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Analytical Review

Use of Electroencephalography Brain-Computer Interface Systems as a Rehabilitative Approach for Upper Limb Function After a Stroke: A Systematic Review

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Abstract

Background: Brain-computer interface (BCI) systems have been suggested as a promising tool for neurorehabilitation. However, to date, there is a lack of homogeneous findings. Furthermore, no systematic reviews have analyzed the degree of validation of these interventions for upper limb (UL) motor rehabilitation poststroke.
Objectives: The study aims were to compile all available studies that assess an UL intervention based on an electroencephalography (EEG) BCI system in stroke; to analyze the methodological quality of the studies retrieved; and to determine the effects of these interventions on the improvement of motor abilities.
Type: This was a systematic review.
Literature Survey: Searches were conducted in PubMed, PEDro, Embase, Cumulative Index to Nursing and Allied Health, Web of Science, and Cochrane Central Register of Controlled Trial from inception to September 30, 2015.
Methodology: This systematic review compiles all available studies that assess UL intervention based on an EEG-BCI system in patients with stroke, analyzing their methodological quality using the Critical Review Form for Quantitative Studies, and determining the grade of recommendation of these interventions for improving motor abilities as established by the Oxford Centre for Evidence-based Medicine. The articles were selected according to the following criteria: studies evaluating an EEG-based BCI intervention; studies including patients with a stroke and hemiplegia, regardless of lesion origin or temporal evolution; interventions using an EEG-based BCI to restore functional abilities of the affected UL, regardless of the interface used or its combination with other therapies; and studies using validated tools to evaluate motor function.
Synthesis: After the literature search, 13 articles were included in this review: 4 studies were randomized controlled trials; 1 study was a controlled study; 4 studies were case series studies; and 4 studies were case reports. The methodological quality of the included papers ranged from 6 to 15, and the level of evidence varied from 1b to 5. The articles included in this review involved a total of 141 stroke patients.
Conclusions: This systematic review suggests that BCI interventions may be a promising rehabilitation approach in subjects with stroke.
Level of Evidence: II

Introduction

Recovery of motor function after stroke is crucial in order to perform activities of daily living, however, this recovery is often incomplete [1,2]. Most stroke survivors have upper limb (UL) symptoms after suffering an acute stroke [3]. The initial stroke severity is the most significant predictor of the long-term outcome, however, the anatomical damage (size and location), the nature of the lesion or the age of onset are also determining factors [4]. According to the Copenhagen Stroke Study [5], which evaluated the functional recovery of the UL (via the basic items contained in the Barthel Index relating to food and hygiene), full UL function is achieved in 79% of patients who present with mild initial paresis, whereas, in patients with severe initial paresis,

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this figure is reduced to 18%. Furthermore, 60% of patients with a nonfunctional UL 1 week after stroke will not recover UL function at 6 months. This dysfunction significantly limits participation within the individual's physical and social environment [6,7].

Motor network reorganization after stroke is time and activity dependent [8,9]. Coincident activation of presynaptic and postsynaptic 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 because of a cortical or subcortical lesion, a concurrent activation of sensory feedback loops and the primary motor cortex may reinforce previously dormant cortical connections through Hebbian plasticity mechanisms, thus supporting functional recovery [10]. Therefore, 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 rehabilitation goals, by providing the potential users with brain state–dependent sensory feedback (ie, 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 certain feedback procedures [10]. Taking this into consideration, BCI systems that are 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 areas [12,13].

BCI systems can use different sources of information: electroencephalography (EEG), magnetoencephalography, functional magnetic resonance imaging, near-infrared spectroscopy, or electrocorticography. Among these, EEG signals are particularly relevant, because of 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 movements. Such information has proved to be valuable in providing feedback at specific moments, which, in turn, induces cortical plasticity and the restoration of the normal motor function [14-16]. In relation to this, the EEG-based observations by Chatrian et al [17] are of particular relevance, together with more recent studies by Pfurtscheller et al [18-20], which revealed that the dynamic neuronal oscillations provide relevant information regarding neuronal activation during the preparation and execution of voluntary movements. A motor event implies neuronal changes in brain structures, among which 2 main cortical patterns have been extensively described in the literature: the low-frequency movement-related cortical potentials, and the movement-dependent fluctuations in the power of the sensorimotor μ (8-12 Hz) and β (13-30 Hz) rhythms, known as event-related desynchronization or event-related synchronization patterns [21-25].

Movement-related cortical potentials used to assess cortical activation patterns provide interesting information, as they are associated with the planning and execution of voluntary movements. In this context, the study of the premotor component of the movement-related cortical potentials (the Bereitschaftspotential) is of special interest because of its predictive nature [26,27]. The Bereitschaftspotential is characterized by a slow negative deflection of the average EEG amplitude that takes place approximately 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 spatiotemporal distribution of the Bereitschaftspotential pattern associated with movement occurs earliest in the supplementary motor area, then in the contralateral motor cortex, and finally in the ipsilateral motor cortex [30]. During resting conditions, the sensorimotor cortex presents variations in the μ and β frequency bands, termed sensorimotor rhythms. The percentage of decrease of EEG signal power in sensorimotor rhythms is referred to as event-related desynchronization. In healthy subjects, during voluntary movements, μ and β event-related desynchronization start contralateral to the side of the movement, about 2 seconds before its onset, becoming bilateral when the movement begins [25,31]. This suggests a role of the contralateral hemisphere in the preparation of voluntary movements. After the movement is completed, the event-related synchronization pattern is observed. Thus, the event-related synchronization refers to the percentage of power increase in the β band after the movement is completed, which indicates a motor cortex deactivation [32].

