the necessary neural substrates to control the BMI is of fundamental importance for further applicability of this technique. In this study 39 severely affected chronic stroke patients with no finger extension underwent a 4-week of daily BMI training for one and half hour and succeeded by one hour of physiotherapy. Patients were separated by three feedback groups: contingent positive (event-related desynchronization (ERD) of the ipsilesional brain side was directly linked to hand orthosis movements); sham (no link between brain oscillations and orthosis movements); and contingent negative (event-related synchronization (ERS) was linked to orthosis movements) and subcategorized according to the integrity of sensorimotor cortex (preserved/affected – 18 subcortical, 21 mixed lesion, respectively) and thalamus (12 preserved, 27 affected). Motor function was tested before and after the intervention using the upper-limb Fugl-Meyer Motor Assessment (uFMA). We observed that patients with preserved sensorimotor cortex presented significantly stronger ERD generation and BMI control since first day of training, but no difference was found for integrity of thalamus. Furthermore, changes in uFMA scores were significant only for the contingent positive feedback group ($p < .000$), with better improvement of patients with subcortical ($p = .002$) than mixed lesion ($p = .013$). We conclude that ERDs generation is directly related to integrity of sensorimotor cortex. Thus patients with subcortical lesion have higher chance to control the BMI.

Keywords: Brain-machine interface (BMI), event related desynchronization (ERD), stroke rehabilitation, cortical/subcortical lesion.

Introduction (491 out of 500 words, including citations)

Brain–computer interfaces (BCI) or brain–machine interfaces (BMI) utilize neurophysiological signals originating in the brain to activate or deactivate external devices or computers (Birbaumer and Cohen, 2007). Each year approximately 20 million people suffer a stroke worldwide. Of those who survive, five million remain severely handicapped and dependent on assistance in daily life (McMahon, 2002). Currently, there is no accepted and efficient rehabilitation strategy available in patients with chronic stroke and no residual hand movements. BMI systems could be a solution for those who suffered a stroke and need to rehabilitate a completely paralyzed limb and a damaged brain at the same time (Birbaumer et al., 2008). Restorative BMI aim at selective induction of use-dependent neuroplasticity to facilitate motor recovery (Broetz et al., 2010; Caria et al., 2010; Nagaoka et al., 2010). BMI training, using e.g. electroencephalogram (EEG), is targeted toward a ‘‘strengthening’’ of the ipsilesional brain regions around the rewarded destroyed tissue and ‘‘weakening’’ of the homotypical regions in the opposite hemisphere (Birbaumer, 2006). This is achieved by using sensorimotor rhythm (SMR) oscillations (from 10 to 20 Hz) as a movement-directing source originating in the immediate neighborhood of the lesion (Birbaumer, 2006).

During various motor tasks, EEG studies showed a transient decrease of EEG power in the alpha band (Pfurtscheller, 1989) which is called event-related desynchronization (ERD) (Pfurtscheller, 1977). This decrease starts 1–2 s prior to the movement onset and is followed by a rebound-like increase just after termination of the movement called event-related synchronization (ERS) (Pfurtscheller, 1992). Numerous studies support the belief that alpha rhythms are strongly influenced by the thalamus (Hughes and Crunelli, 2005) and the strongest indication showing that the thalamus in promoting human alpha activities comes from reports of thalamic lesions, leading to a pronounced disorganization or even complete suppression of EEG alpha activity (Ohmoto

and others 1978; Terao and others 1993; Lukashevich and Sazonova 1996). Animal studies reinforced this concept by showing thalamo-cortical and cortico-cortical components interaction in the generation of cortical alpha rhythms and its propagation over the cortex (Lopes da Silva et al., 1980). Magnetoencephalography (MEG) and EEG studies suggested that the alpha rhythm could appear to arise from the somatosensory cortex, with sources clustered close to the hand region (Pfurtscheller, 1992; Salmelin R and Hari, 1994; Salmelin et al., 1995; Hari and Salmelin, 1997). Anatomical and functional pre-requisites for successful SMR-based BCI learning and mechanisms underlying clinical improvements need to be identified and well characterized (Soekadar et al., 2011a).

Here we investigate the influence of integrity of cortex and thalamus to control SMR in chronic stroke patients and their relationship with functional recovery. Patients were divided in three BMI feedback groups and trained daily for four weeks receiving one hour of physiotherapy after each session. Performance was defined as the difference in power of ERD during motor task. SMR oscillation was measured on the ipsilesional brain area close to the motor area and functional outcomes were measured before and after intervention.

Materials and Methods

Study design

A total of 39 severely affected chronic stroke patients participated on this SMR-ERD based BMI study. Patients were sitting comfortably in an upright position with a hand orthosis attached on the paretic side and using a 16-channel EEG cap. Patients were instructed to try to open and close their paralyzed fingers. A hand orthosis, attached to the paretic arm, would perform these movements. Following the idea that in

a restorative BCI, activity of ipsilesional motor networks becomes contingently rewarded by sensory input to induce central nervous system (CNS) plasticity and that might facilitate restoration of normal motor control (Soekadar et al., 2011b), the patients were separated in 3 different groups receiving 3 different feedback contingencies. The first group (n = 17) received contingent positive feedback (moving the orthosis with ERD), the second (n = 17) received sham feedback (the orthosis moved independently from brain activity but participants believed in their control) and the third (n = 5) received contingent negative feedback (moving the orthosis with ERS) (Ramos-Murguialday et al., 2012). The amount of time the orthosis was moving in sham feedback group was kept in the same range as in contingent feedback group (between 55-80% of each trial). All patients trained for one and half hour per day over four consecutive weeks and underwent one hour of physiotherapy after each session. Motor function of the upper limb was tested two months and one day before (pre1 and pre2), and immediately after (post1) the intervention using a modified version of the upper-limb Fugl-Meyer Motor Assessment (uFMA). All participants gave written informed consent. The study was approved by the University of Tübingen Ethics Committee.

Stroke Patients

Patients were recruited all over Germany via public information (German stroke association, hospitals and rehabilitation centers). A total of 504 were potentially eligible and contacted. From these, 39 (24 male, mean age: 54.6±11.7 years old; range 29 to 73 years; interval since stroke: 61.5±56.3 months; range: 10 to 232 months – Table 1; for characterization of lesion location see Table 2) were selected for the intervention and fulfilled the following inclusion criteria: age between 18 and 80 years, complete paralysis of one hand without ability for active finger extension, interval since stroke of

at least 8 months, no psychiatric or neurological condition other than stroke, no cerebellar lesion or bilateral motor deficit, no epilepsy, Mini-Mental State (MMS) score beyond 21, no contraindication for TMS assessment, no pregnancy, no claustrophobia, and ability to understand and follow instructions. Two patients (n = 1 from the contingent feedback group and n = 1 from the fake feedback group) didn't finish the intervention and only the first training sessions were considered. Patients were subcategorized according to the integrity of sensorimotor cortex (preserved/affected – 18 subcortical, 21 mixed lesion, respectively) and thalamus (12 preserved, 27 affected) using T1 brain images.

Insert Table 1 here

Assessments

Functional magnetic resonance (fMRI)

Patients' anatomical images were accessed before and after the intervention. Data were acquired using a 3 Tesla Siemens MRI system (Siemens TIM Trio, Erlangen, Germany). Functional MR images were acquired using a gradient-echo planar imaging (EPI) aligned in axial orientation: TR = 2000 ms; TE = 30 ms; flip angle = 90°; FOV = 210 mm; matrix size = 64; interslice gap = 0·75 mm; slices = 28; slice thickness = 3 mm. A T1-weighted anatomical MR images was acquired using a 1 mm isotropic MPRAGE sequence with the following parameters: TR = 2300 ms; TE = 3·03 ms; TI = 1100ms; flip angle = 8°; FOV = 256 x 256; matrix size = 256 x 256; number of slices = 176; slice thickness = 1 mm, bandwidth = 130 Hz/Px.

Insert Table 2 here

Motor function assessment

Motor function of the upper limb was repeatedly determined before (pre1 and pre2) as well as after intervention (post1) using the combined hand and arm motor part of the modified upper limb Fugl-Meyer Motor Assessment (uFMA) (Fugl-Meyer et al., 1975) (for a detailed description of the tested functions in each sub-score please see Table 3) a well-established and reliable measure of upper extremity function after stroke (Duncan et al., 1983; Gladstone et al., 2002) excluding sub-scales for coordination speed and reflexes as these measures showed to be unreliable in severe stroke (Crow and Harmeling-van der Wel, 2008). The uFMA, has 2 sub-scores for different functional domains (hand/finger and arm). The achievable maximum score is 54 ($FMA_{hand/finger}$: 24; FMA_{arm}: 30).

