Use of Electroencefalography Brain Computer Interface systems as a rehabilitative approach for upper limb disabilities after a stroke.A systematic review.

Running head: Electroencefalography Brain Computer Interface for stroke upper-limb rehabilitation.

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ABSTRACT

Objectives. To compile all studies available that assess an UL intervention based on an EEG-BCI system in stroke, to analyse their methodological quality and to determine the effects of these interventions for improving motor abilities.

Type. Systematic review.

Literature Survey. Pubmed, PEDro, Embase, Cumulative Index to Nursing and Allied Health, Web of Science and Cochrane Central Register of Controlled Trial from inception to the September 30, 2015.

Methodology. This systematic review compiles all available studies that assess an upper limb intervention based on an electroencefalography-based brain computer interface systems in patients with stroke, analysing their methodological quality using Critical Review Form for Quantitative Studies, and determining the grades of recommendation of these interventions for improving motor abilities established by the Oxford Centre for Evidence-based Medicine. The articles were selected according to the following criteria: 1) the study assesses an electroencefalography-based brain computer interface intervention; 2) patients included were people with stroke with a hemiplegia, regardless of lesion origin or evolution time; 3) interventions using electroencefalography-based brain computer interface were applied for training functional abilities of the affected upper limb, regardless of the interface used or of its combination with other therapies; and 4) studies that used validated tools to evaluate the motor function.

Synthesis. After the literature search, 13 articles were included in this review. Four studies were randomized controlled trials, one was a controlled study, four were case series studies, and four were case reports. Methodological quality for the works included ranged from six to fourteen, and the level of evidence varied from 1b to 5. The included articles imply results of 143 stroke patients.

Conclusions. This systematic review suggests that brain computer interface interventions might be a promising rehabilitation approach in subjects with stroke.

Key Words:brain computer interface;electroencephalography;stroke; upper limb.

Abbreviators:

Action Research Arm test (ARAT).
Activities of Daily Living (ADL).
Bereitschaftspotential: the early component of the MRCPs (BP).
Brain Computer Interface (BCI).
Cumulative Index to Nursing and Allied Health (CINAHL).
Electrocorticography (ECoG).
Electroencephalography (EEG).
Electromyography (EMG).
Even Related Desynchronization (ERD).
Even Related Synchronization (ERS).
Fügl-Meyer Assessment (FMA).
Functional Electrical Stimulation (FES).
Functional Magnetic Resonance Imaging (fMRI).
Goal Attainment Scale (GAS).
Magnetoencephalography (MEG).
Medical Research Council (MRC).
Motor Activity Log (MAL).
Motor Assessment Scale (MAS).
MotricityIdex (MI).
Movement Related Cortical Potential (MRCPs).
Mu (μ) and beta (β) rhythms.
National institute of Health Stroke Scale (NIHSS).
Near-infrared spectroscopy (NIRS).
Nine Hole Pig Test (NHPT).
Stroke Impact Scale (SIS).
Stroke Impairment Assessment Set (SIAS).
Randomized Controlled trial (RCT).
Wolf Motor Functional test (WMFT).

INTRODUCTION

Recovery of motor function after stroke is crucial in order to perform activities of daily living (ADLs), but this recovery is often incomplete.[1,2]The majority of stroke survivors have upper limb (UL) symptoms after acute stroke.[3]The initial severity is the most significant predictor of long-term outcome, but so too are anatomical damage (size and location), the nature of the lesion or the age of onset.[4] According to the Copenhagen Stroke Study (CSS),[5] the study of functional recovery of the UL (through the elementary items of food and hygiene of the Barthel Index) reveals that a full function of the UL is reached in 79% of patients with only mild initial paresis, and only in 18% of patients with severe initial paresis. In this context, 60% of patients with a non-functional UL one week after stroke will not recover the function at 6 months. This dysfunction significantly limits participation in the physical and social environment.[6,7]

Motor network reorganization after stroke is time- and activity-dependent.[8,9]Coincident activation of pre-synaptic and post-synaptic neurons reinforces synaptic strength, resulting in increased and more reliable communication between the activated neurons. The potential relevance of this concept for changes in behavior can be illustrated particularly well in the context of stroke rehabilitation. Assuming that the connection between peripheral muscles and the sensorimotor cortex has been disrupted due to a cortical or subcortical lesion, a coincident activation of sensory feedback loops and the primary motor cortex may reinforce previously dormant cortical connections through Hebbian plasticity, thus supporting functional recovery.[10] It is necessary to develop approaches focused on skill learning, involving enhanced activity of the primary motor cortex to promote plasticity.[9,11]

Brain computer interface (BCI) systems allow the use of brain signals both for assistance and rehabilitative goals, by providing the potential users with brain state-dependent sensory feedback (e.g., through functional electrical stimulation, virtual reality environments or robotic systems). BCI systems can be used to detect primary motor cortex activation (*intention to move*), and provide a matched sensory stimulation according to some feedback procedures.[10] Taking this into consideration, BCI systems applied for motor neuromodulation purposes are used to induce activity-dependent plasticity by making the user pay close attention to a task requiring the activation or deactivation of specific brain signals.[12,13]