Previous studies have evaluated the cortical EEG activity in subjects who had a stroke by analyzing the cortex reorganization processes throughout the recovery period [33]. Several authors [34,35] have found a significantly reduced event-related desynchronization in the injured hemisphere for UL movements in patients with poor recovery, whereas those with a good prognosis showed a greater involvement of the injured hemisphere, comparable to what is observed in healthy people. Regarding movement-related cortical potentials, the premovement Bereitschaftspotential is significantly reduced over the injured hemisphere in patients with stroke [36]. Furthermore, a marked amplitude in frontal areas of movement-related cortical potentials has been observed [37], indicating lower task automation, which forces the use of compensatory strategies for motor execution [38].

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

Although there are other recent reviews addressing similar topics [13,16,39-47], they have not evaluated the validity of the articles reviewed using standardized methodological quality tools. This aspect is essential in order to recommend an appropriate intervention based on these technologies. To our knowledge, this is the first review to exclusively include clinical trials based on UL interventions with BCI systems in subjects with stroke and that uses standardized methodological quality tools to evaluate these articles and to draw clinical recommendations. There are reviews in the literature that explore technical features and BCI processing methods [48]; however, these do not focus on clinical applications. Considering the number 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, 3 primary goals are targeted here: (1) to compile all studies available that assess an UL intervention based on an EEG-BCI system in stroke; (2) to analyze 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 was conducted on Pubmed (Medline), PEDro, Embase, Cumulative Index to Nursing and Allied Health, Web of Science and Cochrane Central Register of Controlled Trial. The search covered studies published between 2005 and 2016. Only full-text articles published in English, French, or Spanish were selected. The combinations of keywords used are detailed in Table 1.

Table 1
Search strategy

	Keyword combinations
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	"Sensorimotor rhythms" AND "stroke"

BCI = brain-computer interface; EEG = electroencephalography; ERD = event-related desynchronization.

Study Selection

The articles were selected according to the following inclusion criteria: (1) studies assessing an EEG-based BCI intervention; (2) papers featuring stroke patients with hemiplegia, regardless of lesion origin or evolution time; (3) interventions using EEG-based BCI systems to restore functional abilities of the affected UL, regardless of the interface used or of its combination with other therapies; and (4) studies using validated tools to evaluate motor function, such as the Fugl-Meyer Assessment, the Action Research Arm test, the Motor Assessment Scale testing form, the Volitional Index finger, the Wolf Motor Functional Test, the Goal Attainment Scale, the Nine-Hole Peg Test, the Stroke Impairment Assessment Set, the Motor Activity Log, the European Stroke Scale, or the Medical Research Council tool.

This systematic review excluded articles according to the following exclusion criteria: (1) studies that recruited only healthy subjects or subjects with other neurological diseases; (2) studies that did not include motor outcome measures; (3) studies that did not use EEG to guide the rehabilitation; and (4) studies that did not develop an intervention with a BCI (ie, trials evaluating stroke recovery or trials analyzing the activation of sensorimotor rhythms).

Data Extraction

We extracted the general characteristics of the selected studies, including the number of patients, type of central nervous disorder, nature of the injury, stage of the disorder (acute, subacute, and chronic), experimental protocols analyzed (number of trials), and their main results,. The authors carried out independent screenings of the article abstracts and decided which ones could potentially meet the inclusion criteria. In the case of a lack of consensus, the researchers held discussions to reach an agreement. For the studies that met the inclusion criteria, the full-text articles were obtained. The reviewers subsequently performed a new screening of all articles to confirm their relevance until a consensus was reached.

The methodological quality was assessed using the Critical Review Form for Quantitative Studies [49]. This tool, developed by the McMaster University Occupational Therapy Evidence-Based Practice Research Group, included 15 questions (Table 2).

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 3) [50].

Results

A total of 248 articles were retrieved, but only 45 were selected for further review and critical reading,

Table 2
Methodological quality assessment

Critical Review Form for Quantitative Studies	
1	Was the purpose clearly stated?
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 dropouts reported?
15	Were conclusions appropriate given the study methods and results?

according to the previously established selection procedure. Finally, 13 of the 45 articles met the inclusion criteria [8,51-62], and 32 were excluded [29,63-93] (Table 4) (Figure 1). The methodological quality of the included articles, measured with the Critical Review Form, ranged between 6 and 15 (Table 5). Table 6 summarizes the characteristics of the included studies and classifies the trials according to the level of evidence and grade of recommendation.

