Advanced Brain-computer Interface for Upper Limb Stroke Rehabilitation

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BY

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Advanced Brain-computer Interface for Upper Limb Stroke Rehabilitation

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Acknowledgments

I dedicate this work to the souls of my parents, whose love, support, and inspiration have never ended.

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I am lucky to have friends and colleagues who have been a constant source of inspiration and support, making this journey an unforgettable one. I am also thankful to my beloved children, who bring joy and light to my life every day.

Finally, I would like to dedicate this work to my wife, who has always believed in me and supported me throughout my journey. Her unwavering love and encouragement has been my greatest source of strength and motivation.

Abstract

This thesis investigates the challenges associated with the use of Brain-Computer Interface (BCI) technology for post-stroke upper limb rehabilitation. Although BCI has gained increasing attention as a potential tool for stroke rehabilitation, different BCI designs have been used in clinical trials, resulting in different clinical outcomes. One of the main motivations of this research is to investigate the differences in BCI designs, including differences in the settings and parameters of the BCI system, in order to find the most effective BCI paradigms for upper limb stroke rehabilitation.

Another challenge with the use of BCI for stroke rehabilitation is that a considerable number of stroke patients are dismissed from the study due to their inability to use the BCI. Most of the clinical studies in BCI rehabilitation use the brain signals from the ipsilesional hemisphere, which may not be suitable for all patients, as their ability to modulate these signals can be significantly affected depending on the lesion size and location. Therefore, this thesis also investigates the use of contralesional hemisphere signals as an alternative approach to BCI rehabilitation.

Finally, the current BCI equipment is expensive, complex, and mainly used in a hospital or lab. This research develops a portable BCI system for home-based

rehabilitation, allowing patients to use the technology with remote supervision. The proposed BCI system is evaluated through a clinical trial to assess its feasibility and acceptability.

Altogether, by addressing the challenges associated with BCI-based rehabilitation, this thesis contributes to the development of more effective and accessible BCI-based rehabilitation methods.

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1 Thesis Background

1.1 Background

Stroke is the second leading cause of death worldwide, and it is correspondingly one of the leading disabilities [1]. In the UK, there are more than 100,000 people experience their first stroke every year and there are over 1.2 million stroke survivors across the country [2]. Stroke affects men and women equally and causes significant social and economic burdens to society [3]. The annual financial burden of the stroke in the UK is around £ 25.6 bn, and that amount is predicted to increase significantly over the next 20 years [4, 5].
Therefore, there is a need to develop a more effective therapy in order to reduce the disabling effects of stroke [5]. Typically, the arm movements of one side are mostly controlled by the opposite side (contralateral hemisphere) of the brain [6]. Thus, a stroke affecting the right side of the brain will cause weakness in left limb and vice versa.
Around 65% of stroke survivors experience permanent disability at six months [7].

It is believed that the neural plasticity is the underlying mechanism of improvement in motor function outcome after stroke [8]. Hence, it is crucial to develop more effective and efficient rehabilitation approaches that better induce the neural plasticity and promote functional recovery.

Many studies have assessed different therapeutic interventions for post stroke upper limb rehabilitation. They include constraint-induced movement therapy (CIMT) [9], robot-assisted therapy [10], non-invasive neuro-stimulation [11], and brain-computer interface (BCI) [12]. In CIMT, the patient is encouraged to perform specific tasks using his/her affected hand, while the unaffected hand is constrained [13–15].

Indeed, the success of this approach showed that neuroplasticity and motor recovery would be more influenced by relearning instead of the time after stroke [16]. Despite success to some extent, CIMT is not suitable for stroke patients who suffer from severe impairment since the residual movement of the affected limb is essential for such rehabilitation approaches [6].

Recently, robot-assisted therapy has been widely used in stroke rehabilitation [17]. The main benefit of using the robot-assisted therapy is the ability to perform high-intensity of repetition while less intervention is required from a therapist [18]. The intensity of the intervention in the robot-assisted therapy was reported being an essential parameter of the upper limb motor function recovery for chronic stroke patients. A randomized control trial conducted by [19] revealed that the group of patients who received a higher intensity robot-assisted therapy achieved significantly more motor function improvements compared to the stroke patients who received a lower intensity robot-assisted therapy. Nevertheless, a robot-assisted therapy provides passive movements which might reduce patients' engagements and motivation in long-term.

Functional electrical stimulation (FES) is another intervention that has some evidence to facilitate motor recovery after stroke [20]. FES generates muscle movements through tiny electrical pulses delivered using electrodes placed on the patient's skin near to the nerve [21]. FES can provide sensory and visual feedback in a repetitive manner, which are stated as essential elements of a successful rehabilitation approach inducing motor function recovery after stroke [7, 20]. Nonetheless, a rehabilitation intervention using FES is typically a passive practice that does not take into account the patient's volitional effort [22].

Mental practices such as motor imagery (MI) have been stated to be helpful for recovery after stroke [23]. Functional imaging research indicated that during MI as well as planning of movement the brain motor network is activated [24]. Thus, such mental practices could be potentially used as a rehabilitation strategy to trigger the motor network in the stroke patients [25]. However, unlike physical practice, MI is not observable and it might be difficult for the patient and therapist to verify if the mental task has been performed correctly and effectively.

Brain-computer interface (BCI) as a novel rehabilitation approach has attracted a lot of attention. A BCI records, analyses and decodes brain signals and translates them to commands for communication and control [16]. BCI can potentially enhance neuroplasticity in stroke patients by providing feedback about the performed mental practices relevant to the impaired limb [26]. In other words, BCI couples the performed motor mental practice (i.e. either MI or the intention of the movement) with some sorts of feedback such as robotic-based movements. The other existing rehabilitation therapies are typically unpaired, since the performed tasks are not associated with the patients' brain activities [27]. On the other hand, BCI can be coupled with the existing therapies and enhance their outcomes by providing an active rehabilitation.

A number of recent clinical trials examined the efficacy of BCI for stroke rehabilitation and compared the outcomes with those obtained from other existing therapies [28–31]. Interestingly, there is a recent meta-analysis study showing the effectiveness of the BCI on upper extremity motor recovery [32]. Despite the encouraging results achieved up to now, several BCI designs reported different clinical outcomes. For example, clinical trials conducted by [29–31] and [28] have found significant motor function improvements in BCI groups as compared to other existing therapies. On contrast, the clinical trials in [33, 34] have reported non-significant difference in motor function improvements after the BCI intervention when compared with the control groups. Furthermore, even for those clinical studies that reported positive outcomes of the BCI group, a high variance in BCI outcomes was observed among stroke patients, where some patients achieved considerably larger motor function improvements as compared to the rest of patients.