BCI systems can make use of different sources of information: electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), near-infrared spectroscopy (NIRS), or electrocorticography (ECoG). Among these, the EEG signals are relevant, given their highly accurate temporal resolution and their suitability in clinical environments. EEG-based technologies allow the real-time characterization of motor-related cortical activities to obtain predictive information regarding intended movement actions. Such information has proven to be valuable in providing feedback at specific instant that in turn induces cortical plasticity and restoration of the normal motor function.[14-16] Of particular relevance in this regard, EEG-based observations by Chatrian et al.[17] and more recent studies by Pfurtscheller and colleagues,[18-20] revealed that the dynamic neuronal oscillations provide relevant information regarding neuronal activation during preparation and execution of voluntary movement. A motor event implies neuronal changes in brain structures, among which, two main cortical patterns have been extensively described in the literature: the slow cortical potentials, termed movement related cortical potentials (MRCPs) and, the movement-dependent fluctuations in the power of the sensorimotor mu (μ, 8-12 Hz) and beta (β, 13-30 Hz) rhythms, known as event-related desynchronization (ERD) or event-related synchronization (ERS) patterns.[21-25]

MRCPs are interesting in assessing cortical activation patterns, as they are associated with the planning and execution of voluntary movements. In this context the study of pre-motor component of the MRCPs (the Bereitschaftspotential or BP) is of special interest, given its predictive nature.[26,27] The BP is characterized by a slow negative deflection of the average EEG amplitude about 1.5 seconds before the onset of the voluntary movement in the precentral regions (over the supplementary motor area and the premotor cortex), reaching a maximum negativity around the vertex at the onset of the movement.[28,29] Cui and Deecke demonstrated that the spatio-temporal distribution of the BP pattern associated to the movement occurs earliest in the supplementary motor area, then in the contralateral motor cortex, and lastly in the ipsilateral motor cortex.[30]

During resting conditions, the sensoriomotor cortex presents variations in the μ and β frequency bands, termed sensoriomotor rhythms. The percentage of decrease of EEG signal power in sensoriomotor rhythms is referred to as ERD. In healthy subjects, during voluntary movements, μ- and β-ERD start contralaterally to the side of the movement about 2 seconds before its onset, becoming bilateral at about the time the movement begins.[25,31]This suggests a contralateral hemisphere role in the preparation of voluntary movements. After the movement is finished, the ERS pattern is observed. The ERS refers to the percentage of power increase in the β-band after the movement finishes, which reflects motor cortex deactivation.[32]

Previous studies have evaluated the cortical EEG activity in subjects who have suffered a stroke, analysing cortex reorganization processes throughout the recovery period.[33]Several authors[34,35]have found a weaker ERD in the injured hemisphere for UL movements in patients with poor recovery, while those with a good prognosis showed a greater involvement of the injured hemisphere, comparable to what is found in healthy people. Regarding MRCPs, the BP is significantly reduced over the injured hemisphere in patients with stroke.[36]Furthermore;a marked amplitude in frontal areas of MRCPs has been observed[37], reflecting lower task automation, which forces the use of compensatory strategies for motor execution.[38]

This study provides an extensive review of BCI strategies that have been proposed during recent years in the field of stroke motor neurorehabilitation focused on UL interventions.

While there are other recent reviews[13,16,39-45], these reviews have not evaluated the validity of the encountered articles by using standardized methodological quality tools. This aspect is essential in order to recommend an adequate intervention based on these technologies. To our knowledge, this is the first review to discuss exclusively clinical trials that perform an UL intervention with BCI systems in subjects with stroke and to use standardized methodological quality tools to evaluate the articles and extract clinical recommendations. Considering the amount of trials in the literature that study the use of EEG-based BCI technologies for the UL rehabilitation in stroke, and the lack of specific reviews, three primary goals are targeted: 1) to compile all studies available that assess an UL intervention based on an EEG-BCI system in stroke; 2) to analyse the methodological quality of the studies; and 3) to determine the effects of these interventions for improving motor abilities.

METHODS

Search strategy

An in-depth literature search on Pubmed (Medline), PEDro, Embase, Cumulative Index to Nursing and Allied Health, Web of Science and Cochrane Central Register of Controlled Trial was carried out. The searches took place for studies published between 2005 and 2015. Only full-text articles published in English, French or Spanish were selected. The combinations of keywords used are described in detail in Table 1.

Study selection

The articles were selected according to the following criteria: 1) the study assesses an EEG-based BCI intervention; 2) patients included were patients with stroke and a hemiplegia, regardless of lesion origin or evolution time; 3) interventions using EEG-based BCI systems for training functional abilities of the affected UL, regardless of the interface used or of its combination with other therapies; and 4) the studies use validated tools to evaluate the motor function, such as Fugl Meyer Assessment (FMA), Action Research Arm test (ARAT), Motor Assessment Scale testing form (MAS), Volitional Index finger, Wolf Motor Functional Test (WMFT), Goal Attainment Scale (GAS), Nine-Hole Pig Test (NHPT), Stroke Impairment Assessment Set (SIAS), Motor Activity Log (MAL), European Stroke Scale (ESS), Medical Research Council (MRC).

This systematic review excluded articles according to the following exclusion criteria: 1) studies that only recruited healthy subjects or subjects with other neurological diseases; 2) studies that did not include motor outcome measures; 3) studies that did not use EEG; 4) studies that did not develop an intervention with BCI (e.g. trials that evaluate the stroke recovery or trials that analyse the sensorimotor rhythms activation).