The included articles contain results based on a total of 141 participants, all of which were patients with stroke. All patients had a topographical distribution of hemiplegia. The clinical status of the stroke was acute for 7 subjects, whereas 4 were in a subacute state and 78 chronic. The remaining 52 patients were from the studies by Ang et al [8,53] and Young et al [59]. In these cases, only the average ranges of days since injury were

Table 3
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; eg, <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

provided (57-1053 and 37-831 days, in the case of the patients recruited by Ang et al [8,53], and 12.9 $\pm$ 7.9 months in the study by Young et al [59]). These 3 studies did not specify the exact number of acute, subacute, and chronic stroke patients. The affected hemisphere was the right one for 65 patients, the left one for 55, and no data were given for the 21 patients recruited by Ang et al [62], who stated that 11 patients were dominant hand affected and 10 were nondominant hand affected, although this study did not specify the laterality. The stroke etiology was ischemic in 31 patients and hemorrhagic in 45. There was no data for 65 subjects [54,57-60]. The stroke was located in cortical areas for 20 participants and subcortical areas for 88 patients. Also, 18 patients suffered combined lesions; in the case of 1 patient, the lesion was located in the brainstem pons, and for 14 patients, data were missing regarding the lesion location [54,59]. The participants did not experience apraxia or sensory changes. To our knowledge, the articles did not report any recurrent stroke or speech deficits.

In 4 studies [51,58,60,61], actual movements were performed, whereas in the other 9 studies [8,52-57,59,62], the tasks were imagined (motor imagery). The tasks performed or imagined were as follows: (1) moving the paretic limb toward a goal on a screen [8,53,57,59]; (2) grasping [54,55,58,62]; (3) index extension [51]; (4) finger flexion and extension [56,60]; (5) hand opening and closing [61]; and (6) reaching [52,58]. Five studies combined conventional physical therapy with the BCI intervention [52,55,58,61,62]. The feedback provided was visual in 1 study [54] and haptic in another [62]; 1 study combined haptic and auditory feedback [58], and 10 used a combination of visual and haptic feedback [8,51-53,55-57,59-61]. Concerning the studies that used haptic feedback, 3 studies used an electrical stimulation interface [51,59,61], 7 studies applied a rehabilitation robot [8,52,53,55,57,58,60,62], and 1 study used a mechanical orthosis [56]. The methodology applied in the papers combining 2 types of feedback was as follows: upon hearing or seeing the auditory or visual cue, the patient was instructed to execute or to imagine a specific task. Successful cortical changes measured with EEG triggered immediate activation of robotic devices, mechanical orthoses, or electrical stimulation. A mean ($\pm$ standard deviation) of 13.69 $\pm$ 4.64 training sessions were performed per patient.

Regarding the outcome measures, significant improvements in Fugl-Meyer Assessment scores were observed in several studies, both immediately after the intervention [8,52,53,55,57,58,62] and after the follow-up [8,53,62], in chronic [52,57,58,62] and subacute [8,53] stroke patients. Significant gains in Action Research Arm test scores were found in acute [61], subacute [59], and chronic stroke patients [54,59]. Two studies described significant changes in the Wolf Motor

Table 4
Articles excluded from the systematic review

Authors [Reference]	Exclusion Criteria
Niazi et al [29]	The sample was composed of healthy subjects
Tam et al [63]	Intervention effectiveness was not analyzed; authors studied channel selection parameters on the classification accuracy of BCI
Tan et al [64]	The intervention effectiveness was not analyzed with motor outcome measures; authors intended only to demonstrate that movement intention was detectable during a training session for using BCI
Cincotti et al [65]	This study did not use motor outcome measures; the authors analyzed only the BCI systems ability to induce cortical plasticity
Kasashima et al [66]	This study analyzed the stroke patients' ability to use EEG-based BCI to detect motor imagery
Ang et al [67]	Motor outcome measures were not used to analyze intervention effectiveness; the authors considered only the changes in cortical excitability
Gómez-Rodriguez et al [68]	Motor outcome measures were not used; this paper demonstrated that artificially closing the sensoriomotor feedback loop facilitates decoding of movement intention by means of a BCI system
Lew et al [69]	This study demonstrates successful single-trial detection of movement intention from EEG
Arvaneh et al [70]	This article presents research on the need for a calibration session for long-term BCI users
Arvaneh et al [71]	The authors propose a novel algorithm for EEG-BCI to extract features of EEG signals
Bundy et al [72]	This study sought to evaluate whether stroke survivors could achieve BCI control with motor activity from their unaffected hemisphere
Aono et al [73]	This study presented research regarding the relationship between ERD magnitude and cortical excitability in healthy subjects and subjects with stroke
Ang et al [74]	This study presented research on the feasibility of using EEG calibration data from passive movement to detect motor imagery
Leamy et al [75]	Motor outcome measures were not used; this study did not analyze the intervention effectiveness for functional improvements, only neuroplastic changes associated with the recovery process
Liu et al [76]	Motor outcome measures were not used; the authors developed a scheme to detect motor imagery EEG patterns
Petti et al [77]	The authors proposed an analysis based on data acquired from stroke patients, using an EEG-BCI based on motor imagery
Schreuder et al [78]	This study did not develop an intervention; the authors researched how to develop a suitable user-centered BCI design
Takemi et al [79]	This was a research study on the relationship between ERD magnitude and cortical excitability in healthy subjects
Bermudez et al [80]	The sample was composed of healthy subjects
Ang et al [81]	This study analyzed stroke patients' ability to use EEG-based BCI to detect motor imagery
Kaiser et al [82]	This was a study on the relationship between ERD and ERS and the degree of stroke impairment; however it did not develop an intervention
Tangwiriyasakul et al [83]	An exploration of the temporal evolution of ERD during stroke recovery, this study did not develop an intervention
Zhou et al [84]	The sample was composed of healthy subjects
Bai et al [85]	Healthy subjects and patients with other neurological diseases (amyotrophic lateral sclerosis) were recruited; motor outcome measures not used; the study was based on the neurophysiological analysis of ERD and ERS
Buch et al [86]	This study did not use an EEG-BCI system
González-Franco et al [87]	The sample was composed of healthy subjects
Mihara et al [88]	This study did not use an EEG-BCI system to guide the intervention
Faller et al [89]	This study recruited subjects with other neurological diseases (spinal cord injury) and did not use motor outcome measures
Song et al [90]	This study did not use an EEG-BCI system
King et al [91]	The sample was composed of healthy subjects
Cantillo-Negrete et al [92]	The sample was composed of healthy subjects
Looned et al [93]	The sample was composed of healthy subjects