Another matter is that typically the clinical studies conduct a screening session before the BCI intervention to evaluate the ability of post-stroke patients to use BCI. Subsequently, those patients who could not achieve a BCI classification accuracy above the chance level are excluded from the study [33, 35]. According to [36], about 20% of stroke patients are excluded from BCI rehabilitation due to their inability to operate the BCI.

Finally, medical care provided at home rather than in a hospital has grown in popularity [37]. Stroke patients may also benefit from such developments. However, most of BCI systems are bulky, expensive, technically challenging, and difficult to set up with a large number of electrodes to be placed on scalp. Because of the hardware's current limits, rehabilitation must currently take place in a hospital or lab, which has its own set of challenges. For stroke survivors with limited mobility, it may be difficult to make regular trips to the hospital for rehabilitation. This restricts access for individuals who do not have access to hospitals, particularly during a pandemic when hospital resources are scarce. Additionally, stroke patients face a heightened risk of contracting a virus during these times.

Therefore, in order to improve the effectiveness of BCI for stroke rehabilitation, it could be remarkably helpful to address the following challenges. The first challenge is improving the BCI design by investigating why some clinical studies that used BCI for upper limb motor function recovery were very successful, while some others were not that much successful. The second challenge is to make BCI rehabilitation applicable for more (preferably all) stroke patients. Thus, for those patients who are initially excluded from BCI studies due to their inefficiency to operate BCI, the BCI can be changed in a way to include them also. Finally, there is a need to develop a novel BCI system for stroke rehabilitation that is portable and can be used at the patient's home with only remote supervision.

1.2 Motivation and research direction

Recently, BCI has garnered increasing attention as a potential tool for post-stroke upper limb rehabilitation. However, clinical trials utilizing different BCI designs have reported varying outcomes [28, 35, 38], making it challenging to determine the most effective BCI paradigms. Variations in BCI settings and parameters, such as mental practice methods, extracted brain features, feedback types, and the hemisphere used for BCI operation, may contribute to these disparities. The primary motivation of this research is to investigate the design differences of BCI configurations and identify the optimal setups based on existing clinical trial results. Additionally, this research aims to evaluate the effectiveness of BCI for upper limb stroke rehabilitation in both the short and long term. Furthermore, many studies screen stroke patients for their ability to use BCI, leading to the exclusion of a significant percentage (approximately 20%-30%) who cannot achieve classification accuracy above chance level. Most studies focus on using brain signals from the ipsilesional hemisphere (the damaged hemisphere) to operate BCI [28, 31, 35].

However, depending on lesion size and location, stroke patients may struggle to modulate signals from the ipsilesional hemisphere effectively [39]. Recent findings suggest that using the contralesional hemisphere (unaffected side) for BCI control may offer signals of better quality and consistency [40]. Despite this potential advantage, there is currently no guideline for predicting which BCI approach would be more suitable for individual patients, especially those capable of controlling both contralesional and ipsilesional BCIs.

Finally, while BCI-based rehabilitation shows promise in improving upper limb motor function post-stroke, its clinical application is hindered by lengthy setup and calibration times (20 minutes) and the requirement for in-person visits [41–43].

Motivated by the potential benefits of BCI for stroke patients, this thesis aimed to enhance the effectiveness of BCI-based upper limb stroke rehabilitation by addressing these challenges. By doing so, it is hoped to develop advanced BCI technologies capable of significantly enhancing motor function recovery in stroke patients, potentially expanding its utility across a broader patient population.

1.3 Aim and Objectives

The aim of this thesis is to improve the effectiveness of BCI design for upper limb stroke rehabilitation. In order to achieve this overall aim, this thesis intend to fulfill the following objectives, as shown in figure 1.1.

Objective 1: Conduct a comprehensive meta-analysis to answer the following questions:

- How effective is BCI in short-term compared to conventional therapies in terms of motor function improvements in upper-limb stroke rehabilitation?
- How effective is BCI in long-term (follow-up) compared to conventional therapies in terms of motor function improvements in upper-limb stroke rehabilitation?

Objective 2: Evaluate the efficacy of different BCI settings in improving upper limb motor functions of post-stroke patients by conducting a number of sub-groups meta-analyses. It is particularly interested in answering the following questions:

- What is the most effective mental practice used for BCI-rehabilitation?
- What are the most effective neural features for classification used for BCI-rehabilitation?
- What is the most effective type of BCI feedback for BCI rehabilitation?

Therefore, it is anticipated that the findings from these objectives will offer valuable insights into different BCI designs, thus aiding in the enhancement of BCI design for upcoming clinical trials.

Objective 3: Evaluate the ability of stroke patients to control BCI using either ipsilesional hemisphere, contralesional or both hemisphere. To address this, a large EEG dataset from 136 stroke patients who performed motor imagery of their stroke-impaired hand will be analyzed. The datasets were originally collected as part of four clinical trials [44–47]. It is important to clarify that the data collection was conducted by researchers who contributed to these clinical trials. BCI features will be extracted from channels covering either the ipsilesional, contralesional, or bilateral hemispheres. Offline BCI accuracy will be calculated using 10x10-fold cross-validation to answer the following questions:

- Are the stroke patients able to meaningfully operate a BCI-based rehabilitation system using EEG signals from only the contralesional hemisphere?
- Is there a difference in the performance of stroke patients in controlling BCI using EEG from the contralesional hemisphere when compared to using EEG from the ipsilesional hemisphere or even from both hemispheres and

how much is this different?

- Are there any relationships between the BCI performance and the patient's demographic data including Fugl-Meyer assessment score and time since stroke?

  Therefore, it is hoped that the findings of the aforementioned objectives can provide some insights into various BCI settings, thereby helping to improve the BCI design when conducting clinical trial.

Objective 4: Design a home-based BCI-FES system that operates using only a limited number of electrodes placed on the scalp. This could significantly decrease the cost and increase the convenience of the user. The patient will use the EEG signals during attempted arm movements to operate a FES. The commercially available FES, directed by the user thoughts will deliver the stimulation to activate upper limb muscles. Importantly, the entire delivery of BCI rehabilitation will be made over telecommunication networks and the internet. This allows patients to interact with BCI therapist remotely and can be used to monitor the rehabilitation remotely and troubleshoot the system if needed.
The following aims are aimed to be answered by conducting this clinical trial:

- To develop a home based BCI-FES system for rehabilitation of arm weakness following stroke
- To assess if the patients can use BCI-FES system at home for post stroke upper limb rehabilitation?
- To assess the patient's perspective about use of BCI-FES device for home based arm rehabilitation.