Data collection

General characteristics of the studies, including number of patients, type of central nervous disorder, nature of the injury, stage of disorder (acute, subacute, and chronic), experimental protocols analysed (number of trials), and their main results, were collected. The authors carried out independent screenings of the abstracts obtained from the research and decided which ones could potentially meet the inclusion criteria.They discussed those articles on which there was no consensus. For the studies that met the criteria, the full-text articles were obtained. The reviewers executed a new screening for all articles to confirm their relevance until absolute agreement was reached.

Methodological quality was assessed using Critical Review Form for Quantitative Studies.[46] This tool developed by the McMaster University Occupational Therapy Evidence-Based Practice Research Group, included 15 questions: 1) Was the purpose stated clearly? 2) Was relevant background literature reviewed? 3) Was the design appropriate for the study question? 4) Was the sample described in detail? 5) Was sample size justified? 6) Was the intervention described in detail? 7) Was contamination avoided? 8) Was co-intervention avoided? 9) Were the outcome measures reliable? 10) Were the outcome measures valid? 11) Were the results reported in terms of statistical significance? 12) Were the analysis method(s) appropriate? 13) Was clinical importance reported? 14) Were drop-outs reported? 15) Were conclusions appropriate given the study methods and results?

The articles were classified according to the levels of evidence and grades of recommendation established by the Oxford Centre for Evidence-based Medicine (updated March 2009) (Table 2).[47]

RESULTS

A total of 248 articles were found, but only 45 were selected for further review and critical reading, according to the previously established selection procedure. Finally, 13 articles were included meeting the inclusion criteria,[8,48-59]and 32 were excluded[29,60-90] for different reasons (Table 3) (Figure 1). Methodological quality for the included articles, measured with the Critical Review Form, ranges between six and fourteen (table 4).The table 5 summarized the characteristics of the studies and classifies the trials according to the level of evidence and grade of recommendation.

The included articles imply results with a total of 143 participants, all of them patients with stroke. All patients had a topographic affectation of hemiplegia. The clinical status was acute for seven subjects; 25 were in a subacute state, 59 were chronic patients, and for 52 there was no concrete data. The affected hemisphere was the right one for 57 patients, the left one for 63 and no data was given for 23 patients. The stroke was ischemic in 21 patients and haemorrhagic in 34; for 88 subjects there was no relevant data. The nature of the lesions was cortical for 20 participants; subcortical for 74 patients; two patients suffered combined lesions; and for 47 patients there was no data about the aetiology.

In six studies[48,49,54,56,58,59] actual movements were performed, while in the other seven studies[8,50-54,56] the task to be performed was motor imagery. The tasks performed or imagined were: 1) moving the paretic limb towards a goal on a screen[8,50,52,54,56], 2) grasping [51,52,55], 3) index extension[48], 4) fingers flexion and extension[49,57], 5) hand opening and closing[58,59], and 6) reaching.[55]Five studies combined conventional physical therapy with the BCI intervention.[49,52,55,58,59]

The feedback provided was visual in two studies[51,54], haptic in another two[49,59]; one combined haptic and auditory feedback[55], and eight used a combination of visual and haptic feedback.[8,48,50,52,53,56-58] From the studies using haptic feedback, three of them used an electrical stimulation interface[48,56,58], seven applied a rehabilitation robot[8,49,50,54,55,57,59], and one used a mechanical orthosis.[53] Those articles which provide two types of feedback combined do it as follows: upon hearing or seeing the auditory or visual cue, the patient was instructed to execute or imagine the task proposed within each article. Successful cortical signals measured at EEG electrodes triggered immediate activation of robotic devices, mechanical orthoses or electrical stimulation. On average, 13.69 ± 4.64 training sessions were performed per patient (mean±standard deviation).

In relation to the outcome measures, significant gains in FMA scores were observed in several studiesimmediately after the intervention[8,49,50,52,54,55,59] and after the follow up[8,50,59] in chronic[49,54,55] and subacute[59]stroke patients. Significant gains in ARAT scores were found in actue[58], subacute[56] and chronic stroke patients.[51,56]Two studies described significant improvements in WMFT.[49,52]One trial reported significant improvement in fine motor function evaluated with the NHPT.[56]However, in the majority of the studies, no statistical significance were found compared with the control group.Several trials found a correlation between the improvements obtained in the motor outcome measures (FMA and ARAT) and the neural functional connectivity evaluated with neuroimaging techniques.[52,54-56]The EMG activity was recorded in two trials.[53,57]Shindo et al.[53] observed new voluntary EMG activity in the affected finger extensors. In addition, five trials evaluated the muscle spasticity with Asworth scale.

One of these revealed relevant improvements in this parameter.[49]Finally, several studies described improvements in arm function[53] and volitional index extension.[48,52]

In general terms, trials itemize the EEG pattern studied. Three studies[49,52,55]specify that they took into account ipsilesional ERD of the μ-rhythm. One study[51] analysed the bilateral ERS and ERD of both μ and β rhythms, and the other authors[8,48,50,53,54,56,57,58,59] also looked bilateral ERD of μ and β rhythms. Four of these studies evaluated the changes in the EEG activity during and after the BCI interventions.[51,52,55,57]

DISCUSSION

The present review provides, to our knowledge, the first revision of EEG-BCI interventions for UL in subjects with stroke, using standardised methodological quality tools.