Insert Table 3 here

Interventions

BMI training

The training was done accordingly to individual impairment. Patients with FMA_{arm} scores smaller or equal to 10 started the BMI using the robotic arm (ReoGo, Motorika, Israel) and after two weeks – or accordingly to Physiotherapist decision, started to use the hand orthosis device. On the other hand, patients with FMA_{arm} scores

higher than 10 started the BMI training directly on the hand orthosis device. Functioning of both devices was the same, with ERD (for contingent positive feedback group) or ERS (for contingent negative feedback group) of SMR. For online signal processing and orthosis control during the training the BCI2000 software platform was used (www.BCI2000.org) (Wolpaw et al., 2002; Schalk et al., 2004). BCI2000 is based on a system model that consists of four modules (source, signal processing, user application and operator interface) (Schalk et al., 2004) and incorporates customizable signal filtering as well as extraction of signal features for translation into device control signals (Soekadar et al., 2011b).

During the training, electric brain activity was recorded by 16-channel EEG (BrainAmp 32-channel amplifier from Brain Products GmbH, Munich German) placed according to the international 10/20 system on the following channels (Fp1, Fp2, F3, F4, Fz, T7, T8, C3, C4, Cz, CP3, CP4, P3, P4, Pz, Oz). SMR changes in signal amplitudes recorded from the ipsilesional brain hemisphere during attempted arm or finger motions were translated online (delay 240ms) into reaching motions or hand opening and closing motions, respectively, driven by an robotic arm (ReoGo, Motorika, Israel) or an orthotic device fixed to the patient's paralyzed fingers (see Fig 1) (Buch et al., 2008; Soekadar et al., 2011a).

Insert Figure 1 here

Behavioral physiotherapy

After each training session patients received one-hour of behavioral physiotherapy in which improvements in execution of daily life relevant activities, e.g. grasping a stick, opening a door, holding a toothbrush, were systematically rewarded verbally and

by tapping the patient's arm or hand (Broetz et al., 2010). During attempted movements with the paralyzed limb, relevant muscles were touched and motions passively assisted.

Data Analysis

Event-related desynchronization (ERD)

Studies using EEG cap based on the 10-20 system showed that the electrodes C3 – on the left side, and C4 – on the right side, are located over the hand area (Pfurtscheller et al., 2000; Ramoser et al., 2000). On this study we compared alpha-ERD from the ipsilesional channel C on the beginning (ICb) and the end (ICe) of the training. ICb was chose from the better of the first two training sessions – where patients were naïve to BMI training – and ICe from the better of the two last training sessions.

ERD were computed based on the power method described by Pfurtscheller (1979) using the following equations:

$$RV = \frac{1}{|T_{ref}|} \sum_{t \in T_{ref}} P_t \qquad (1)$$

$$ERD(t) = \frac{P_t}{RV} - 1, \qquad t \in T_{task} \qquad (2)$$

Where: RV = reference value; P_t is the power estimate in a given frequency band of the t sample block.

Computation of ERD involved the power spectrum estimation (an autoregressive model of order 16 using the Yule–Walker algorithm) of the ongoing EEG signal associated with the specified SMR rhythm frequency range (9-13 Hz) (Soekadar et al., 2011b).

Patients were grouped into three groups according to ERD generation: Good control (ERD (power) < -15%) (Soekadar, 2011b), Medium control (-15% < ERD < -10%), Poor control (ERD > -10%).

Statistical Analyses

A one-way analysis of covariance (ANCOVA) [between-subjects factor: feedback (contingent positive, sham, contingent negative); covariates: lesion (cortical, subcortical) and thalamus (affected, preserved)] was conducted for ERD and uFMA on the beginning and end of training. A post-hoc independent samples t-test was applied. Comparisons of changes across training were done using a general linear model (GLM) based repeated-measures [between-subjects factor: feedback (contingent positive, sham, contingent negative); covariates: lesion (cortical, subcortical) and thalamus (affected, preserved)]. A paired-sample student's t-test was used to evaluate differences of within-group uFMA changes after the interventions in the total score and each sub-score ($FMA_{hand/finger}$; FMA_{arm}).

Intervention related changes of uFMA were calculated as the mean difference between pre1/pre2 and post. Statistical tests were performed by SPSS for Windows v.20 (SPSS Inc, Chicago, Illinois, USA). P-values < 0.05 were considered statistically significant.

Results

ERD

On the beginning of training an ANCOVA revealed for ICb no mean effects of feedback, $F(2, 34) = 1.81$, $p = .179$, $n_p^2 = .096$, but revealed an effect of lesion, $F(1, 34) = 9.30$, $p = .004$, $n_p^2 = .215$ and of thalamus, $F(1, 34) = 5.60$, $p = .024$, $n_p^2 = .142$. Post-hoc independent-samples t-test indicated that scores for ICb were significantly

better for subcortical lesion (*M* = -17.3, *SD* = 8.41) than for cortical lesion (*M* = -11.0, *SD* = 7.69), *t*(37) = 2.43, *p* = .020; but not for thalamus preserved (*M* = -15.2, *SD* = 6.94) than for thalamus affected (*M* = -13.3, *SD* = 9.22), *t*(37) = -0.62, *p* = .540. On the end of training an ANCOVA revealed no significant changes for ICe, with no mean effect of feedback, *F*(2, 33) = 1.32, *p* = .282, n_p^2 = .074, neither of thalamus *F*(1, 33) = 0.26, *p* = .612, n_p^2 = .008, but revealed effect of lesion, *F*(1, 33) = 9.98, *p* = .003, n_p^2 = .232. Post-hoc independent samples t-test indicated that scores for ICe were significantly better for subcortical lesion (*M* = -17.56, *SD* = 9.69) than for cortical lesion (*M* = -7.68, *SD* = 7.17), *t*(36) = 3.60, *p* = .001 (Figure 2). Table 4 shows the patients grouped according to the ERD generation and separated according the type of lesion on the beginning and end of training.

Insert Figure 2 here

Insert Table 4 here

Across training GLM repeated measures showed no difference for ERD of feedback *F*(2, 33) = 1.08, *p* = .325, n_p^2 = .061 nor of lesion *F*(1, 33) = .163, *p* = .689, n_p^2 = .005; but showed a significant difference of thalamus *F*(1, 33) = 7.57, *p* = .010, n_p^2 = .187. Post-hoc paired samples t-test indicated that scores were significantly better for thalamus preserved of ICb (*M* = -14.5, *SD* = 6.86) than of ICe (*M* = -7.90, *SD* = 7.46), *t*(10) = -5.72, *p* < .000; but no difference was seen for thalamus affected of ICb (*M* = -13.3, *SD* = 9.21) than of ICe (*M* = -14.2, *SD* = 10.1), *t*(26) = .530, *p* = .601. Figure 3

shows the distribution of patients with thalamus preserved/affected according to feedback group.

Insert Figure 3 here

Figure 4 show that ERD values were similar comparing the beginning and end of training, regardless the kind of lesion (cortical, subcortical), or integrity of thalamus.

Insert Figure 4 here

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uFMA

On the beginning of training an ANCOVA revealed for uFMA no mean effects of feedback, $F(2, 30) = .053$, $p = .948$, $n_p^2 = .004$, nor of lesion, $F(1, 30) = 0.316$, $p = .578$, $n_p^2 = .010$, nor of thalamus, $F(1, 30) = 1.35$, $p = .254$, $n_p^2 = .043$. In the end of training an ANCOVA revealed no significant changes for uFMA, with no mean effect of feedback, $F(2, 30) = .332$, $p = .720$, $n_p^2 = .022$, nor of lesion, $F(1, 30) = .077$, $p = .784$, $n_p^2 = .003$, nor of thalamus, $F(1, 30) = 2.53$, $p = .122$, $n_p^2 = .078$. Figure 5 shows correlation of ERD x uFMA improvement across training according to feedback group.

Insert Figure 5 here

Across training GLM repeated measures showed a significant difference for uFMA of feedback $F(2, 30) = 5.52$, $p = .009$, $n_p^2 = .269$, but no difference of lesion $F(1,$

30) = .657, p = .424, n_p^2 = .021, neither of thalamus $F(1, 30) = 2.17$, p = .151, n_p^2 = .067. Post-hoc paired-samples t-test indicated that uFMA scores were significantly higher for the contingent positive feedback group in the post (M = 14.6, SD = 7.81), than in the pre assessment (M = 11.2, SD = 6.93), $t(15) = -6.09$, $p < .000$; but were not significant different for the sham feedback group in the post (M = 13.6, SD = 10.9), than in the pre assessment (M = 13.3, SD = 10.7), $t(13) = -.316$, p = .757 (A. Ramos-Murguialday et al., unpublished observations); nor for the contingent negative feedback group in the post (M = 15.8, SD = 12.4), than in the pre assessment (M = 14.9, SD = 11.3), $t(4) = -.794$, p = .472. Figure 6 shows the differences in uFMA and ERD on the contingent positive feedback group.