BCI = brain-computer interface; EEG = electroencephalography; ERD = event-related desynchronization; ERS = event-related synchronization.

Functional Test in chronic stroke patients [52,55]. One trial reported a significant improvement in fine motor function evaluated with the Nine-Hole Peg Test in subacute and chronic stroke patients [59]. However, in most studies, no statistically significant differences were found between the control and experimental groups. Four of these studies evaluated the changes in the EEG activity during and after the BCI interventions [54,55,58,60]. Four trials found a correlation between the improvements obtained in the motor outcome measures (Fugl-Meyer Assessment and Action Research Arm test) and the neural functional connectivity evaluated with neuroimaging techniques [55,57-59]. Changes in electromyography activity were analyzed in 2 trials [56,60], both of which observed new voluntary electromyographic activity in the affected finger extensors. In addition, 4 trials [52,55,56,58] evaluated the muscle spasticity with the Modified Ashworth Scale. Two of these trials revealed relevant improvements in this parameter [52,55]. Finally, the included articles did not describe the functional recovery pattern (proximal to distal or distal to proximal), nor did studies describe whether the recovery after the intervention was complete or incomplete.

In general terms, trials detailed the EEG pattern studied. Three studies [52,55,58] considered the

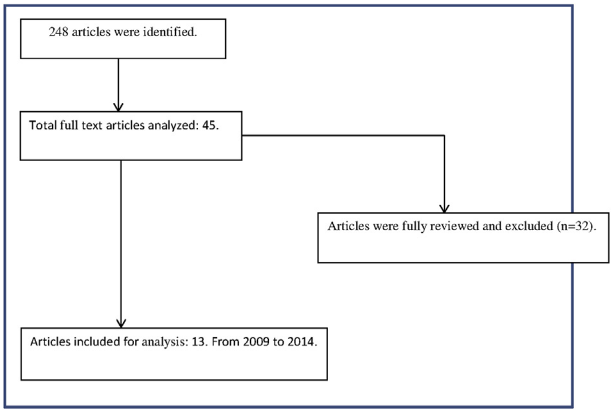

Figure 1. Flowchart.

ipsilateral

ipsilesional event–related desynchronization of the μ rhythm for the BCI. One study [54] analyzed the bilateral event-related synchronization and the event-related desynchronization of both μ and β rhythms, and the remaining studies [8,51,53,56,57,59-62] considered the bilateral event-related desynchronization of μ and β rhythms.

Most of the studies reviewed were conducted in referral hospitals or universities.

Discussion

To our knowledge, the present article provides the first systematic review of EEG-BCI interventions for UL in subjects with stroke, using standardized methodological quality tools.

In relation to methodological quality, 4 of the 13 included studies were randomized controlled trials [8,53,58,62], 1 was a controlled study [57], 4 were case series studies [54,56,59,60], and 4 were case reports [51,52,55,61]. The level of evidence of the studies evaluated with the scale established by the Oxford Centre for Evidence-based Medicine included scores varying from 1b (randomized controlled trials) to 5 (case reports/case studies). The grades of recommendation are distributed among A, B, C, and D.