In relation to methodological quality, four out of 13 included studies were randomized controlled trials (RTC)[8,50,55,59], one was a controlled study[54], four were case series studies[51,53,56,57] and four were case reports.[48,49,52,58] The level of evidence of the studies evaluated with the levels established by the Oxford Centre for Evidence-based Medicine included scores varying from 1b (RTC) to 5 (case reports/case studies). The grades of recommendation are distributed among A, B, C and D.

These review include case series studies and case reports because they are exploratory studies that analyzed little known issues such as the BCI intervention effects in acute stroke participants, the correlation between outcome motor measures and the cortical functional connectivity, and the modifications in the fine motor function after a BCI intervention.

TheRCTobtained a score ranging from 13 to 14 points on the Critical Review Form, according to the Quantitative Review Form Guidelines.[46]Three of these did not describe in detail the sample[50,55,59] which may result in a sample bias. The controlled study[54] had 11 points on the Critical Review Form. This article did not report the results in terms of statistical significance. The case series studies[51,53,56,57]and the case reports[48,49,52,58] had a score ranging from 6 to 12 on the Critical Review Form. Many of these did not describe in detail the participants recruited.[51,56,57] However, all of the studies describe adequately the intervention and most studies avoided the contamination.[8,48,50,51,53-59]In all trials, participants were the same from start to finish, therefore fulfilling the intention-to-treat analysis. Overall, several studies illustrated a strong commitment by the participants for the intervention, since there were hardly any reports of desertion. Only three studies reported dropouts,[50,58,59] but these were not due to a clinical-related cause or being unsatisfied or tired with the intervention, suggesting that such approaches are easily bearable by patients.

According to the interventions, the use of EEG-BCI to drive a robotic device generated improvements in the FMA.[8,49,50,53,55,59]However, most studies did not observe significant differences compared to conventional robot-assisted therapy.[8,50,59]Only one studyrevealed a clear superiority of the BCI therapy coupled with a robotic orthosis as compared to a conventional robot-assisted therapy.[55]In relation to the comparisons between BCI interventions and conventional physical therapy, one study compared a BCI intervention withconventional physical therapy, showing improvements in FMA scores in all groups. Some of the included articles combined the BCI intervention with other therapy approaches, such as passive mobilisations or goal-directed physical therapy.[49,52,55,58]According to the results of these studies, the combination of BCI interventions with conventional physical therapy are generally accepted to provide more benefits and greater functional recoveries than BCI interventions alone. An explanation for this isthat BCI systems can promote the functional connectivity between the brain areas and muscles, leading toabetter “neurophysiological condition” that in turn maximises the effects of conventional physical therapyapplied after stimulation with a BCI intervention.[91]

Some articles included in this review used neuroimaging techniques to analyse the changes obtained by the experimental intervention in terms of brain functional connectivity.[49,53-56,58] Specifically, there was greater functional connectivity in the supplementary motor area, the contralesional and ipsilesional motor cortex, and several areas of the visuospatial system with the association cortex regions and the cerebellum. Both results might suggest that the BCI interventions could be a potential facilitator of neuroplasticity.

Regarding follow-up of the participants, few studies carried out several measures after the BCI intervention. According to these investigations, the BCI interventions may increase the cortical excitability even afterthe therapy ends.[8,50,59] Therefore, the BCI interventions could have long-term benefits; howevermore investigations with follow-up that use neuroimaging techniquesare necessary in order to clarify these effects.

In relation the type of task performed, the majority of the studies showed that training with BCI produces improvements in the UL functionality, such as finger extension, hand opening, handgrip and reaching tasks. There is a maximum level of evidence to recommend the BCI interventions for improving the reaching task, using a combined strategy of motor imagery and robotic rehabilitation.[8,50,55]Those who examinedsimple movements, such as Shindoet al.,[53] Ono et al.,[57] Daly et al.[48] and Broetz et al.[52]usingfinger extension, also obtainedsatisfactory results, but in very small samples. The way in which the complexity of the taskmodifies the outcomes of BCI interventions is an aspect that further studies should analyse.Several studies in this review used motor imagery, obtaining positive results.[8,50,51,53.54,56,59]Motor imagery was shown to activatethe same areas that are involved in the execution or attempt of actual motor tasks.[91]Several studies that used neuroimaging techniques[92,93] have detailed overlap in cortical activation patterns between actual and imagined movements.

Improvements in outcome measures were found in subacute and acute patients, and the studies that recruited chronic patients also obtained improvements in motor function and even reductions in spasticity.This may suggest that BCI interventionsproduce plastic changes that result in functional motor improvement, regardless of the time of evolution of the lesion. A differential aspect across studies was whether they used EEG signals from one hemisphere (the injured side) or both hemispheres, and this decision was uniform for the whole sample of patients contemplated in each study.This is in contrast with other reports, asDi Pinoet al.[94], in which it was proposed that the intervention carried out with each patient should be adequate to the structural reserve, *i.e.*,the quantity of strategic neural pathways and relays that are spared by the lesion and can reallocate previous or outsource new functions. Future studies should be focused on how different EEG-based decoding algorithms (in terms of spatial areas considered) influence the outcomes of the BCI interventions at different post-stroke stages.