Insert Figure 6 here

Discussion

In the present study we investigated the effects of lesion location in the ability to generate alpha-band event-related desynchronization (ERD) during attempt to move the hand in severely affected stroke patients. Patients trained to modulate alpha-ERD in the ipsilesional hemisphere for one month during brain-machine interface training. Our findings showed that patients with subcortical lesions (i.e., with preserved cortex) present significantly stronger alpha-ERD on the ipsilesional hemisphere as compared to patients with mixed lesions (i.e., affecting the sensorimotor cortex). The difference between the two groups was significant across all training sessions. Thus, these patients performed a more efficient BMI rehabilitation training due to the consistent control of the hand orthosis. On the other hand, patients with mixed lesion presented a poorer ERD generation and the BMI control decreased across training. The type of

lesion seems to have a stronger influence on the volitional ERD generation than the integrity of the thalamus. Functional outcomes improved only on the patients who received contingent positive feedback. In this group, patients with subcortical lesion presented better improvement in uFMA scores than patients with cortical lesion, and no difference was found according to thalamus integrity.

ERD

Our results are in line with previous findings, where ipsilesional hemispheres with pure subcortical lesions showed stronger ERD than the ones with mixed lesions (Pfurtscheller et al., 1981; Stepien et al., 2011). The significantly stronger SMR desynchronization was found during all training sessions regardless the integrity of thalamus. Thalamus integrity itself didn't show any significant difference in the ERD generation on the beginning or on the end of training. No difference was found for feedback group during the training time, in contradiction to results for healthy subjects, who showed improvements in ERD power across training for those in the contingent positive feedback group (Ramos-Murguialday, 2012). These results support a recent study that shows ipsilesional neural activity leading to control of paralyzed hand grasping function through a BCI after longitudinal training relies on structural and functional connectivity in both ipsilesional and contralesional parietofrontal pathways involved in visuomotor information processing (Buch et al., 2012) suggesting this component as an alternative to the thalamo-cortical and cortico-cortical for ERD generation. Therefore, the generation of alpha rhythms is structured on different levels with a definite role for thalamic regions, but also an active role for cortical circuits (Isaichev et al., 2001; Pritchard and Duke, 1997; Schurmann et al., 2000). These results therefore argue against the presence of a simple set of isolated thalamic "pacemakers," instead favoring a complex

interaction between cortical and thalamic oscillators as the basis for human α rhythms (Hughes and Crunelli, 2005).

We further investigated the effects of lesion location on ERD strength during training. Patients in the contingent positive feedback group presented an improvement in ERD generation across training, while patients on the other groups presented a weaker ERD. We also found a significant difference in ERD generation related to thalamus integrity. Patients with thalamus preserved showed a significant decrease of ERD during the training sessions. One possible explanation to this finding is related to the feedback group. Three patients were in the contingent negative feedback group had the thalamus preserved. In this group, patients were rewarded with ERS instead of ERD and some of these patients started to synchronize instead of desynchronize SMR. Thus, ERD generation got weaker across training. Besides these three patients, seven were in the sham feedback group, and only one was in the contingent positive feedback group - whose ERD kept significantly better across training. Inter-individual variations may have also influenced the results (Stepien et al., 2011).

Stroke patients presented a lower ERD power when compared to healthy volunteers (unpublished observation). One possible explanation is that the amplitude of brain waves oscillations is proportional to the number of synchronously active neurons (Elul, 1971; Nunes and Srinivasan, 2006). Since the generation of neuronal oscillations depends on local and remote connections between neurons (Jones et al., 2000), the disruption of such connectivity, e.g., due to stroke, might influence the reactivity of the neuronal networks (Stepien et al., 2011). For this reason, we suggest that for patients with mixed lesion, the use of the contralesional hemisphere might represent a more efficient solution for assistive or restorative BMI training (F. L. Brasil et al., unpublished observations).

uFMA

A review of 36 trials involving 3,717 patients, found a statistically significant negative association between effect sizes in individual trials, in terms of the effectiveness of rehabilitation, and the post-stroke timing of the first therapeutic intervention (Ottenbacher and Janell, 1993). Their finding suggests that stroke rehabilitation has an optimal time window for obtaining favorable effects (Kwakkel et al., 1999).

In this study we worked with severely affected chronic stroke patients. This patient group has in this moment no efficient rehabilitation strategy available, and no more spontaneous recovery is expected after 6 months of stroke. The relationship between skill and this property of ipsilesional structural connectivity is consistent with damage to descending corticospinal or corticothalamic pathways typically observed in patients with severe motor deficits (Newton et al., 2006; Ward et al., 2006). Across training functional outcomes showed significant improvements in uFMA scores in the contingent positive feedback group, but not on the sham feedback nor in the contingent negative feedback groups. No significant difference was found related to type of lesion or integrity of thalamus.

Conclusion

We conclude that type of lesion (subcortical/mixed affecting the sensorimotor cortex) has a significant influence in the generation of alpha-ERD. Therefore, patients with pure subcortical lesion were able to control the BMI during the process of rehabilitation. Besides that, ERD-based BMI with contingent positive feedback resulted in significant improvements in uFMA scores for the patients in this group. Thus, this BMI rehabilitation strategy rises as an alternative solution for treatment of chronic stroke patients. We hope that this knowledge could eventually be used in concert with non-invasive brain stimulation protocols (Hummel et al., 2005; Boggio et al., 2007; Nowak

et al., 2008; Celnik et al., 2009; Edwards et al., 2009; Grefkes et al., 2010) to sculpt plasticity in a manner that promotes the formation of adaptive network solutions allowing for better volitional control of sensorimotor or other brain rhythms (Buch et al., 2012), including beta (Bai et al., 2008), gamma (Grosse-Wentrup et al., 2011b) and slow cortical oscillations (Hinterberger et al., 2005), not studied in this investigation.

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Legends

Figure 1 – Robotic arm and orthosis device.

Figure 2 – Boxplot comparing ERD on the beginning (ICb) and end (ICe) of training according to type of lesion (lower values are better). Whiskers bars represent standard deviation (SD) and circle represent outlier.

Figure 3 – Distribution of patients with thalamus preserved/affected according to feedback group. Note that 3 patients with thalamus preserved were on the contingent negative feedback group. These patients showed stronger event-related desynchronization (ERD) on the beginning of training (ICb) than on the end (ICe). One possible cause for that is that patients were controlling the brain-machine interface (BMI) using event-related synchronization (ERS) and they noticed that the hand orthosis was working more often during ERS instead of ERD and stopped to desynchronize the sensorimotor rhythm (SMR).

Figure 4 – Patients event related desynchronization (ERDs) on ipsilesional channel C on the beginning (ICb) and end (ICe) of training. Figure a) shows ERD value according to type of lesion (cortical x subcortical). Figure b) shows ERD value according to the integrity of thalamus. Note that for type of lesion there is a clear group polarization, but not for thalamus. For both cases, lower values are better.

Figure 5 – 3-D scatter plot showing ERDs on ipsilesional channel C on the “beginning (ICb)” x “end (ICe)” of training x delta u_FMA scores.

Figure 6 – Difference of uFMA across training on the contingent feedback group according to the type of lesion. The comparison of uFMA on this group according to the thalamus can't be done due to the number of patients with thalamus preserved on this group (n=1), as showed on Figure 3. Asterisks denote *$p < .05$; **$p < .01$; n.s. = not significant. On figure a) higher is better; b) lower is better. Only patients with subcortical lesion kept the BMI control constant across training.

Table 1 – Patients demographics

Table 2 – Lesion description

Table 3 – Modified upper-limb Fugl-Meyer Motor Assessment (FMA) scores

Table 4 – Patients grouped according to the ERD generation and separated according the type of lesion on the beginning and end of training.

Illustration and Tables

Table1

Table 1. Patients demographics

		Lesion			Age	Months		ERD	
Patient	Feedback	Side	Type	Gender	(years)	Since Stroke	uFMA	Pre	Post
1	P	R	S	M	48	45	9/6/14	-6,38	-9,24
2	P	L	S	F	53	30	5/5/5	-28,70	-16,45
3	P	R	M	F	35	28	11/11/15	1,65	0,03
4	P	R	S	F	35	60	24/27/29	-37,35	-23,09
5	P	R	M	M	29	25	13/17/18	-23,30	-21,41
6	P	L	S	F	72	44	2/2/3	-16,80	-7,18
7	P	L	M	F	36	16	11/11/19	-14,47	-9,48
8	P	L	S	M	60	130	6/13/12	-17,70	-24,21
9	P	L	S	M	69	72	6/5/9	-21,04	-22,05
10	P	R	M	M	51	139	25/23/26	-12,13	-5,18
11	P	R	S	M	65	45	4/3/5	-16,14	-11,45
12	P	L	M	F	52	156	4/7/7	-21,10	-22,00
13	P	L	S	F	55	45	12/21/24	-19,92	-20,96
14	P	R	S	M	47	80	9/15/16	-11,80	-16,47
15	P	R	M	M	64	23		-8,39	
16	P	L	M	M	70	23	9/7/11	-0,70	-6,79
17	P	R	S	M	57	122	17/17/20	-8,16	-20,58
18	F	R	M	M	69	89	25/27/22	-10,76	-8,41
19	F	L	S	M	40	46	32/29/29	-25,85	-20,69
20	F	R	M	M	40	53	4/3/5	-4,88	2,05
21	F	R	M	M	54	121	14/18/26	-24,18	-19,86
22	F	L	S	F	53	20	16/19/12	-26,34	-24,53
23	F	L	M	F	54	10	9/7/13	-2,25	-4,99
24	F	L	S	M	50	215	35/32/34	-11,90	-30,42
25	F	L	M	M	51	16	5/2/5	-3,45	1,99
26	F	R	M	M	66	48	6/9/8	-17,23	-8,93
27	F	R	S	M	47	232	14/13/10	-17,14	-38,51
28	F	R	M	F	73	23	2/0/0	-5,78	-8,55
29	F	R	M	M	58	28	9/8/4	-3,89	-10,74
30	F	R	S	M	62	10		-11,61	-14,90
31	F	L	M	F	66	23	17/16/21	-12,69	-5,28
32	F	R	M	M	59	28		-11,47	-2,44
33	F	R	S	F	55	17	1/0/2	-19,03	-6,76
34	F	R	M	M	50	10		-22,48	
35	N	R	S	M	65	67	8/6/10	-8,05	-12,23
36	N	R	M	F	65	131	8/9/10	-8,15	-10,66
37	N	R	S	F	65	99	6/9/6	-6,78	3,66
38	N	R	M	F	31	15	33/34/37	-8,61	1,60
39	N	R	M	M	60	14	14/22/16	-16,76	-10,68