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

The randomized controlled trials obtained a score ranging from 14-15 points in the Critical Review Form, according to the Quantitative Review Form Guidelines [49]. One of the randomized controlled trials did not describe the sample in detail [58], which may result in a sample bias when attempting to generalize the results to the entire stroke population. The controlled study [57] had 11 points on the Critical Review Form. This article did not report the results in terms of statistical significance. The case series studies [54,56,59,60] and the case reports [51,52,55,61] had a score ranging from 6 to 12 on the Critical Review Form. Many of these did not offer detailed descriptions of the participants recruited [54,59,60]. However, all studies adequately described the intervention, and most studies avoided contamination [8,51,53,54,56-60,62]. In all trials, participants were the same from start to finish, therefore fulfilling the intention-to-treat analysis. Overall, many studies reflected a strong commitment by the

Table 5
Methodological quality of articles included

Authors [Reference]	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 [8]	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	14
Daly et al [51]	1	1	1	1	0	1	1	1	1	1	0	0	1	0	1	11
Caria et al [52]	0	1	1	1	0	1	0	0	1	1	0	0	0	0	0	6
Ang et al [53]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15
Prasard et al [54]	1	1	1	0	0	1	1	1	1	1	0	1	1	0	1	11
Broetz et al [55]	1	1	1	1	0	1	0	0	1	1	1	0	1	0	0	9
Shindo et al [56]	1	1	1	1	0	1	1	1	1	1	0	1	1	0	0	11
Várkuti et al [57]	1	1	1	1	0	1	1	1	1	1	0	0	1	0	1	11
Ramos-Murguialday et al [58]	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	14
Young et al [59]	1	1	1	0	0	1	1	1	1	1	1	1	1	0	1	12
Ono et al [60]	1	1	1	0	0	1	1	1	1	1	0	0	1	0	1	10
Young et al [61]	0	1	1	1	1	1	0	0	1	1	0	0	1	0	1	9
Ang et al [62]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15

Items: 1) Was the purpose clearly stated? 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 results reported in terms of statistical significance? 12) Were the analysis methods appropriate? 13) Was clinical importance reported? 14) Were drop-outs reported? 15) Were conclusions appropriate given the study methods and results?

Table 6
Characteristics and main results of included articles

Authors [Ref]	Design	Participants	Protocol	Task and Feedback	Outcome Measures	Main Results
Level of evidence 1b/Grade of recommendation A*						
Ang et al [8] randomized controlled trials	RCT	N = 18 10 Right hemiparesis, 8 left hemiparesis; 57-1053 days since injury; 6 ischemic and 12 缺血性 hemorrhagic;出血性 5 cortical and 13 subcortical	Subjects were randomly allocated to 2 groups: EEG-based motor imagery BCI to drive robotic device (n = 8) vs standard robotic rehabilitation (MIT-manus) (n = 10) 12 Sessions of 1 h during 4 wk 122 Movement experimental trials vs 960 movement control trials	Task: Moving a mark on a screen to a target position Visual and haptic feedback	FMA 27 Channels of EEG Measurements: baseline, midrehabilitation, postrehabilitation and 2 mo postrehabilitation Bilateral ERD μ/β	Significant gains in FMA in both groups at postrehabilitation (P = 0.001) and 2 mo post-rehabilitation (P = 0.002); the experimental group yielded higher 2-mo postrehabilitation gain than the control, but no significance was found
Ang et al [53] randomized controlled trials	RCT	N = 25 23 Right hemiparesis, 2 left hemiparesis; 37-831 days since injury; 10 ischemic and 15 hemorrhagic; 7 cortical and 18 subcortical	Subjects were randomly allocated to 2 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 lasting 1 h during 4 wk 122 Movement experimental trials vs 960 movement control trials	Task: Moving 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, postrehabilitation, and 2 mo postrehabilitation Bilateral ERD μ/β	Significant gains in FMA in both groups at postrehabilitation (P = 0.032) and 2 mo postrehabilitation (P = 0.020), but no significant differences were observed between groups
Ramos-Murguialday et al [58] randomized controlled trials	RCT Double blind	N = 30 (chronic stroke subjects) 16 Left hemiparesis and 14 right hemiparesis; 14 subcortical and 16 combined lesion No data regarding the nature of the injury	Subjects were randomly allocated to 2 groups: BCI coupled with a robotic orthosis under 2 conditions: in the experimental group, movement of the robot orthosis was driven by ERD rhythms (n = 16); in the control group (n = 16), movement of the robot orthosis was independent of their ERD; both groups received goal-directed physical therapy (1 h) 20 Sessions during 4 wk of daily training (excluding weekends) No concrete data concerning number of trials	Task: Reaching and grasping movements Haptic and auditory feedback	FMA, Ashworth Scale, MAL, GAS, and EMG fMRI Measurements: baseline, postintervention, and 1 wk postintervention Ipsilesional ERD μ/β	FMA scores improved more in the experimental group, 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 [62] randomized controlled trials	RCT Single blind	N = 21 (chronic stroke subjects) 11 dominant hand affected and 10 nondominant hand affected; 11 ischemic and 10 hemorrhagic; 6 cortical and 15 subcortical	Subjects were randomly allocated to 3 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 wk 3, end-intervention at wk 6, and follow-up at wk 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 wk 12 and 24