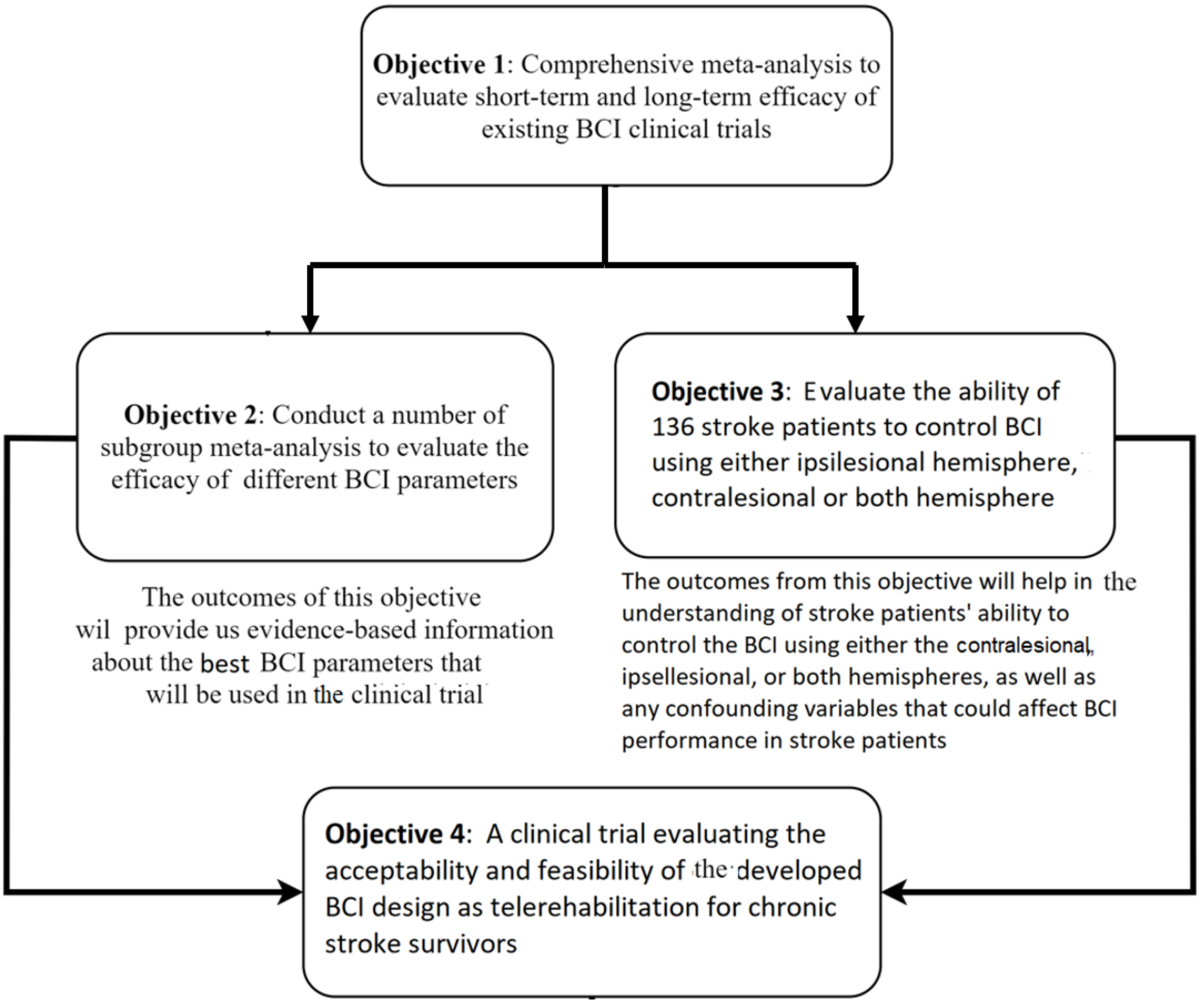


Figure 1.1.: Four objectives are planned for achievement. Objective 4 is dependent upon fulfillment of the objectives presented above them in the figure.

1.4 Thesis Overview

- Chapter two: The literature review will provide an insight into stroke-related disabilities, particularly upper extremity motor disabilities, and technological interventions for upper extremity stroke rehabilitation. It will also outline the research conducted in the field of BCI to improve upper extremity recovery.

- Chapter three: The first and second objectives were achieved by performing a meta-analysis to assess the efficacy of different BCI designs for upper extremity stroke rehabilitation. This chapter included 12 clinical trials involving 298 patients. The effect sizes of pooled and individual studies were assessed by computing Hedge's g values with a 95% confidence interval. Subgroup analyses were also performed to examine the impact of different BCI designs on the treatment effect. The chapter concludes with a discussion of the chapter's findings and recommendations for future clinical trials.

- Chapter four: The third objective was achieved by investigating the effectiveness of the BCI in detecting motor imagery of the affected hand from contralesional hemisphere. A large EEG dataset from 136 stroke patients who performed motor imagery of their stroke-impaired hand were analyzed. BCI features were extracted from channels covering either the ipsilesional, contralesional or bilateral hemisphere, and the offline BCI accuracy was computed using 10x10-fold cross-validations. The chapter concluded with a discussion of the chapter's findings.

- Chapter five: The home-based BCI-FES stroke rehabilitation system is designed to achieve the ultimate objective. There were seven participants participated in the clinical study. The BCI-FES intervention took place in participants' homes. The home session consisted of one practice session and three rehabilitation sessions per week for three weeks. On average, each session lasted for roughly 60 minutes, with 10 minutes spent on preparation, 40 minutes on the intervention, and 10 minutes on an interview about the user's experience with the device and any adverse effects they may have encountered. The chapter concludes with a discussion of the chapter's findings and recommendations for future clinical trials.

- Chapter six: The overall conclusions of the thesis are discussed, including the achievement of the objectives and the significance of the progress made in the field of BCI for upper limb stroke rehabilitation. Furthermore, future works are outlined.

1.5 Key Contributions

- A systematic review and meta-analysis of the short- and long-term effects of BCIs on upper limb rehabilitation after stroke; Additionally, the impact of different BCI design characteristics on the effectiveness of upper extremity rehabilitation after stroke was investigated. Chapter 3 presents this contribution in more detail.