Feedback: P = Contingent Positive, S = Sham, N = Contingent Negative
Lesion type: S = Subcortical, M = Mixed (cortical + subcortical)

Table 2

Table 2. Lesion location

Patient	Lesion
1	SL; CIa, CIg, CIp, EC, Pu, Th, HCd, CR, INS.
2	SL; CR, EC, Th, Pu, CIa, CIg, CIp.
3	ML; FL, PL, TL; IFG, PrG, PoG; CR, HCd, CIa, CIg, CIp, EC, Th, Pu, INS.
4	SL; FL, PL, TL; PoG, MTG, AG; CIa, CIg, CIp, Th, EC, Cd.
5	ML; FL, PL; IFG, PrG; EC, CIa, CIg, CIp, HCd, Pu, Th, INS.
6	SL; FL, PL; IFG, PrG, PoG, SMG; TCC, HCd, CR, Pu, EC, CIa, CIg, CIp, Th.
7	ML; FL, PL; MFG, IFG, PoG; CR, Cd, EC CIa, CIg, CIp, Th Pu, INS.
8	SL; PL; PrG; CR, CIa, Pu, EC, Th, INS.
9	SL; FL, PL; IFG, PrG, CR, HCd, CIa, CIg, CIp, EC, Pu, Th, INS.
10	ML; FL, PL; MFG, IFG, PrG, PoG, SMG.
11	SL; PL; IFG, PrG, PoG, SMG; CR, Th, CIa, CIg, CIp, EC.
12	ML; FL, PL, TL; SFG, MeFG, MFG, IFG, PrG, PoG, SMG, AG; MTG, ITG; CR, HCd, CIa, CIg, CIp, Pu, Th, EC, TCC, INS.
13	SL; CR, HCd, EC, CIa, CIg, CIp, Pu, Th.
14	SL; CIa, CIg, CIp, EC, Pu, HCd, Th.
15	MS; PL, TL; PrG, PoG, MTG; CR, HCd, Pu, CIa, CIg, CIp, Th, EC.
16	ML; FL, PL; IFG, PrG; EC, Pu, Th, CIa, CIg, CIp, INS.
17	SL; CR, EC, Pu, ICp, Th.
18	ML; FL, PL, TL; MFG, IFG, PrG, PoG, SMG, MTG, ITG; CR, HCd, CIa, CIg, CIp, EC, Pu, TCC, INS, Th.
19	SL; Hcd, CIa, CIg, CIp, EC, Pu, CR.
20	ML; FL, PL, TL; IFG, PrG, PoG, SMG; CR, HCd, CIa, CIg, CIp, Pu, EC, Th, TCC, INS.
21	ML; FL, PL; SFG, MeFG, MFG, IFG, PrG, PoG, SMG; CR, HCd.
22	SL; HCd, CIa, CIg, CIp, Pu, Th, CR, EC.
23	ML; FL, PL, TL; IFG, PrG, PoG, MTG; CR, CIa, CIg, CIp, EC, Pu, Th.
24	SL; CR, CIa, CIg, CIp, Th, EC, Pu, INS.
25	ML; FL, PL, MFG, IFG, PrG, PoG, MTG.
26	ML; FL, PL, TL; MFG, IFG, PrG, PoG; CR, EC, Pu, INS.
27	CSL; FL, PL; PrG; CR, Th, Pu, CIp, EC, INS.
28	ML; FL, PL, TL; SFG, MeFG, MFG, IFG, PrG, PoG; CR, Th, Pu, CIg, CIp, EC, TCC.
29	ML; FL, PL, TL; MFG, IFG, PrG, PoG, SMG, AG; TCC, CR, Cd, Pu, CIa, CIg, CIp, Th, EC, INS.
30	ML; FL, PL, TL; SMG, PoG; HCd, CR, Pu, EC, CIa, CIg, CIp, Th, TCC, INS.
31	ML; FL, PL; SFG, MeFG, MFG, IFG, PrG, PoG.
32	ML; FL, PL; SFG, MeFG, MFG, IFG, PrG; EC, Pu, INS.
33	SL; CR, Cd, EC, Pu, CIa, CIg, INS.
34	MS; FL, PL, TL; PrG, PoG, MTG; CIa, HCd, CR, Pu, EC, INS.
35	SL; FL, PL, TL; PrG, PoG, SMG; CR, CIa, CIg, CIp, EC, Pu, Th, HCd, TCC, INS.
36	ML; FL, PL; SFG, MeFG, IFG, PrG, PoG, SMG.
37	SL; FL, PL, TL; IFG, PrG, PoG; HCd, CR, CIa, CIg, CIp, Pu, EC, Th, INS.
38	ML; FL, PL; SFG, MeFG, MFG, IFG, PrG, PoG. CR, Pu, EC, INS.
39	ML; FL, PL; PrG, PoG, CR.

Lesion: SL = subcortical, ML = mixed. Lobe: FL = frontal, PL = parietal, TL = temporal.
Gyrus: SFG = superior frontal, MeFG = medial frontal, MFG = midle frontal, IFG = inferior frontal, PrG = precentral, SMG = supramarginal, PoG = postcentral, AG = angular, MTG = midle temporal, ITG = inferior temporal.
HCd = head of caudate nucleus; CR = corona radiata; Pu = putamen; EC = external capsule; Th = thalamus; CIa = anterior capsula interna; CIg = genu; CIp = posterior capsula interna; TCC = trunk of corpus callosum; Cd = caudate nucleus; GP = globus pallidus; INS = insula;

Table 3

TABLE 3: Fugl-Meyer Assessment (FMA) Subscores

FMA SubScore	Functional Domain	Tested Function	Maximum Score
$FMA_{hand/finger}$	Motor skills hand and finger	wrist stability in 15° extension, elbow at 90°	2 points
		wrist flexion/extension elbow at 90°	2 points
		wrist stability in 15° extension, elbow at 0°	2 points
		wrist flexion/extension elbow at 0°	2 points
		wrist circumduction	2 points
		finger flexion	2 points
		finger extension	2 points
		grasp against resistance with metacarpophalangeal joints of digit 2and flex the proximal interphalangeal joints	2 points
		grasp of a scrap of paper	2 points
		grasp a pencil	2 points
		grasp a cylinder	2 points
		grasp a tennis ball	2 points
FMA_{arm}	Motor skills upper arm and forearm	"Touching the ipsilateral ear": elevation, shoulder retraction, abduction, external rotation, forearm supination	12 points
		"Touching the contralateral knee": shoulder adduction/internal rotation, elbow extension, forearm pronation	6 points
		Hand to lumbar spine	2 points
		Shoulder flexion 0-90°	2 points
		Pro-supination while elbow in flexion	2 points
		Shoulder abduction 0-90°	2 points
		Shoulder flexion 0-90°	2 points
		Pro-supination while elbow in extension	2 points

Table 4

Table 4 - Patients grouped according to ERD generation

		Subcortical		Mixed	
ERD	Control	Thalamus Affected	Thalamus Preserved	Thalamus Affected	Thalamus Preserved
ICb	Good	9	2	2	4
	Medium	3	0	2	3
	Poor	4	0	7	3
ICe	Good	10	1	2	2
	Medium	3	0	1	2
	Poor	3	1	8	6

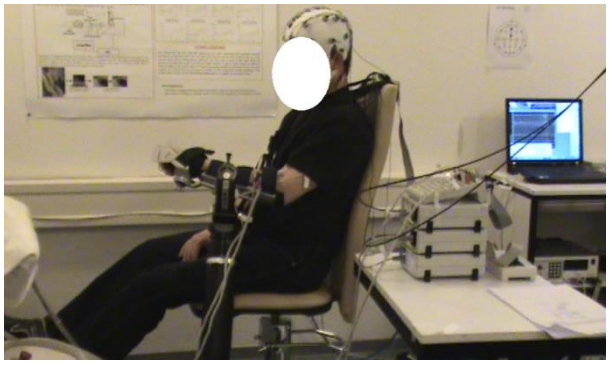
ICb = ipsilesional channel C on the beginning of training