Level of evidence 2b/Strength of recommendation B*						
Várkuti et al [57] controlled study	Non-RCT	N = 9 (3 chronic, 4 acute, and 2 subacute stroke subjects); 6 left and 3 right hemiparesis; 2 cortical and 7 subcortical; No data regarding the nature of the lesion	Subjects were allocated to 2 groups: EEG-based motor imagery BCI (n = 6) and robot-assisted rehabilitation (MIT-Manus) (n = 3) 12 Sessions over 1 mo 80 Movement experimental trials	Task: movement of the 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 BCI group
Level of evidence 4/Strength of recommendation C*						
Prasad et al [54] case series studies	Case series	N = 5 (Chronic stroke subjects); 3 left hemiparesis and 2 right hemiparesis No data regarding the nature of the injury and the lesion location	The participants first performed a sequence of motor execution and then motor imagery of the same; they began 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; feedback was provided through the EEG-based BCI during the motor imagery part of the session only 12 Sessions of 1 h (30 min motor imagery and 30 min motor execution) during 6 wk 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 6-wk intervention period, and at the follow-up assessment 1 wk 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 2 participants
Young et al [59] case series studies	Case series	N = 9 7 Right hemiparesis and 2 left hemiparesis; 12.9 ± 7.9 months since injury No data regarding the nature of the injury or the lesion location	Motor imagery-BCI to drive a functional electrical stimulation 15 Sessions of 2 h during 6 wk 80-120 Movement experimental trials	Task: moving 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, 1 wk postintervention, and 1 mo postintervention Bilateral ERD μ/β	Average motor network functional connectivity was increased after 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 SIS domains (hand function: $P = 0.00001$; ADL: $P = 0.01$)
Shindo et al [56] case series studies	Case series	N = 8 (Chronic stroke patients); 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, once or twice a week, for a period of 4-7 mo 100 Movement experimental trials	Task: finger extension Visual and haptic feedback	SIAS, knee-mouth test, and finger test, MAL, amount of use, Modified Ashworth Scale, and EMG 10 Channels of EEG: ERD, TMS Measurements: baseline and postintervention 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

(*continued on next page*)

Table 6 (*continued*)

Authors [Ref]	Design	Participants	Protocol	Task and Feedback	Outcome Measures	Main Results
Ono et al [60] case series studies	Case series	N = 12 (2 acute, 2 subacute, 8 chronic stroke subjects); 9 left hemiparesis and 3 right hemiparesis; 12 subcortical No data about the nature of the injury	EEG-based BCI with different feedbacks; 6 patients received simple visual feedback in which the hand open/grasp picture on screen was animated at eye level, following significant ERD; 6 patients received somatosensory feedback in which the motor-driven orthosis was triggered to extend the paralyzed fingers from 90° to 50° 1 h of BCI treatment with 12-20 training days 100 Movement experimental trials	Task: repeated attempts to open fingers on the affected side Visual and haptic feedback	EMG, SIAS 10 Channels EEG channels Measurements: baseline and postintervention Bilateral ERD μ/β	Participants learned to increase ERD after training, in both groups; the haptic feedback group obtained better results for affected finger extensor voluntary EMG activity in 4 cases and the SIAS score was improved in 3 cases
Level of evidence 5/Strength of recommendation D*						
Daly et al [51] case reports	Case study	N = 1 Right hemiparesis; chronic (10 mo) and ischemic stroke Combined lesion	Brain signals from the injured hemisphere were used to trigger FES for movement practice 9 Sessions over 3 wk 75 Movement experimental trials	Task: attempting index extension and relax conditions or imagined index extension and relax conditions Visual and haptic feedback	Volitional Index Finger testing, video documentation, and standard goniometry; 58 channels of EEG Measurements: preintervention, midintervention, and postintervention Bilateral ERD μ/β	The participant demonstrated recovery of volitional isolated index finger extension
Broetz et al [55] case reports	Case study	N = 1 Left hemiparesis; chronic (14 mo) and hemorrhagic stroke; subcortical	EEG and MEG motor imagery BCI combined with 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 y No concrete data about number of trials	Task: imagining grasp movements of the affected hand Visual and haptic feedback	FMA, WMFT, Modified Ashworth Scale, 10-m walk speed, and goal attainment score fMRI and MEG Measurements: pre- and postintervention. Ipsilesional ERD μ	The skill of hand and arm movements improved significantly on FMA, WMFT, and Modified Ashworth Scale; improvement of motor function was associated with increased micro-oscillations in the ipsilesional motor cortex
Caria et al [52] case reports	Case study	N = 1 Left hemiparesis; chronic (14 mo) and hemorrhagic stroke; subcortical	Motor imagery BCI coupled with an upper limb robot device (Motorika) 20 Sessions of BCIs and 1 h of active and passive physical therapy after each session No concrete data about number of trials	Task: imagining reaching movements of the affected arm Visual and haptic feedback	FMA, WMFT, MAS, GAS, Modified Ashworth Scale fMRI and MEG Measurements before and after intervention Ipsilesional ERD μ	Improvements in FMA (85.6%), WMFT (85.7%), Modified Ashworth Scale (50%)

Young et al [61] case reports	Case study	N = 1, acute, ischemic and with left hemiparesis; located in brainstem pons	BCI device with visual, functional electrical stimulation, and tongue stimulation feedback modalities Botulinum toxin injection just before the study 13 Sessions (2 h) and 1-2 h per week of additional therapy and occupational therapy 80-120 Movement experimental trials	Task: opening and closing the hand Visual and haptic feedback	ARAT, SIS, MAL, MAS 16 Channels of EEG fMRI Measurements: baseline, midintervention, postintervention, and 1 mo postintervention Bilateral ERD μ/β	Improvements over the course of BCI therapy, with >10-point gains in both the ARAT scores and scores for the SIS hand function domain