As for the nature of the injury, only Ono et al.[57] took into account subcortical lesions as an inclusion criteria, but recommendationscannot be established, given that the results werebased on very heterogeneous samples. As the pattern of reorganisation depends on the size of the lesion,[94] the site is possibly important too. The areas where brain changes are monitoredwith neuroimaging techniques after BCI interventions weremostly examinedin the motor cortex[54] and thalamus,[56] so one possibility is that it is more difficult to obtain changes in subcortical structures, but we cannot obtain strong conclusions about this issue based onthe articles included.

Regarding the feedback employed, only one manuscript revealed differences between the types of feedback applied,[57] obtaining better results for those patients who received haptic feedback versus visual. According to these findings, an interesting focus in future studies could be the comparison between different types of feedback. However, all studies except Broetzet al.[52] employed haptic stimulation, and the most frequent was mechanical stimulation, which provides a more natural approach for inducing sensory feedback since it mimics real movement.

The latency between motor intention and associated feedback is an essential factor of an effective BCI intervention. Timing is essential forlong term potentiation, increasing synaptic efficacy whichis one of the mechanisms underlying the Hebbian association.[92]

All studies used a non-invasive method to acquire the characteristics of motor cortex activation, allowing the patient to modulate their signals through learning based on receiving afferent feedback. Some articles did not reportdata about the strategies used for extracting EEG-characteristics of brain signals,[8,50,54-56,58]but others explained that they used brain oscillations, ERD and ERS as outcome measures. There wereno included articles that used an assessment of MRCPs to evaluate the components of motor planning. Motor intention detection using sensorimotorrhythms have lower efficiency thatderives from the lack of control in the timing of the detection of the motor-related corticalstate, so feedback triggered by such detection reaches the motor cortex too late to promote plasticity. The delay from MRCPs to the onset of movement intention is smaller (hundreds of milliseconds), whichis sufficient for establishing a Hebbian association.[92]

Study limitations

Although this review was conducted with care, there weresome methodological limitations, such as not hand-searching conference proceedings, missing outcome data, or not performing meta-analyses of individual patient data. In addition, this review included articles with several methodological limitations. The included manuscripts presented heterogeneity in the outcome measures employed, in the patients' characteristics, the protocols developed and the small samples.

CONCLUSIONS

This systematic review provides an updated review of the validity of BCI systems for functional rehabilitation of UL in patients with stroke according to existing experimental evidence. It suggests that the BCI interventions may be an encouraging intervention in subjects with stroke, improving the motor outcome measures such as FMA, ARAT or WMFT.The included articles do not clarify the superiority of the BCI interventions versus conventional physical therapy. However, it seems that the combination of BCI interventions with conventional physical therapy could provide greater functional recoveries. In addition, EEG-BCI interventions coupled with a robotic device provide positive changes in motor outcome measures.

The BCI interventions usinghaptic feedbacks for closing-loop information and to strengthen motor cortex and muscle joints may be an adequate therapy to assist motor recovery of UL in patients with stroke. However, it is necessary to continue developing RTCs, with larger and clearly stratified samples of patients and employing novel low-cost feedback strategies, which can be applied in clinical settings.Also, additional studies have to establish well-defined criteria for selecting participants and ensure that samples are as homogeneous as possible, and we consider it necessary to carry out trials to establish comparisons between subjects with different evolution times. Finally, these studies should use functional outcome measures correlated with neuroimaging changes in order to addressthe transfer of learning into daily-life and as well as the social impact of these interventions.

Due to the novelty of these interventions, some of the studies have low levels of methodological quality; therefore their results should be interpreted with caution before making recommendations for clinical practice.

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Tables

Table 1. Search strategy.

	Keywords combination.
1.	“BCI” AND “stroke rehabilitation”.
2.	“BCI” AND “neuroplasticity” AND (stroke OR hemiplegia).
3.	“BCI” AND “EEG” AND (stroke OR hemiplegia).
4.	“BCI” AND “ERD” AND (stroke OR hemiplegia).
5.	“Stroke rehabilitation” AND “upper limb”.
6.	“Stroke rehabilitation” AND “neuroplasticity”.
7.	“Sensoriomotor rhythms” an “stroke”.

Brain computer interface (BCI); Electroencephalography (EEG); Event-related Desynchronization (ERD).

Table 2. Levels of evidence and grades of recommendation.

Level of evidence.	
1a	Systematic reviews of randomized controlled trials.
1b	Individual randomized controlled trials (with narrow Confidence Interval).
1c	All or none.
2a	Systematic reviews of cohort studies.
2b	Individual cohort study (including low quality randomized controlled trial; e.g., <80% follow-up).
2c	"Outcomes" Research; Ecological studies.
3a	Systematic reviews of case-control studies.
3b	Individual Case-Control Study.
4	Case-series (and poor quality cohort and case-control studies).
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".
Grades of Recommendation.	
A	Consistent level 1 studies.
B	Consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies.
C	Level 4 studies ***or*** extrapolations from level 2 or 3 studies.
D	Level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level.

Table 3. Articles excluded in the systematic review.