ICe = ipsilesional channel C on the end of training

Good: ERD < -15; Medium: -15 < ERD < -10; Poor: ERD > -10

Figure 1

a) Robot – arm movement



b) Orthosis – finger movement

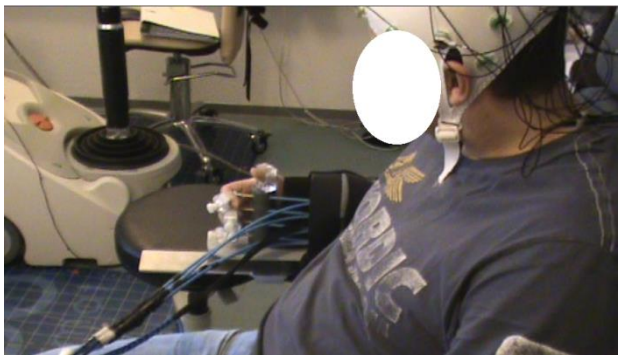


Figure 2

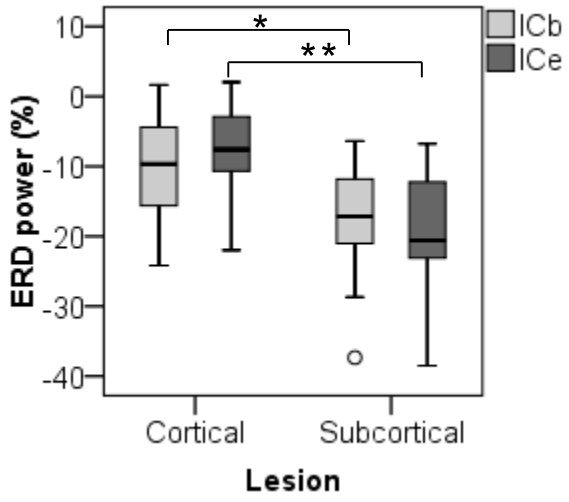


Figure 3

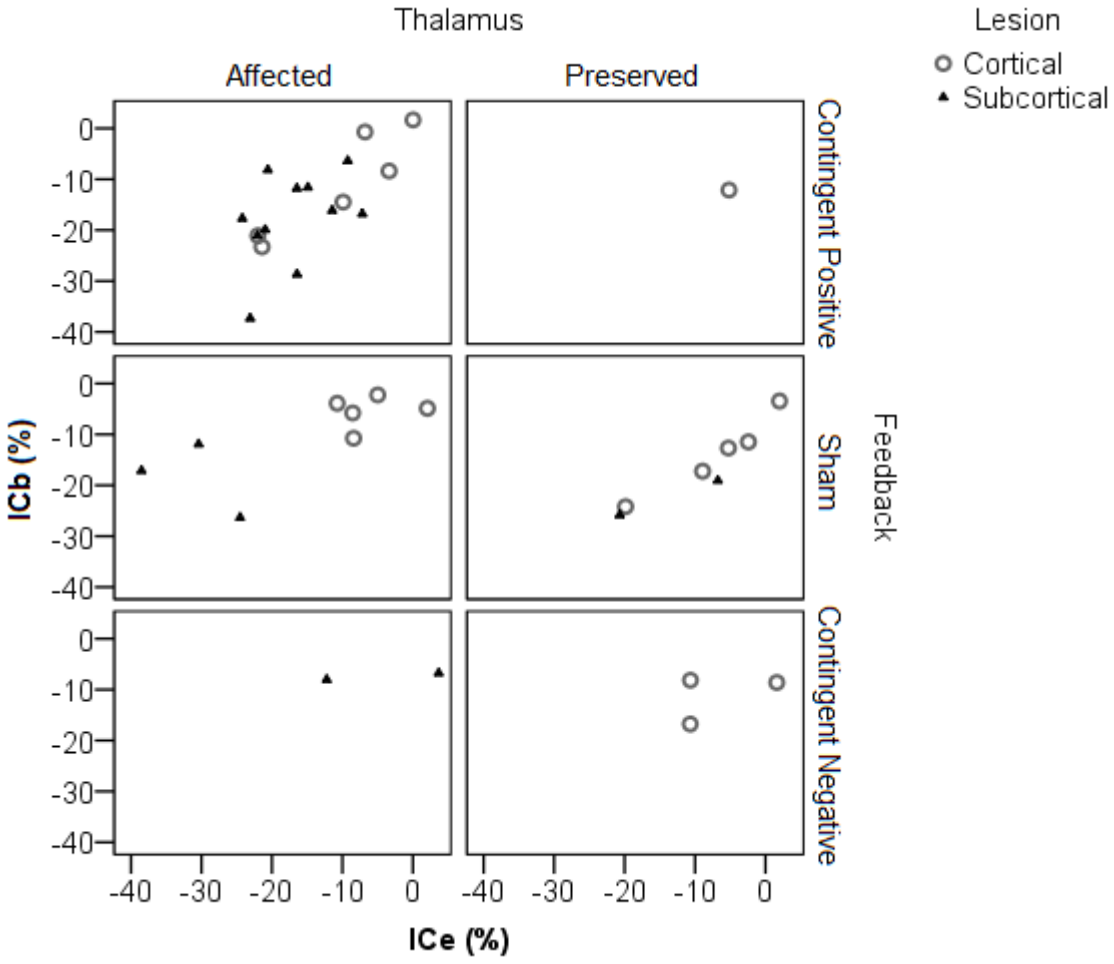
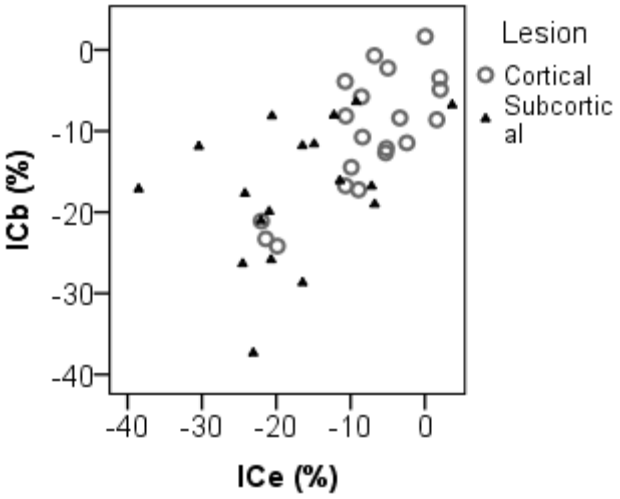

Thalamus
Affected
Preserved
Lesion
Cortical
Subcortical
Contingent Positive
Sham
Contingent Negative
Feedback
ICb (%)
ICe (%)
0
-10
-20
-30
-40

Figure 4

a)


Lesion
Cortical
Subcortical
ICb (%)
ICe (%)
0
-10
-20
-30
-40
-40
-30
-20
-10
0

b)