ARAT = Action Research Arm test; ADL = activities of daily living; BCI = brain-computer interface; EEG = electroencephalography; EMG = surface electromyography; ERD = event-related desynchronization; ERS = event-related synchronization; FMA = Fugl-Meyer Assessment; fMRI = functional magnetic resonance imaging; GAS = Goal Attainment Scale; MEG = magneto-encephalography; MRC = Medical Research Council; MAL = Motor Activity Log; MAS = Motor Assessment Scale; MI = Motricity Index (MI); NIHSS = National Institutes of Health Stroke Scale; NHPT = Nine-Hole Peg Test; RCT = randomized controlled trial; Ref = reference; SIS = Stroke Impact Scale; SIAS = Stroke Impairment Assessment Set; WMFT = Wolf Motor Functional test; TMS = transcranial magnetic stimulation.

* Levels of evidence and grades of recommendation established by the Oxford Centre for Evidence-based Medicine.

participants toward the intervention, as there were hardly any reports of desertion. Only 3 studies reported drop-outs [53,58,62]. The drop-outs were not due to a clinically related cause or to being unsatisfied with or tired of the intervention; rather, this suggests that such approaches are well tolerated by patients.

According to the interventions, the use of EEG-BCI to drive a robotic device generated improvements in the Fugl-Meyer Assessment [8,52,53,56,58,62]. However, most studies did not observe significant differences compared to conventional robot-assisted therapy [8,53,62]. Only 1 study revealed a clear superiority of BCI therapy coupled with a robotic orthosis as compared to conventional robot-assisted therapy [58]. One study compared a BCI intervention with conventional physical therapy, showing improvements in Fugl-Meyer Assessment scores in all groups [62]. Some of the included articles combined the BCI intervention with other treatment approaches, such as passive mobilizations or goal-directed physical therapy [52,55,58,61]. According to the results of these studies, the combination of BCI interventions with conventional physical therapy may provide more benefits and greater functional recoveries than BCI interventions alone. The rationale for this is that BCI systems can promote the functional connectivity between the brain areas and muscles, leading to a better "neurophysiological condition," which, in turn, maximizes the effects of conventional physical therapy applied after stimulation with a BCI intervention [94]. The included studies used standardized outcome measures, but the recovery pattern was not considered (complete or incomplete, proximal to distal, distal to proximal). This is an interesting issue that future studies should analyze.

然而大多数研究没有观察到与常规机器人辅助治疗的显著差异。

Some articles included in this review used neuroimaging techniques to analyze the changes obtained by the experimental intervention in terms of brain functional connectivity [52,56-59,61]. These articles suggest an increase in 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 after BCI interventions. Both results might suggest that the BCIs could be a potential facilitator of neuroplasticity. In addition, apart from cortical connectivity measures, there is a lack of studies that include neurophysiological tests (eg, testing responses to transcranial magnetic stimulation) to analyze the induced plastic changes in the central nervous system. Such tests should be considered in future studies to further describe the mechanisms of action concerning BCI interventions.

Regarding participant follow-up, few studies carried out any measures after the BCI intervention. According to these reports, BCI interventions may increase the cortical excitability even after the therapy ends [8,53,62]. Therefore, BCI interventions may have long-term benefits; however, more trials with follow-up and use of neuroimaging techniques are necessary to clarify these effects.

The type of task analyzed in most of the studies reviewed shows that training with BCI leads to improvements in UL functionality, such as finger extension, hand opening, handgrip, and reaching tasks. There is a maximal level of evidence to recommend BCI interventions for the improvement of reaching tasks, using a combined strategy of motor imagery and robotic rehabilitation [8,53,58]. Studies examining simple movements (eg, finger extension), such as those by Shindo et al [56], Ono et al [60], Daly et al [51], and Broetz et al [55], also obtained satisfactory results; however, these results were based on small samples. The way that the complexity of the task modifies the outcomes of BCI interventions is an aspect that further studies should analyze. Furthermore, patients were seated during the tasks. It is possible that other positions or movements might modify the response of the EEG signals, as these parameters are highly sensitive, and so other positions might create artifacts during the BCI intervention, which could interfere with the therapy. Future studies should consider analyzing the application of BCI interventions in different positions and how this affects motor function recovery.

Several studies in this review obtained positive results using motor imagery [8,53,54,56,57,59,62]. Motor imagery was shown to activate the same areas that are involved in the execution or attempt of actual motor tasks [94]. Several studies using neuroimaging techniques [95,96] described an overlap in cortical activation patterns between actual and imagined movements.