Manuscript	Exclusioncriteria
Niazi et al.[29]	Healthy subjects.
Tam et al .[60]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Tan et al.[61]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Cincotti et al.[62]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Kasashima et al.[63]	They analyze the ability of stroke patients to use EEG-based motor imagery BCI.
Ang et al.[64]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Gómez-Rodriguez et al.[65]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Lew et al.[66]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Arvaneh et al.[67]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Arvaneh et al.[68]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Bundy et al.[69]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Aono et al.[70]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Ang et al.[71]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Leamy et al.[72]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Liu et al.[73]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Petti et al.[74]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Schreuder et al.[75]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Takemi et al.[76]	They did not use motor outcomes measures. They did not analyze the intervention effectiveness.
Bermudez et al.[77]	Healthy subjects.
Ang et al.[78]	They analyze the ability of stroke patients to use EEG-based motor imagery BCI.
Kaiser et al.[79]	They study the relationship between ERD and ERS and the degree of stroke impairment, but they didn't develop an intervention.
Tangwiriyasakul et al.[80]	They explored temporal evolution of ERD during stroke recovery, but they didn't develop an intervention.
Zhou et al.[81]	Healthy subjects.
Bai et al.[82]	They recruited subjects with other neurological diseases. They did not use motor outcomes measures.
Buch et al.[83]	They did not employ an EEG-BCI system.
González-Franco et al.[84]	Healthy subjects.
Mihara et al.[85]	They did not employ an EEG-BCI system.
Faller et al.[86]	They recruited subjects with other neurological disease, and they did not use motor outcomes measures.
Song et al.[87]	They did not employ an EEG-BCI system.
King et al.[88]	Healthy subjects.
Cantillo-Negrete et al.[89]	Healthy subjects.
Looned et al.[90]	Healthy subjects.

Table 4. Methodological quality of articles included.

Manuscript	**Critical Review Form-Quantitative Studies.**															
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**TOTAL items**
Ang et al (a).[8]	1	1	1	0	1	1	1	1	1	1	1	1	1	0	1	**13**
Daly et al.[48]	1	1	1	1	0	1	1	1	1	1	0	0	1	0	1	**11**
Caria et al.[49]	0	1	1	1	0	1	0	0	1	1	0	0	0	0	0	**6**
Ang et al (b).[50]	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	**14**
Prasard et al.[51]	1	1	1	0	0	1	1	1	1	1	0	1	1	0	1	**11**
Broetz et al.[52]	1	1	1	1	0	1	0	0	1	1	1	0	1	0	0	**9**
Shindo et al.[53]	1	1	1	1	0	1	1	1	1	1	0	1	1	0	0	**11**
Várkuti et al.[54]	1	1	1	1	0	1	1	1	1	1	0	0	1	0	1	**11**
Ramos-Murguialday et al.[55]	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	**14**
Young et al (a).[56]	1	1	1	0	0	1	1	1	1	1	1	1	1	0	1	**12**
Ono et al.[57]	1	1	1	0	0	1	1	1	1	1	0	0	1	0	1	**10**
Young et al (b).[58]	0	1	1	1	1	1	0	0	1	1	0	0	1	0	1	**9**
Ang et al (c).[59]	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	**14**

Items. 1) Was the purpose stated clearly? 2) Was relevant background literature reviewed? 3) Was the design appropriate for the study question?, 4) was the sample described in detail? 5) Was sample size justified? 6) Intervention was described in detail? 7) Contamination was avoided? 8) Co-intervention was avoided? 9) Were the outcome measures reliable? 10) Were the outcome measures valid? 11) Results were reported in terms of statistical significance? 12) Were the analysis method(s) appropriate? 13) Clinical importance was reported? 14) Drop-outs were reported? 15) Conclusions were appropriate given study methods and results.

Table 5. Characteristics and main results of included articles.

Study	Design	Participants	Protocol	Task and feedback	Outcome measures	Main results
Level of evidence 1b /Grade of recommendation A*						
Ang et al (a).[8]	RCT	n=18. 10 right hemiparesis, 8 left hemiparesis. 6 ischemic and 12 hemorrhagic. 5 cortical and 13 subcortical.	Subjects were randomly allocated in two groups: EEG-based motor imagery BCI to drive robotic device (n=8) vs. Standard robotic rehabilitation (MIT-manus®) (n=10). 12 sessions of 1 hour during 4 weeks. 122 movement experimental trials vs 960 movement control trials.	**Task:**To move a mark on a screen to a target position. *Visual and haptic feedback.*	FMA. 27 channels of EEG. *Measurements: baseline,mid-rehabilitation, post-rehabilitation and 2 months post-rehabilitation.* *Bilateral ERD μ/β*	Significant gains in FMA in both groups at post-rehabilitation (p = 0.001) and 2-month post-rehabilitation (p = 0.002). The experimental group yielded higher 2-month post-rehabilitation gain than the control but no significance was found.
Ang et al (b).[50]	RCT	N=25. 15 right hemiparesis, 10 left hemiparesis. 10 ischemic and 15 hemorrhagic. 7 cortical and 18 subcortical.	Subjects were randomly allocated in two groups: EEG-based motor imagery BCI with robotic feedback neurorehabilitation (n=11) compared to robotic rehabilitation that delivers movement therapy(n=14) (MIT-manus®). 12 sessions of 1 hour during 4 weeks. 122 movement experimental trials vs 960 movement control trials.	**Task:**To move the affected upper limb with the robot device towards the goal displayed on the screen when the motor imagery is detected. *Visual and haptic feedback.*	FMA. 27 channels of EEG. *Measurements: baseline, post-rehabilitation and 2 monthspost-rehabilitation.* *Bilateral ERD μ/β*	Significant gains in FMA in both groups at post-rehabilitation (p=0.032) and 2-month post-rehabilitation (p=0.020), but no significant differences were observed between groups.
Ramos-Murguialday et al.[55]	RCT Double blind	N=32 (Chronic). 16 left hemiparesis and 14 right hemiparesis. No data for 2 subjects. No data about the injure nature.	Subjects were randomly allocated in two groups: BCI coupled with a robotic orthosis under two conditions: in the experimental group, movement of robot orthosis was driven by ERD rhythms (n=16); in the control group (n=16), movement of robot orthosis was independently of their ERD. Both groups carried out goal directed physical therapy (one hour). 20 sesions during 4 weeks of daily training (excluding weekends). No concrete data about number of trials.	**Task:**Reaching and grasping movements. *Haptic and auditory feedback.*	FMA, Ashworth Scale, MAL, GAS and EMG. fMRI. *Measurements: baseline, after intervention and one week after intervention.* *Ipsilesional ERD μ/β*	FMA scores improved more in the experimental, presenting a significant improvement of FMA scores (p = 0.018). FMA improvements in the experimental group correlated with changes in fMRI laterality index and with paretic hand EEG activity.