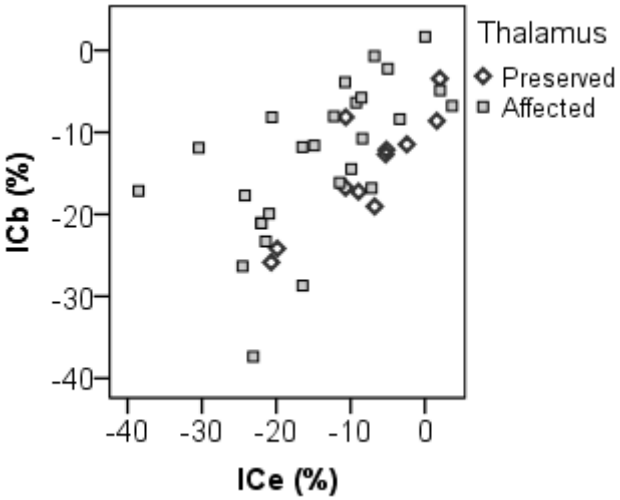

Thalamus
Preserved
Affected
ICb (%)
ICe (%)
0
-10
-20
-30
-40
-40
-30
-20
-10
0

Figure 5

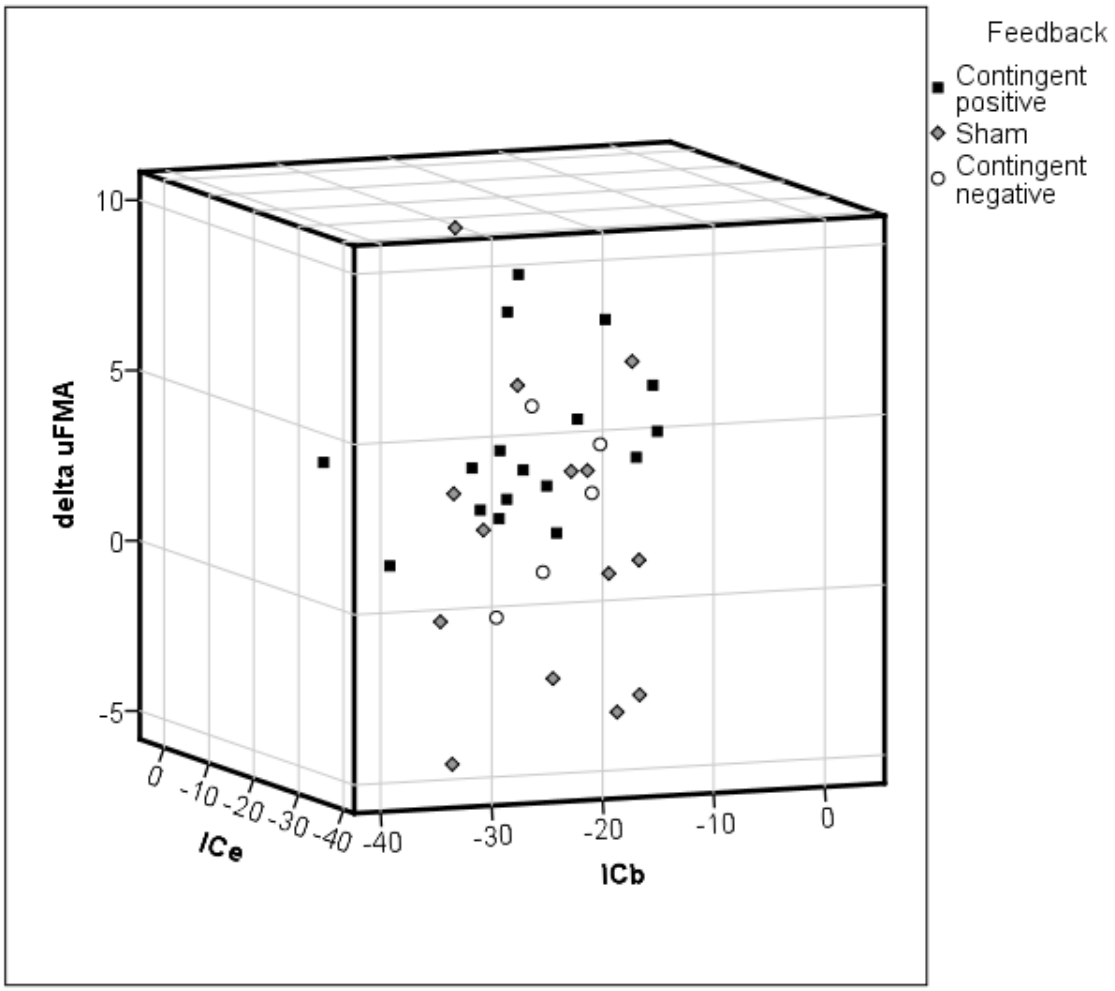
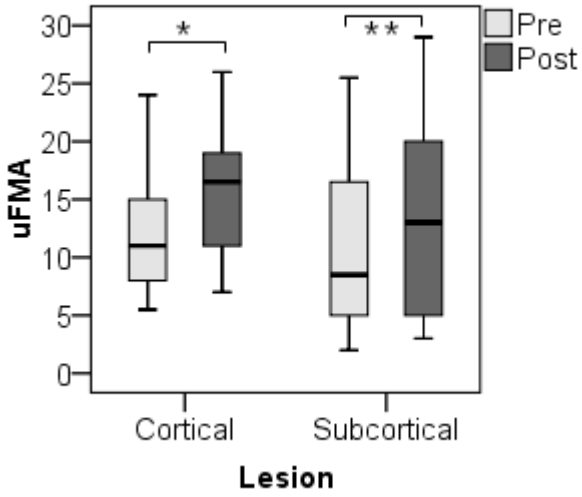
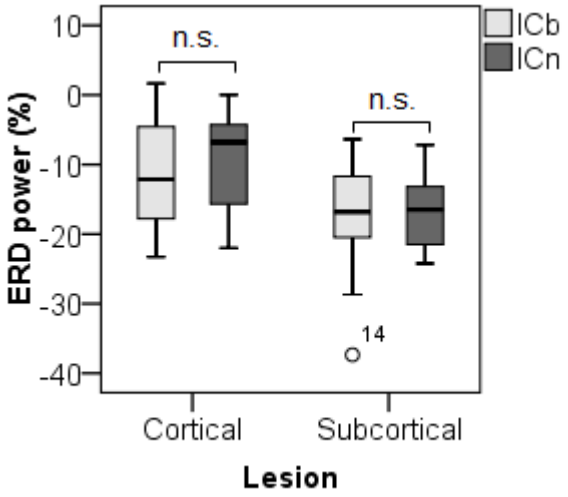

Feedback
Contingent positive
Sham
Contingent negative
delta uFMA
10
5
0
-5
ICe
0
-10
-20
-30
-40
ICb
-40
-30
-20
-10
0

Figure 6

a)


30
25
20
15
10
5
0
uFMA
*
**
Pre
Post
Cortical
Subcortical
Lesion

b)


10
0
-10
-20
-30
-40
ERD power (%)
n.s.
n.s.
14
ICb
ICn
Cortical
Subcortical
Lesion

5.4 – Publication 4 – Controlling assistive machines in paralysis using brain waves and other biosignals

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Personal Contribution:

- Data acquisition: x-x-x
- Data analysis: x-x-x
- Text: all sessions and editing.
- Figures/Tables: x-x-x

Advances in Human-Computer Interaction
Special Issue: Using Brain Waves to Control Computers and Machines

Title: Controlling assistive machines in paralysis using brain waves and other biosignals

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Abstract

The extent to which humans can interact with machines significantly enhanced through inclusion of speech, gestures and eye movements. However, these communication channels depend on a functional motor system. As many people suffer from severe damage of the motor system resulting in paralysis and inability to communicate, the development of brain-machine interfaces (BMI) that translate electric or metabolic brain activity into control signals of external devices promises to overcome this dependence. People with complete paralysis can learn to use their brain waves to control prosthetic devices or exoskeletons. However, information transfer rates of currently available non-invasive BMI systems are still very limited and do not allow versatile control and interaction with assistive machines. Thus, using brain waves in combination with other biosignals might significantly enhance the ability of people with a compromised motor system to interact with assistive machines. Here we give an overview of the current state of assistive, non-invasive BMI research and propose to integrate brain waves and other biosignals for improved control and applicability of assistive machines in paralysis. Besides introducing an example of such a system, potential future developments are being discussed.

Introduction

The way humans interact with computers has changed substantially in the last decades. While for many years, the input from the human to the machine was mainly managed through keystrokes, then later through hand movements using a computer mouse, other potential input sources have been opened up allowing more intuitive and effortless control e.g. based on speech [1], gestures [2] or eye movements [3], all depending on a functional motor system.

As cardiovascular diseases increase and people live longer, an increasing number of people suffer from conditions that affect their capacity to communicate or limit their mobility [4], e.g. due to stroke, neurodegenerative disorders or hereditary myopathies. Motor disability can also result from traumatic injuries, affecting the central or peripheral nervous system or can be related to amputations of the upper or lower extremities. While these handicapped people would benefit the most from assistive machines, their capacity to interact with computers or machines is often severely impeded.

Among the most important causes of neurological disabilities resulting in permanent damage and reduction of motor functions or the ability to communicate are stroke, multiple sclerosis (MS), spinal cord injury (SCI), brachial plexus injury (BPI) and neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) or dementia [4]. Stroke is the leading causes of long-term disability in adults and affects approximately 20 million people per year worldwide [5, 6]. Five million remain severely handicapped and dependent on assistance in daily life [4]. Nearly 30% of all stroke patients are under the age of 65 [7]. Other diseases resulting in paralysis at such early age include MS, affecting more than 2.5 million people worldwide [8], or SCI with 12.1 to 57.8 cases per million [9, 10]. BPI, the disruption of the upper limb nerves leading to a flaccid paralysis of the arm, affects thousands of people every year [11]. Furthermore, every year there are approximately 2,000 new traumatic upper limb amputations in Europe [12].

While there is major progress in the development of assistive apparatuses built for instance to compensate for a lost or paralyzed limb e.g. lightweight and versatile prostheses or exoskeletons [13], intuitive and reliable control of such devices is an enormous challenge.

Previous surveys on the use of artificial hands revealed that up to 50% of the amputees are not using their prosthetic hand regularly, mainly due to low functionality, poor cosmetic appearance and low controllability [14].