Improvements in outcome measures were found in subacute and acute stroke patients, and the studies that recruited chronic stroke patients also obtained improvements in motor function as well as reductions in spasticity. This may suggest that BCI interventions produce plastic changes that result in functional motor improvement, regardless of the time since the lesion. A differential aspect across studies was whether they used EEG signals from 1 hemisphere (the injured side) or both hemispheres. This decision was uniform for the entire sample of patients recruited in each study. This is in contrast to other reports, such as that of Di Pino et al [97], which proposes that the intervention carried out with each patient should be appropriate in relation to the structural reserve, that is, the quantity of strategic neural pathways and relays that are spared by the lesion and that are able to reallocate previous functions or outsource new ones. Future studies should focus on how different EEG-based decoding algorithms (in terms of spatial areas considered) influence the outcomes of the BCI interventions at different poststroke stages. In addition, the influence of hand dominance on outcome measures is an issue that most of the included studies in this review did not analyze. Young et al [61] reported that the Action Research Arm test score improved in a stroke subject with an impaired dominant left hand. This improvement was higher than the minimal clinically important difference established for the Action Research Arm test in stroke patients with impairments in their dominant hand (from 6 points to 12 points). In this sense, hand dominance is an interesting factor that further studies should evaluate.

As for the location and type of injury, only Ono et al [60] considered subcortical lesions as an inclusion criterion. We cannot establish specific recommendations, however, given that the results were based on very heterogeneous samples. As the pattern of reorganization depends on the size of the lesion [97], the area of the injury is also important. The areas where brain changes were evidenced with neuroimaging techniques after BCI interventions were mostly located in the motor cortex [57] and thalamus [59]. It might be hypothesized that it is more difficult to induce changes in subcortical structures; however, we cannot establish strong conclusions, in this regard, based on the included articles. Future studies should address possible differences in the response to BCI therapy in relation to the stroke type (ischemic versus hemorrhagic, cortical versus subcortical, etc). Also, the sample of ischemic patients should be increased in subsequent studies, as this type of stroke is significantly more prevalent [98] and may have been underrepresented up to now (considering the total number of ischemic and hemorrhagic strokes in previous studies).

Regarding feedback, only 1 manuscript revealed differences between the types of feedback applied [60], obtaining better results for patients who received haptic versus visual feedback. According to these findings, an interesting focus in future studies could be the comparison between different types of feedback. However, all studies except Broetz et al [55] used haptic stimulation, and the most frequent was mechanical stimulation, which provides a more natural approach for inducing sensory feedback because it mimics real movement.

The latency between motor intention and associated feedback is an essential factor for an effective BCI intervention. Timing is essential for long-term potentiation, increasing synaptic efficacy, which is 1 of the mechanisms underlying the Hebbian association [95].

赫布理论（Hebbian theory描述了突触可塑性的基本原理，即突触前神经元向突触后神经元的持续重复的刺激可以导致突触传递效能的增加

All studies used a noninvasive method to acquire the characteristics of motor cortex activation, allowing patients to modulate their signals through learning based on receiving afferent feedback. Some articles did not report data about the strategies used for extracting EEG characteristics of brain signals [8,53,57-59,61]. Others explained that they used brain oscillations, event-related desynchronization, and event-related synchronization as outcome measures. None of the included articles assessed the movement-related cortical potentials to evaluate the components of motor planning. Therefore, it is impossible to understand the role of cognitive changes on motor control improvements. Movement-related cortical potentials have excellent time resolution, providing important information regarding cognitive planning time [37]. Motor-intention detection using sensorimotor rhythms is less effective, deriving from the lack of control in the timing of the detection of the motor-related cortical state, so feedback triggered by such detection may potentially reach the motor cortex too late to promote an efficient level of plasticity. The delay from movement-related cortical potentials to the onset of movement intention has proved to be smaller (hundreds of milliseconds), and therefore better suited for establishing a Hebbian association [95].

There are several factors that could have an influence on stroke patients' progress during BCI interventions, such as the place where the patients receive the therapy, the social support, the family context, the accessibility of environments [99], the onset and frequency of therapy, or the mode of transportation used to reach rehabilitation facilities. None of these factors has been sufficiently addressed in the BCI therapies reviewed in this article. In most cases, the reason for this is the lack of a sufficiently large sample of patients. Therefore, it is advised that future EEG-BCI studies include some of these factors to provide further insight into how these potentially beneficial technologies can promote motor rehabilitation in the different typical scenarios of stroke patients.

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

Conclusions

This article presents a systematic review of studies testing the effectiveness of BCI systems for functional rehabilitation of the UL in patients with stroke. Despite the heterogeneity in the participants and the BCI interventions carried out in the studies considered, the overall results suggest that BCI interventions may be potentially beneficial in improving motor outcome measures, such as the Fugl-Meyer Assessment, the Action Research Arm test, or the Wolf Motor Functional Test in patients with stroke. However, it is necessary to continue developing randomized controlled trials, with larger and clearly stratified samples of patients, which can be applied in clinical settings. Also, additional studies must establish well-defined criteria for selecting participants and must ensure that samples are as homogeneous as possible. Furthermore, there is a need for trials that establish comparisons between subjects with different temporal evolutions. Future studies should include advanced neurophysiological assessments to clearly define the mechanisms of action of the BCI interventions. Finally, these studies should use functional outcome measures correlated with neuroimaging changes to address the transfer of learning into daily life, as well as the social impact of these interventions.

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

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