Ang et al (c).[59]	RCT Single blind	N=21 (subacute subjects). 6 cortical and 15 subcortical.	Subjects were randomly allocated in three groups: EEG-based motor imagery BCI coupled with robot a haptic Knob® (HK), standard robot-assisted rehabilitation (HK) and standard arm therapy (SAT). 18 sessions during 6 weeks, 3 sessions per week, 90 min. per session (BCI-HK: 1 h of BCI coupled with HK intervention; HK group: 1 h of HK intervention; Both BCI-HK and HK groups: 30 min of therapist-assisted arm mobilization; SAT group: 1.5 h of therapist-assisted arm mobilization, forearm pronation-supination movements, wrist control and grasp-release functions). 120 movement experimental trials.	**Task:** hand grasping and HK manipulation. *Haptic feedback.*	FMA. 27 channels of EEG: ERD/ERS. . *Measurements: mid-intervention at week 3, end-intervention at week 6, and follow-up at weeks 12 and 24.* *Bilateral ERD μ/β*	FMA score improved in all groups, but no intergroup differences were found at any time points. Significantly larger motor gains were observed in the BCI-HK (p=0.001) and HK group (p=0.004) compared to the SAT group at weeks 12 and 24.
Level of evidence 2b / Strength of recommendation B*						
Várkuti et al.[54]	Non RCT	N=9 (3 Chronic, 4 acute and 2 subacute subjects) 6 left and 3 right hemiparesis. 2 cortical and 7 subcortical.	Subjects were allocated in two groups: EEG-based motor imagery BCI (n=6) and robot assisted rehabilitation (MIT-Manus®) (n=3). 12 sessions during 1 month. 80 movement experimental trials.	**Task:** to move impaired shoulder and elbow toward the goal displayed on a screen. *Visual and haptic feedback.*	FMA. 27 channels of EEG. fRMI. *Measurements: Baseline and after intervention.* *Bilateral ERD μ/β*	Both the FMA gain and functional connectivity changes were numerically higher in the EEG based motor imagery BCIgroup.
Level of evidence 4 / Strength of recommendation C*						
Prasad et al.[51]	Case Series	N=5 (chronic subjects). 3 left hemiparesis and 2 right hemiparesis. No data about the injure nature.	The participants first performed a sequence of motor execution and then motor imagery of the same. The participants started with 10 repetitions with the unimpaired upper limb followed by 10 repetitions with the impaired limb for both motor execution and motor imagery parts of the session. The participants were provided with feedback through the EEG-based BCI during the motor imagery part of the session only. 12 sessions of 1 hour (30 min. motor imagery and 30 min. motor execution) during 6 weeks. 40+40 movement experimental trials.	**Task:** hand clenching. *Visual feedback.*	MI, ARAT, NHPT, GAS, dynamometer grip strength, fatigue and mood levels, and qualitative feedback. 2 bipolar channels EEG *Measurements: baseline, every week during the six week intervention period, and at the follow up assessment one week later.* *Bilateral ERD/ERS μ/β*	Improvements approached a minimal clinically important difference for the ARAT. The ERD/ERS change from the first to the last session was statistically significant for only two participants.