- Exploring the ability of stroke survivors in using the contralesional, ipsilesional or both hemispheres to control a BCI. Additionally, the study examined the effect of the patient's demographic information, such as Fugl-Meyer assessment scores and time since stroke, on the performance of BCI. Chapter 4 presents this contribution in more detail.

- Conducting a clinical trial to evaluate the acceptability and feasibility of BCI telerehabilitation for chronic stroke survivors. Chapter 5 presents this contribution in more detail.

1.6 Publications Based on this Thesis

1. Published a journal paper based on a meta-analysis and systematic review of the efficacy of brain-computer interfaces and the impact of their design features on upper extremity rehabilitation after stroke.

   Mansour S, Ang KK, Nair KP, Phra KS, Arvaneh M: Efficacy of brain-computer interface and the impact of its design characteristics on post stroke upper-limb rehabilitation: a systematic review and meta-analysis of randomized controlled trials. Clin EEG Neurosci 2022; 53: 79–90. PMID:33913351

2. Published a conference paper based on comparing the performance of contralesional and Ipsilesional brain-computer interface in stroke survivors.

   Mansour S, Giles J, Ang KK, Nair KP, Phua KS, Arvaneh M. Comparing the Performance of Contralesional and Ipsilesional brain-computer interface in stroke survivors. InNeuroergonomics Conference 2021 Proceedings 2021. Neuroergonomics Conference.

3. Published a journal paper based on exploring the ability of stroke survivors in using the contralesional Hemisphere to control a brain-computer interface.

   Mansour S, Giles J, Ang KK, Nair KPS, Phua KS, Arvaneh M. Exploring the ability of stroke survivors in using the contralesional hemisphere to control a brain-computer interface. Sci Rep. 2022 Sep 28;12(1):16223. doi: 10.1038/s41598-022-20345-x. PMID: 36171400; PMCID: PMC951957

4. Mansour, Salem, et al. "A Clinical Trial Evaluating Feasibility and Acceptab-

ility of a Brain-computer Interface for Telerehabilitation in Stroke Patients." under review.

5. Chapter Book: 'Brain-Computer Interface for Rehabilitation of Upper Limb Dysfunction Following Stroke' Authors: Salem SL Mansour, Mahnaz Arvenah, and Krishnan Padmakumari Sivaraman Nair Status: Under editing at Indian Association of Physical Medicine and Rehabilitation Publisher: Textbook of Physical Medicine and Rehabilitation Publisher's Location: Salubris Medical Publisher, New Delhi, India

2

Review of the Research Area

> *A part of this chapter is currently under editing as a chapter book with the Indian Association of Physical Medicine and Rehabilitation*
>
> **– Status: Under editing –**

2.1 Stroke

In the UK, over 1.2 million people suffer from strokes [48]. A stroke is caused by a sudden interruption of blood flow to a specific part of the brain, leading to haemorrhage or ischaemia [49]. Haemorrhage occurs when blood vessels in the brain burst, while ischaemia occurs when the blood supply to the brain is blocked by a blood clot. Ischaemia is more common, affecting four out of five individuals who experience stroke symptoms [50].

Following a stroke, patients may experience impairments such as loss of coordination, weakness in one or more limbs, and spasticity [51]. About 65% of stroke patients have permanent disability six months after onset, and rehabilitation interventions are critical to reduce dependence on caregivers and improve quality of life [52]. Relearning motor function skills is believed to be essential for motor function recovery after a stroke, and this process is associated with neuroplasticity [53]. Therefore, it is crucial to develop more effective and efficient rehabilitation interventions that focus on maximizing functional regain and inducing neuroplasticity. The impact of stroke on body movements, particularly which side of the body is affected, is depicted in Figure 2.1. This figure illustrates how stroke can influence motor functions on either the left or right side of the body.