Since early on, use of electromyographic (EMG) signals for prosthetic control, e.g. from the amputee's stump or contralateral chest muscles, was an important concept [15, 16]. However, its broader success is still limited due to many practical reasons that are valid for all assistive systems that depend on recording biosignals, primarily the effort and costs to provide good signal quality, a fast and effective calibration process and, last but not least, the benefit of the system in the user's everyday life. Increasing signal-to-noise ratios or specificity of such recordings, e.g. by introducing electric nerve stimulation [17] or other techniques, are variables in a complex cost-benefit equation [18]. Adding sensory qualities during utilization of prosthetic devices increasing the bi-directional interaction between users and the machine improves functionality of assistive systems [19]. Here, however, the same limitation applies as to the motor domain that the majority of such systems depends on an intact peripheral sensory system.

Thus, development and provision of assistive machines that are independent of the peripheral nervous system's integrity represents a promising and appealing perspective. Particularly, if controlled intuitively and without requiring extensive training to gain reliable control.

Brain-Computer and Brain-Machine Interfaces – A general overview

Since it was discovered that brain waves contain information about cognitive states [20, 21] and can be functionally specific [22, 23], the idea to use such signals for direct brain control of assistive machines became a major driving force for the development of so called brain-computer or brain-machine interfaces (BCI / BMI) [24]. Such interfaces allow direct translation of electric or metabolic brain activity into control signals of external devices or computers bypassing the peripheral nervous and muscular system.

As neural or metabolic brain activity can be recorded from sensors inside or outside the brain, BCI/BMI are categorized as invasive or non-invasive systems [25]. Other categorizations relate to the specific brain signal used for BCI/BMI control or the mode of operation (see table 1).

Invasively recorded brain signals that were successfully used for BCI/BMI control include single-spike or multi-unit activity and local field potentials (LFP) [26]. These signals are necessarily recorded from inside the skull, while electric or magnetic brain oscillations reflecting pattern formation of larger cell assemblies' activity [27] can also be recorded from outside the skull using electro- or magnetoencephalography (EEG/MEG), while each method offers access to specific unique properties of brain

activity [28]. These non-invasive techniques allow e.g. detection and translation of slow cortical potentials (SCP), changes of sensorimotor rhythms (SMR) or event-related potentials (ERP), e.g. the P300, translating them into control signals for external devices or computers. More recently, online interpretation of changes in metabolic brain activity [29, 30] was introduced for BCI/BMI application offering high spatial (in the range of mm), but low temporal resolution (in the range of seconds). These systems use functional magnetic resonance imaging (fMRI) [29] or near-infrared spectroscopy (NIRS) [30, 31], both measuring changes in brain tissue's blood oxygenation level dependent (BOLD) signals [25].

In 1969, Eberhard Fetz demonstrated that single neurons in precentral cortex can be operantly conditioned by delivery of food pellets [32]. Since then, operant conditioning of cortical activity was demonstrated in various paradigms [33], requiring, though, opening of the skull and insertion of electrodes into the brain with the risk of bleedings and infections [34, 35]. An intermediate, semi-invasive approach uses LFP recorded by epidural electrocorticography (ECoG) [26, 36]. LFP reflect neural activity of an area of up to 200□m comprising hundreds of thousands of neurons with numerous local recurrent connections and connections to more distant brain regions [37], while brain oscillations recorded non-invasively (e.g. using EEG or MEG) contain information of millions of neurons [38].

To control assistive devices or machines in paralysis, the following non-invasively recorded neurophysiologic signals were successfully used up to now: 1. slow cortical potentials (SCP) [39, 40], 2. sensorimotor rhythms (SMR) and its harmonics [41, 42], and 3. event-related potentials (ERPs), e.g. P300 [43].

Use of SCP in BCI/BMI applications goes back to Niels Birbaumer's work in the late 1970ies showing that operant control of SCPs (slow direct-current shifts occurring event-related after 300ms to several seconds) is possible while exhibiting strong and anatomically specific effects on behavior and cognition [44-46]. A tight correlation of central SCPs and blood-oxygen-level dependent (BOLD) signals in the anterior basal ganglia and premotor cortex was found [47] suggesting a critical role of the basal-ganglia-thalamo-frontal network for operant control of SCP.

In contrast to SCP's, SMR are recorded over the sensorimotor cortex usually at a frequency between 8-15 Hz. In analogy to the occipital alpha and visual processing [48], the SMR (or rolandic alpha) shows a clear functional specificity, disappearing during planned, actual or imagined movements [49]. Accordingly, a close association with

functional motor inhibition of thalamo-cortical loops was suggested [50]. Depending on the context, the SMR is also called μ-rhythm [51] or rolandic alpha, and was extensively investigated by the Pfurtscheller group in Graz [52] and the Wolpaw group in Albany [53, 54] .

Another extensively tested BCI/BMI controller is the P300-based ERP-BCI introduced by Donchin [55]. While SCP- and SMR-control is learned through visual and auditory feedback often requiring multiple training sessions before reliable control is achieved, the P300-BCI needs no training at all. While in the classical P300-ERP-BCI paradigm, the user focuses his attention to a visual stimulus, other sensory qualities such as tactile [56] or auditory stimuli [57, 58] were successfully implemented in ERP-BCI. Information rates of ERP-BCI can reach 20-30 bits/min [59].

In terms of operation mode, active, passive and re-active BCI/BMI applications can be distinguished [60]. While active and reactive BCI/BMI require the user's full attention to generate voluntary and directed commands, passive BCI/BMI relates to the concept of cognitive monitoring introducing the assessment of the users' intentions, situational interpretations and emotional states [61].

In active BCI/BMI applications two forms of control can be distinguished: synchronous and asynchronous control [62]. In synchronous control, translation of brain activity follows a fixed sequence or cue. The user is required to be fully attentive, while in asynchronous or uncued control, a specific brain signal is used to detect the user's intention to engage in BCI/BMI control [62, 63].

Brain-machine interfaces in neurorehabilitation of paralysis

BMI used in neurorehabilitation follows two different strategies: While assistive or biomimetic BMI systems strive for continuous high-dimensional control of robotic devices or functional electric stimulation (FES) of paralyzed muscles to substitute for lost motor functions in a daily life environment [64-66], restorative or biofeedback BMI systems aim at normalization of neurophysiologic activity that might facilitate motor recovery [67-71]. Insofar, restorative or biofeedback BMI can be considered as "training-tools" to induce use-dependent brain plasticity increasing the patient's capacity for motor learning [41, 72].

These two approaches derive from different research traditions and are not necessarily related to the invasiveness of the approach: In the early 80ies of the last century, de-

coding of different movement directions from single neurons was successfully demonstrated [73]. Since then reconstruction of complex movements from neuronal activity was pursued, using both, invasive and non-invasive methods.

Firing patterns acquired through single cell recordings from the motor cortex [74] or parietal neuronal pools [75] in animals were remarkably successful for reconstruction of movement trajectories. Monkeys learned to control cursors towards moving targets on a computer screen activating neurons in motor, premotor and parietal motor areas. It was shown that 32 cells were sufficient to move an artificial arm and perform skillful reaching movements enabling a monkey to feed himself [64]. Learned control of movements based on single cell activity was also shown using neurons outside the primary or secondary motor representations [76]. In 2006, successful implantation of densely packed microelectrode arrays in two quadriplegic human patients was demonstrated, enabling them to use LFP in order to move a computer cursor in several directions [65]. Most recently, a study using two 96-channel intracortical microelectrodes placed in the motor cortex of a 52-year-old woman with tetraplegia demonstrated robust seven-dimensional movements of a prosthetic limb [77].

In contrast to this work aiming at assistive appliance of invasive and non-invasive BMI technology, the development of restorative/biofeedback BMI systems is tightly associated with the development and successes of neurofeedback (NF) and its use to purposefully up-regulate or down-regulate brain activity – a quality that showed to have some beneficial effect in the treatment of various neurological and psychiatric disorders associated with neurophysiologic abnormalities [68]. In NF subjects receive visual or auditory on-line feedback of their brain activity and are asked to voluntarily modify e.g. a particular type of brainwave. Successful modification becomes contingently rewarded. NF was successfully used in the treatment of epilepsy [78, 79], ADHD [80-82] chronic pain syndrome [83] and complete paralysis after stroke [84]. The rational to use this approach in the context of neurorehabilitation is based on data indicating that stroke patients with best motor recovery are the ones in whom ipsilesional cortical function is closer to that found in healthy controls [84, 85]. A negative correlation between impairment and activation in ipsilesional M1 during hand motions has been documented [86]. Thus, a larger clinical study was performed at the University of Tübingen in Germany and the National Institute of Neurological Disorders and Stroke (NINDS, NIH) in the USA with over 30 chronic stroke patients testing the hypothesis that augmentation of ipsilesional brain activity would improve motor recovery [87]. In this study,

all participating patients suffered from complete hand paralysis and were unable e.g. to grasp. The study showed that one month of daily ipsilesional BMI training combined with goal-directed physiotherapy resulted in significant motor improvements, while random BMI-feedback did not. Further analysis of neurophysiological parameters indicated that motor evoked potentials (MEP) from the ipsilesional hemisphere reflecting the integrity of the corticospinal tract could predict motor recovery of the trained patients [88]. Currently, further improvements of this training paradigm, e.g. related to the feedback or specificity and effectiveness of training [41], e.g. using electric brain stimulation to enhance neuroplasticity [89], are being tested.