Young et al (a).[56]	Case Series	N= 9 (Subacute and chronic subjects) 7 right hemiparesis and 2 left hemiparesis. No data about the injure nature.	Motor imagery-BCIs to drive a Functional Electrical Stimulation. 15 sessions of 2 hours during 6 weeks. 80-120 movement experimental trials.	**Task:** to move a cursor onto a target area on a screen. *Visual and haptic feedback.*	ARAT, NHPT, SIS domains of hand function and ADL, functional connectivity. 16 channels of EEG. fMRI. *Measurements: baseline, mid-intervention, one week post-intervention and one month post-intervention.* *Bilateral ERD* μ/β	Average motor network functional connectivity was increased post-therapy, and changes in average network functional connectivity correlated ($p < 0.05$) with changes in performance on ARAT ($p=0.049$), NHPT ($p=0.01$) and SISdomains [Hand function: $p=0.00001$; ADL: $p=0.01$].
Shindo et al.[53]	Case Series	N=8 (Chronic). 6 left hemiparesis and 2 right hemiparesis. 6 hemorrhagic, 2 ischemic. 7 subcortical and 1 combined lesion.	EEG based motor imagery BCI coupled with a mechanical orthosis. . 12-20 sessions, 1 or twice a week, for a period of 4-7 month. 100 movement experimental trials.	**Task:** to extend the fingers. *Visual and haptic feedback.*	SIAS, Knee-mouth test and finger test, MAL, amount of use, Ashworth Scale and EMG. 10 channels of EEG: ERD. TMS. *Measurements: baseline and post-intervention.* *Bilateral ERD* μ/β	New voluntary EMG activity was measured in the affected finger extensors (4 cases), improvements in finger function. TMS showed increased cortical excitability in the damaged hemisphere.
Ono et al.[57]	Case Series	N=12 (2 acute, 2 subacute, 8 Chronic subjects). 9 left hemiparesis and 3 right hemiparesis. 12 subcortical.	EEG based BCI with different feedbacks. Six patients were received a simple visual feedback in which the hand open/grasp picture on screen was animated at eye level, following significant ERD. Six patients were received a somatosensory feedback in which the motor-driven orthosis was triggered to extend the paralyzed fingers from 90 to 50°. 1 hour of BCI treatment with 12-20 training days. 100 movement experimental trials.	**Task:** an attempt of finger opening in the affected side repeatedly. *Visual and haptic feedback.*	EMG, SIAS, EMG. 10 channels of EEG *Measurements: baseline and post-intervention.* *Bilateral ERD* μ/β	Participants learned to increase ERD after training, in both groups, but haptic feedback group obtained better results.

Level of evidence 5 / Strength of recommendation D*						
Daly et al.[48]	Case Study	n=1. Right hemiparesis. Chronic (10 months) and ischemic stroke. Combined lesion.	Brain signals from the lesioned hemisphere were used to trigger FES for movement practice. 9 sessions during 3 weeks. 75 movement experimental trials.	**Task:** to attempt finger movement and relax conditions or imagined finger movement and relax conditions. *Visual and haptic.*	Volitional Index Finger testing, video document and standard goniometry. 58 channels of EEG. *Measurements: before, mid-intervention and post-intervention.* *Bilateral ERD μ/β*	The participant demonstrated recovery of volitional isolated index finger extension.
Broetz et al.[52]	Case Study	N=1 Left hemiparesis. Chronic (14 months) and ischemic stroke. Subcortical.	EEG and MEG-BCI combined with a specific daily life-oriented physical therapy. The BCI used electrical brain activity (EEG) and magnetic brain activity (MEG) to drive an orthosis and a robot affixed to the patient's affected upper extremity. 3 training blocks over 1 year. No concrete data about number of trials.	**Task:** to imagine grasp movements of his affected upper limb. *Visual feedback.*	FMA, WMFT, Modified Asworth Scale, 10-m walk speed and goal attainment score. fMRI and MEG. *Measurements: before and post-intervention.* *Ipsilesional ERD μ*	The ability of hand and arm movements improved significantly. Improvement of motor function was associated with increased micro-oscillations in the ipsilesional motor cortex.
Caria et al.[49]	Case Study	N=1. Left hemiparesis. Chronic (14 months) and hemorrhagic stroke. Subcortical.	BCI coupled with an upper limb robot device (Motorika®). 20 sessions of BCIs and 1 hour of active and passive physical therapy after each session. No concrete data about number of trials.	**Task:** to modulate the μ-rhythm. *Haptic feedback.*	FMA, WMFT, MAS, GAS, Modified Asworth Scale. fMRI and MEG. *Measurements before and after intervention.* *Ipsilesional ERD μ*	Improvements in FMA (85.6%), WMFT (85.7%), Asworth (50%).
Young et al (b).[58]	Case Study	N=1, acute, ischemic and with left hemiparesis. No data about the injure nature.	BCI device with visual, functional electrical stimulation, and tongue stimulation feedback modalities. Botulinum toxin injection just prior the study. 13 sessions (2 hours) and 1-2 hours per week of additional therapy and Occupational Therapy. 80-120 movement experimental trials.	**Task:** to open and close the hand. *Visual and haptic feedback.*	ARAT, SIS, MAL, MAS. 16 channels of EEG. fMRI. *Measurements: baseline, mid-intervention, post-intervention and one month post-intervention.* *Bilateral ERD μ/β*	Improvements over the course of BCI therapy, with more than 10 point gains in both the ARAT scores and scores for the SIS hand function domain.

* Levels of evidence and grades of recommendation established by the Oxford Centre for Evidence-based Medicine. Action Research Arm test (ARAT). Activities of Daily Living (ADL).Brain Computer Interface (BCI). Electroencephalography (EEG).Electroencephalography (EEG).Electromyography (EMG).ERD. Even Related Desynchronization. ERS. Even Related Synchronization. Fügl-Meyer Assessment (FMA).Functional Magnetic Resonance Imaging (fMRI). Goal Attainment Scale (GAS). Magnetoencephalography (MEG). Medical Research Council (MRC).Motor Activity Log (MAL). Motor Assessment Scale (MAS). Motricity Index (MI). National institute of Health Stroke Scale (NIHSS).Nine Hole Pig Test (NHPT). Randomized Controlled trial (RCT). Stroke Impact Scale (SIS). Stroke Impairment Assessment Set (SIAS). Wolf Motor Functional test (WMFT).

Figure 1. Summary of the selection process (flow diagram).