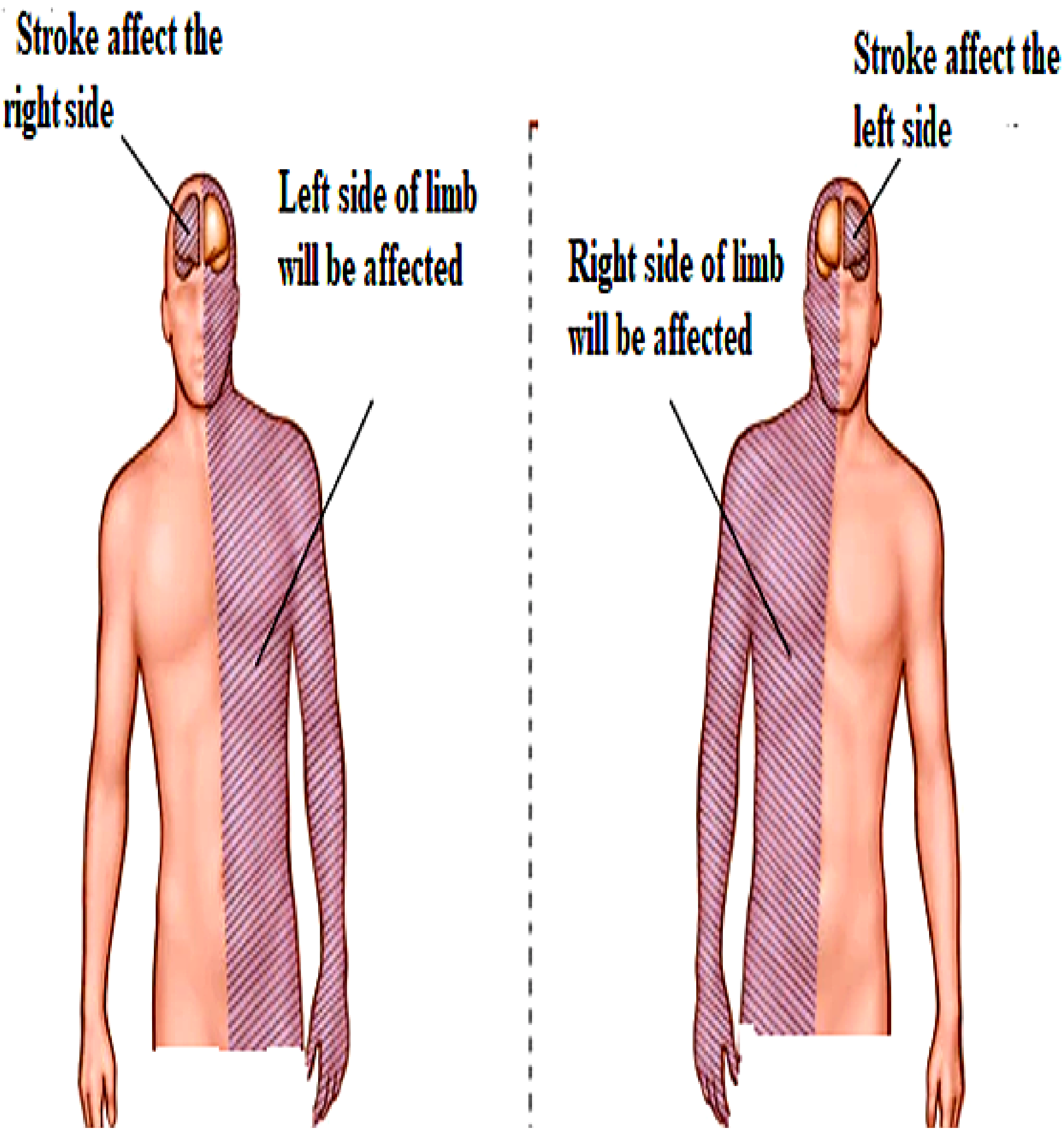


Figure 2.1.: Shows the impact of the stroke on the movement of the body. A stroke that affects the right hemisphere will affect movement on the left side of the body, and vice versa. The image adapted from [54]

2.2 Neuroplastisity and its role in stroke recovery

The recovery after a stroke depends on the capability of the brain to reconstruct itself through neuroplasticity [55]. Neuroplasticity happens when brain cells attempt to restore, rebuild, and reorganize neural connections in response to the damage imposed by a brain lesion [56]. Thus, the brain works around the damaged cells and tries to build other neural pathways to compensate[57]. Currently, researchers believe that one of the best approaches to induce brain plasticity is through repetitive training [58]. Hence, the repetition of specific activities can promote the brain to generate new neural pathways and connections in order to take over the skills of the damaged neurons [58].

2.3 The Involvement of the Contralesional Hemisphere versus the Ipsilesional Hemisphere in the Process of Stroke Recovery

It is widely agreed that, in a healthy subject, movement of the hand causes an increase in the activation of the contralateral motor cortex and a decrease in the activation of the ipsilateral motor cortex as compared to the resting state [59]. Strokes commonly result in significant changes to the brain's connections and functionality [60].

Stroke patients with motor impairment, usually show increased motor cortex excitability on the ipsilateral hemisphere (i.e. contralesional region commonly referring to the unaffected part of the brain) during movements of the affected side [61]. In other words, post-stroke patients demonstrate an inter-hemispheric asymmetry where the the contralesional hemisphere is not inhibited by ipsilesional hemisphere (i.e. the affected hemisphere of the brain) [62]. Additional details, along with a figure, can be found in Appendix B. More in-depth details can be found in Chapter 4.

Understanding the neural mechanisms underlying motor recovery might be crucial for developing effective rehabilitation strategies. In recent years, research has begun to focus on the role of the ipsilesional and contralesional hemispheres in motor recovery after stroke [63].

It is well established that the ipsilesional hemisphere is critical for the recovery of motor function after a stroke [64]. However, recent research has shown that the contralesional hemisphere also plays a crucial role in motor recovery [65].

Interestingly, neural plasticity can occur in either the ipsilesional or contralesional hemisphere during recovery[40]. The ipsilesional hemispheric reorganization is typically considered to play a critical role in motor function recovery [28, 38]. However, the contralesional hemisphere can also contribute in motor recovery where the damage on the ipsilesional hemisphere is more severe [66].

Importantly, the ability to modulate ipsilesional brain activity decreases with increasing cortical damage [67]. Moreover, our recent study involving 136 stroke patients showed that motor-related brain signals can also be detected in the contralesional hemisphere of patients using EEG [68].

Thus, it may be especially crucial for rehabilitation intervention to concentrate on the contralesional hemisphere if the patients could not modulate the brain signal in the ipsilesional hemisphere, although the exact role of contralesional hemisphere in the patient's recovery is not well clear yet.

Further research is needed to fully understand the neural mechanisms underlying their contribution to post-stroke motor recovery. This information can be used to develop rehabilitation strategies that optimize motor recovery in stroke survivors.

2.4 Overview of a number of existing and emerging stroke rehabilitation approaches

The objective of rehabilitation intervention after a stroke is to help the patient recover their normal motor function and improve their quality of life. To achieve this goal, various rehabilitation methods can be employed.

2.4.1 Constraint-induced movement therapy

As shown in figure 2.2, constraint-induced movement therapy (CIMT) is a therapeutic approach that encourages the stroke patients to perform the functionally oriented activities using the affected upper limbs (arm and hand), while constrained the unaffected arm and hand [13]. It has been indicated that the repetitive practice using the affected upper limb, while the unaffected one is restricted, may better induce the neural plasticity [69]. Moreover, recent studies reported that strategies such as CIMT could be valuable approaches to recover motor function in chronic stroke patients [14].
However, CIMT usually requires one-to-one interaction between the patient and a trained therapist that helps and encourages the patient to perform specific tasks. CIMT is also not suitable for severe stroke patients, since the residual physical movement is required for such a rehabilitation intervention [6].

2.4.2 Robot assisted therapy

A repetitive exercise of specific functional training is reported to be beneficial for motor function improvement after stroke [71]. Because of this requirement, stroke rehabilitation requires additional therapist intervention. The most significant benefit of using robot devices in stroke rehabilitation is the ability to carry

Figure 2.2.: A stroke patient performing CIMT. The unaffected hand was constraint and then the stroke patient was encouraged to use the affected arm for drinking a glass of water as a regular exercise of daily living. The image adapted from [70]

high-intensity training with less therapist intervention.

There have been many robot-assisted therapy devices presented to facilitate upper limb rehabilitation for post-stroke patients. The next section presents the MIT-MANUS robot because it has been extensively tested for the upper limb of stroke patients [72] .

MIT-MANUS robot

The MIT-MANUS robot was firstly introduced by Hogan and co-workers to explore whether repetitive tasks using a robotic-assisted therapy can induce improvement of the arm function in hemiparetic post-stroke patients [73]. As shown in figure 2.3, the MIT-Manus robot is a wearable robot that has been extensively studied for providing individualized rehabilitation after stroke. The MIT-MANUS robot enables a post-stroke patient to move the affected arm in the horizontal plane.