Non-invasive assistive brain-machine interfaces in paralysis

Both, invasive and non-invasive BCI/BMI found its way into assistive systems, e.g. allowing communication in locked-in patients [39] or restoration of movement in patients with paralysis [25, 90]. The Graz group was the first to use volitional SMR modulation for control of electric stimulation of a quadriplegic patient's paralyzed hand [66, 91]. While the patient imagined a movement, the associated modulation of SMR was translated into functional electric stimulation (FES) of his upper limb muscles resulting in grasping motions. After this proof-of-concept study, numerous publications addressed the different aspects that are important to allow intuitive and seamless control of biomimetic devices [17] or FES [92] in a daily life environment [93]. While many challenges were successfully mastered in the last years, three major aspects were not satisfyingly solved yet: 1. Intuitive, asynchronous BCI/BMI control, 2. 100% reliability, 3. Unambiguous superiority (in terms of ITR and necessary preparation effort) over the use of other biosignals (e.g. related to speech, gestures or eye-movements).

These aspects do no apply to BCI use for communication in complete paralysis, e.g. complete locked-in-state (CLIS) in ALS, as no asynchronous mode is necessary, reliability is secondary and no other biosignals are available anymore [94].

A system that is unreliable in daily life does not only limit its practicality, but would be also associated with ethical difficulties [95, 96]. While there are good arguments suggesting that invasive BCI/BMI can provide a higher ITR [97], it is still unclear how much meaningful information, e.g. for reconstruction of hand movements, can be extracted from non-invasively recorded brain signals [98]. Recently, work by Jose Contreras-Vidal's group at the University of Houston suggested that slow-frequency EEG (oscillations with a frequency of up to 4 Hz) might provide as much information as invasive recordings [99, 100], e.g. for reconstruction of three-dimensional hand movements

[100]. Currently, implementation of this approach in closed-loop paradigms is being pursued. Nevertheless, it's conceivable that the only viable solution to satisfyingly solve those three aspects will be the inclusion of other biosignals into a system merging different biosignal sources to detect user's intentions and integrating this information into the current context of the user to further increase intuitive control and assure reliability of the system.

Particularly promising is integrating eye movements using electrooculography (EOG) or eye-tracking into prosthetic control. At the University of Tübingen, a first prototype system was established that allows asynchronous BCI/BMI control while solving the reliability issue by using eye tracking, EOG and computer vision-based object recognition. A 3D-camera recognizes objects placed on a table. It detects when the user fixates any of the objects recognized as graspable, e.g. a cup or ball. Once an object is fixated with the eyes, the BCI/BMI mode switches on, detecting whether the user wants to grasp the object. A robotic hand or exoskeleton (both developed by the BioRobotics Institute, Scuola Superiore Sant'Anna, Pisa, Italy) performs the grasping motion (Fig. 1). The motion becomes interrupted if the user does not fixate the object anymore as measured by eye tracking and EOG (see Fig. 2). This assures that no action of the systems depends exclusively on brain wave control that might be susceptible to inaccuracies. Further studies will investigate the system's applicability in patient populations with complete hand or finger paralysis.

Conclusion

The development and implementation of BCI/BMI promises to enhance applicability of assistive technology in humans with a compromised or damages motor system. While information transfer rates of non-invasive BCI/BMI are sufficient for communication, e.g. in locked-in-state, versatile control of prosthetic devices using brain waves will require major research and development efforts to provide intuitive, asynchronous control with 100% reliability, particularly in daily-life environments. Many reasons suggest that using the combination of brain waves with other biosignals represents the only feasible solution for sufficiently reliable control of assistive, non-invasive technology in the near future.

Acknowledgments

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Figure 1. Organization of the University of Tübingen' prototype system controlling assistive devices using brain waves and eye movements.

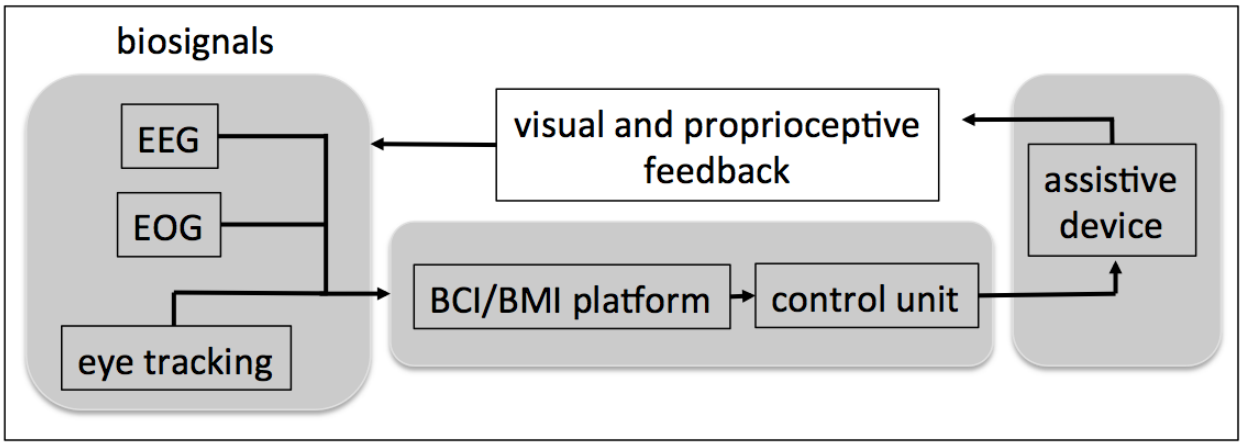

Figure 2. Illustration of the processing chain for performing grasping motions of an assistive system using brain waves and eye movements. The grasping motion stops once the user does not fixate the object with his eyes anymore.

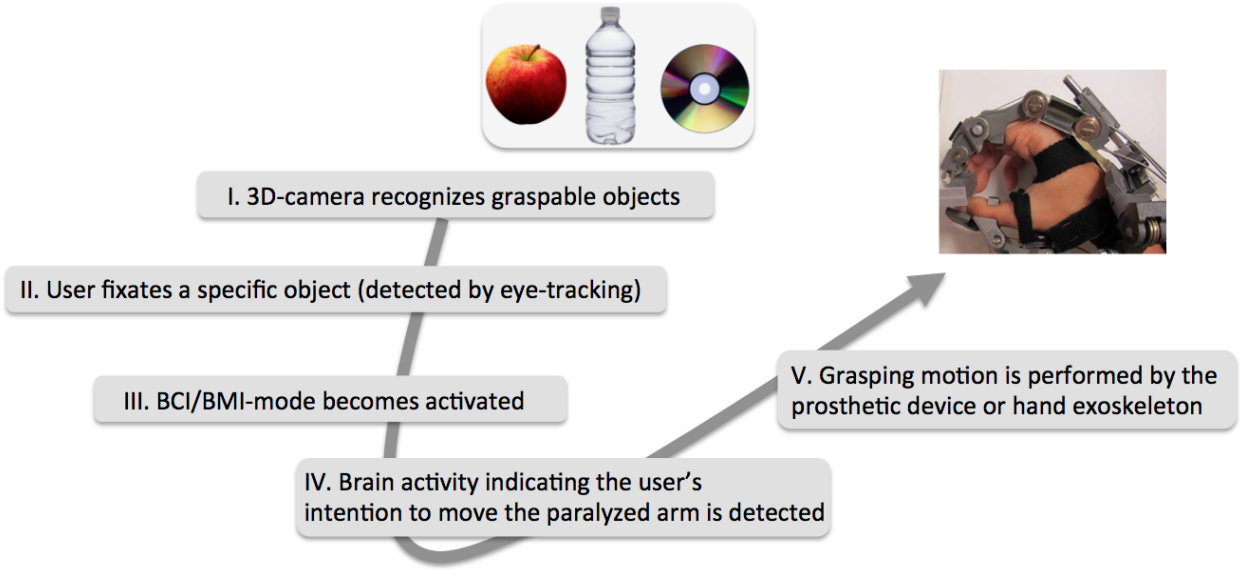

Table 1

Categories of Brain-Computer and Brain-Machine Interfaces

Based on:				
recording site of brain signals	**invasive**		**non-invasive**	
brain signal used		*recording technique*		*recording technique*
	single spike	single cell recordings	electric brain potentials	electroencephalography (EEG)
	multi-unit activity	multi-unit arrays (MUA)	neuromagnetic fields	magnetoencephalography (MEG)
	local field potentials (LFP)	electrocorticogram (ECoG)	BOLD	functional magnet resonance imaging (fMRI)
			oxy/deoxy-hemoglobin	near-infrared spectroscopy (NIRS)
mode of operation	**active**	**reactive**	**passive**	
	asynchronous control			
	synchronous control			
purpose	**assistive / biomimetic**	**restorative / biofeedback**		
	used for restoration of	*tested in the treatment of*		
	communication	stroke		
	paralysis	chronic pain		
		tinnitus		
		dementia		
		depression		
		schizophrenia		

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