During the intervention, the patient is instructed to reach toward target across the computer screen. If needed, the robot facilitates the movement of the affected arm by providing assistive forces based on the patient's speed and the direction of the movement. Although rehabilitation with the MIT-Manus robot can be potentially effective [74, 75].

However, the movement generated by the MIT-MANUS robot can turn to be a completely passive movement if the patient does not get engaged in generating voluntary attempt. As the system does not force the user to generate voluntary attempts, the patient's motivation may reduce over time, which could lead to a decrease in the potential benefits of the therapy. Studies have shown that patient motivation and engagement are crucial for successful rehabilitation outcomes[76, 77].

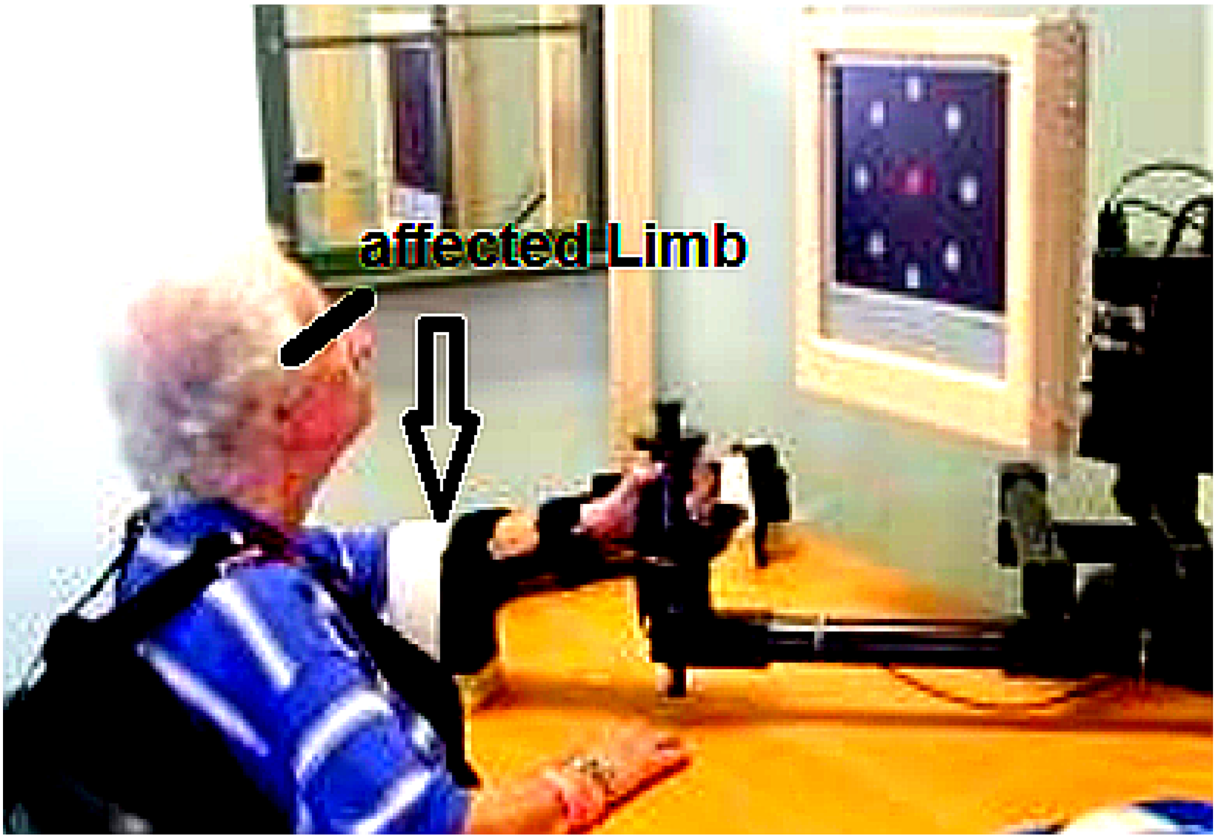


Figure 2.3.: A stroke patient is using MIT-MANUS robot for upper limb stroke rehabilitation . The image adapted from [78]

2.4.3 Functional electrical stimulation (FES)

Functional electrical stimulation (FES) is one of the rehabilitation interventions that has been developed to promote motor function recovery following stroke. FES uses small voltage pulses through electrodes placed on the patient's skin near the nerve to generate muscle movements artificially as shown in figure 2.4. FES can be used to generate hand and arm functions for grasping and reaching in post-stroke patients [79, 80].

Some clinical studies have reported that FES has a positive influence on the motor function recovery after stroke [81, 82]. Additionally, FES could reduce spasticity, strengthen paralyzed muscles and improve the range of movement in post-stroke patients [83, 84].

In particular, it has been reported that the influences of FES might be maximized by generating muscle activity and finally to visualize the movement of the affected limb [84]. In spite of the encouraging results that have been reported from the former studies, there is insufficient evidence to confirm that FES is effective for patients with chronic stroke [85]. In addition to that, the movement of an affected hand by FES is passive because it is not paired with the patient's intentional attempt [86].

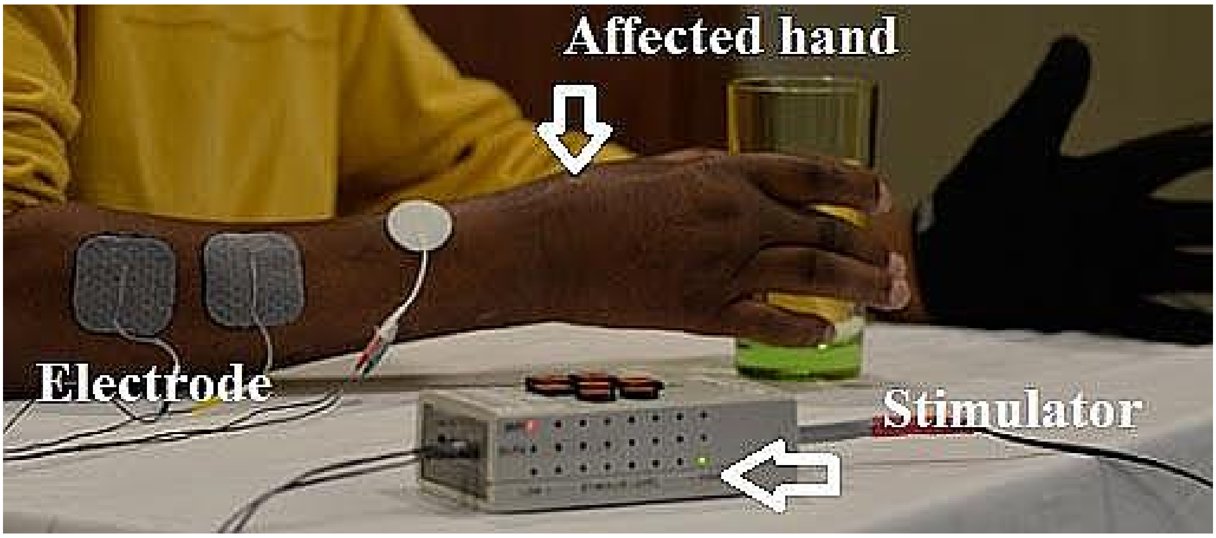


Figure 2.4.: This figure shows a stroke patient using FES to move the affected hand by activating the muscles using electrodes. The image adapted from [87]

2.5 Brain- computer interface as a new approach for stroke rehabilitation

BCI is a hardware-software communication device that measures brain activities and converts them into commands to control an external device in real-time [88, 89]. BCI can be used as a rehabilitation tool by pairing motor-related mental (i.e the imagination or the attempt to move the affected hand) and physical practices to promote neuroplasticity [26, 90].

2.5.1 Components of BCI for upper limb stroke rehabilitation

A BCI system for stroke rehabilitation typically consists of six stages as shown in Figure 2.5.

1. Signal acquisition:A number of modalities for acquisition of brain signals are suitable for the BCI in stroke rehabilitation, namely electroencephalography (EEG), functional near-infrared spectroscopy (fNIRS), and magnetoencephalography (MEG). Due to its lower cost, higher temporal resolution, and portability, EEG is the most commonly used modality in BCI-based stroke rehabilitation [91].

2. Mental practice: : In the motor imagery based BCI studies, the patients are instructed to imagine moving the impaired hand without any physical movements, whereas in the intention of the movement based BCI studies, the patients attempt to perform physical movement of the impaired hand if possible.

   The motor imagery or the intention of the movement produces brain waves, called movement-related cortical potentials (MRCPs) and event-related desynchronization/synchronization (ERD/ERS) [92, 93].

   MRCP and ERD/ERS are distinct movement-related brain patterns. MRCP is characterized as slow changes of the brain signals in the time domain. ERD and ERS are, respectively, described as a suppression and an enhancement in the power of the sensorimotor rhythms [94]. For example, the power of mu and beta rhythm (8-30 Hz) recorded over the sensorimotor regions has been shown to decrease before the motor task, reaches its minimum during the movement execution (ERD), and then recovers sharply after the end of the motor task (ERS). In the application of upper-limb stroke rehabilitation, the BCI is used to detect either MRCP or ERD/ERS in brain signals when the patient performs the relevant mental practice.

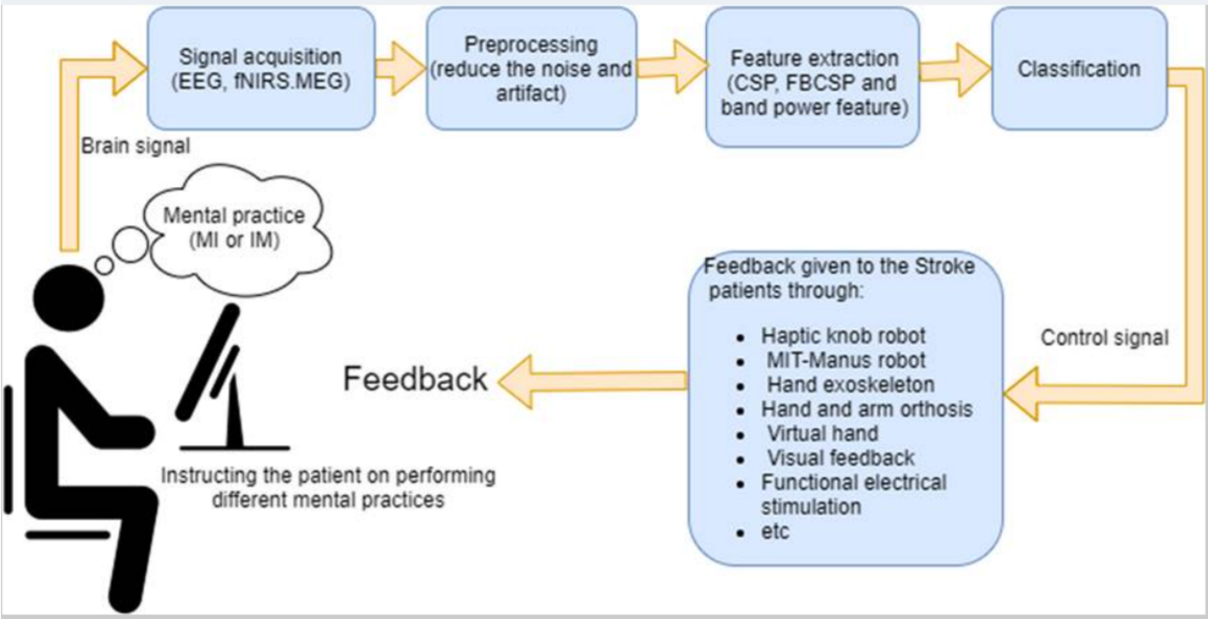


Figure 2.5.: Components of brain–computer interface commonly used for upper-limb stroke rehabilitation. Abbreviations: CSP, common spatial patterns; EEG, electroencephalography; FBCSP, filter bank common spatial patterns; fNIRS, functional near-infrared spectroscopy; IM, intention of movement; MI, motor imagery; MEG, magnetoencephalography.

3. Preprossessing: The recorded brain signals can be contaminated with artifacts caused by blinking, muscle activity, and other sources of noise. In the preprocessing stage, different spectral, temporal, and spatial algorithms are applied on the measured brain signals to reduce these artifacts. Among different preprocessing algorithms, the threshold-based artifact rejection, and 8 to 30 Hz band-pass filtering have been widely used in many BCI-based stroke rehabilitation studies [95].

4. Feature extraction: : In order to accurately detect movement-related brain patterns, it is important to extract informative, non-redundant, and distinctive features from preprocessed brain signals. In previous studies on BCI-based stroke rehabilitation, researchers have used one of three types of features: common spatial patterns (CSP), filter bank CSP (FBCSP), and band power features [29–31, 33–35, 38, 96].

   CSP is a feature extraction algorithm that assigns different weights to dif-

ferent EEG channels, maximizing the weighted sum of the powers of brain signals for one class and minimizing it for the other class [97]. The CSP features are typically the weighted sum of the powers of brain signals within an 8 to 30 Hz band-pass filter. An alternative method is the Filter Bank Common Spatial Patterns (FBCSP) approach, which involves filtering a bank of brain signals through various narrow band-pass filters to extract multiple CSP features across nine frequency bands ranging from 4-8 Hz to 36-40 Hz [98]. This technique has shown to be effective in improving classification accuracy compared to CSP alone [99].
Finally, band power features, specifically from alpha (8–12 Hz) and beta (13–30 Hz) frequency bands in EEG signals, have been utilized in previous studies on BCI-based stroke rehabilitation [29–31, 38]. These features reflect distinct cortical activities during motor imagery and execution, making them valuable for classifying brain states relevant to stroke rehabilitation using BCIs [100].

5. Classification: The extracted features are fed to a classifier to detect whether or not the recorded brain signals prominently represent the movement-related brain patterns associated with the performed mental practice. If the movement-related brain patterns are detected, a control signal is sent to an external device to provide the feedback.

6. Feedback: The patient is presented with feedback indicating whether the classification algorithm accurately interpreted their motor intention/imagination. The commonly used type of BCI feedback in stroke rehabilitation is kinesthetic, whereby following the detection of the movement-related brain patterns, the impaired hand is moved along a predefined trajectory. For instance, Ang et al [36] and Biasiucci et al [31] respectively, used an MIT-Manus robot and FES in order to facilitate the movement of the impaired

hand as the BCI feedback (see Figure 2.6).

To enhance neuroplasticity in the post-stroke upper-limb rehabilitation, the BCI links the movement-related brain patterns (generated during either motor imagery, or the intention of the movement of the affected arm) with feedback such as robotic-based movements, neuromuscular stimulation, virtual reality etc [27]. In other words, the BCI is coupled with the existing therapies to enhance their efficacy by making the rehabilitation more active [101].

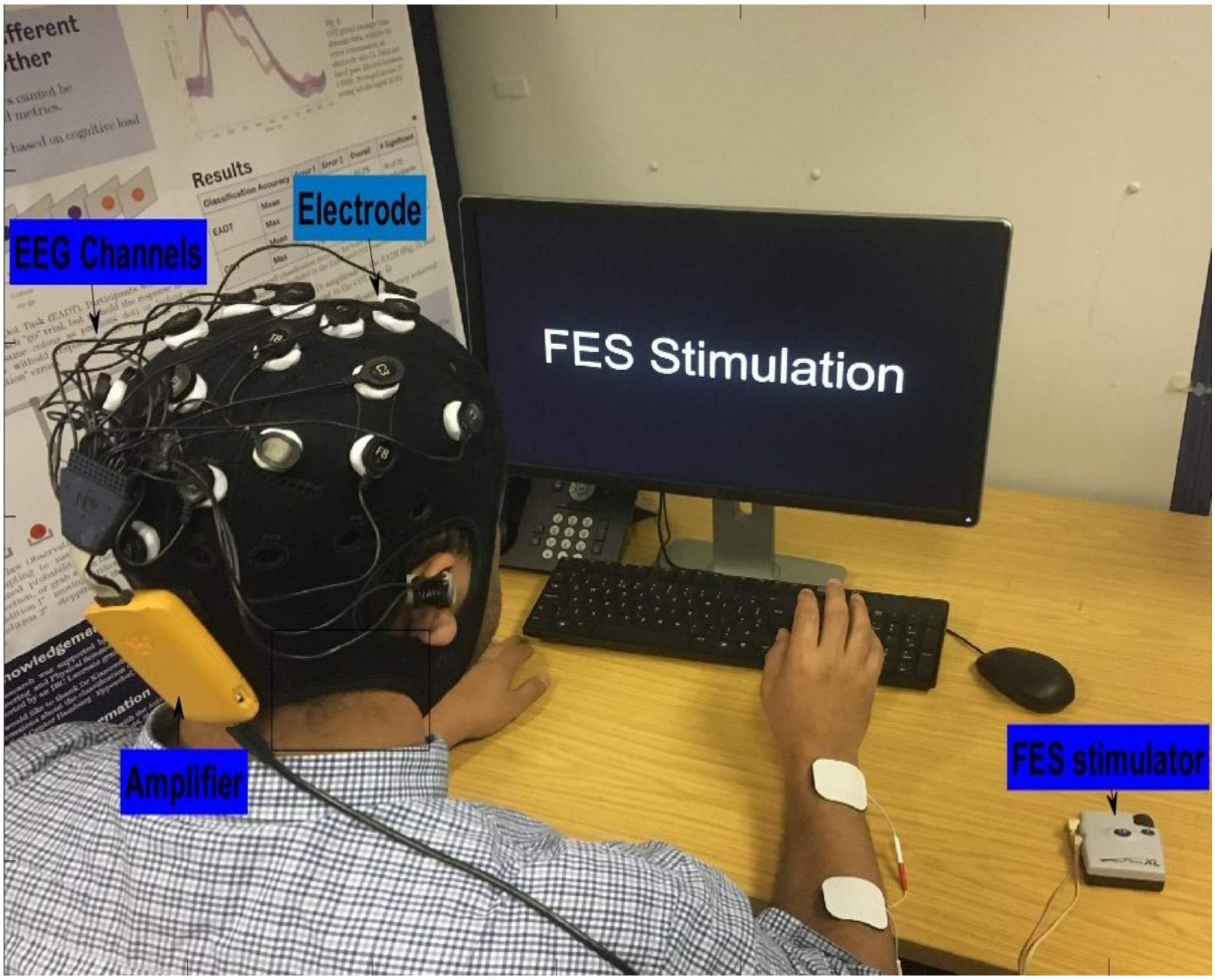


Figure 2.6.: The user sits in front of the desktop and wears an EEG headset, which includes a display with visual cues to guide the user. The EEG headset records brain activities, and the BCI analyses these activities in real time. Once the BCI system identifies the intended hand movement, the FES is triggered to initiate hand movement.

Typically, before using the BCI system, a calibration session needs to be conducted. This session is required to collect subject specific brain signals for training the BCI classifier, where a number of repetitive visual cues are presented to the patient. According to the presented visual cue, the patient is expected to either rest or perform the desired mental practice related to the impaired limb as shown in Figure 2.7.

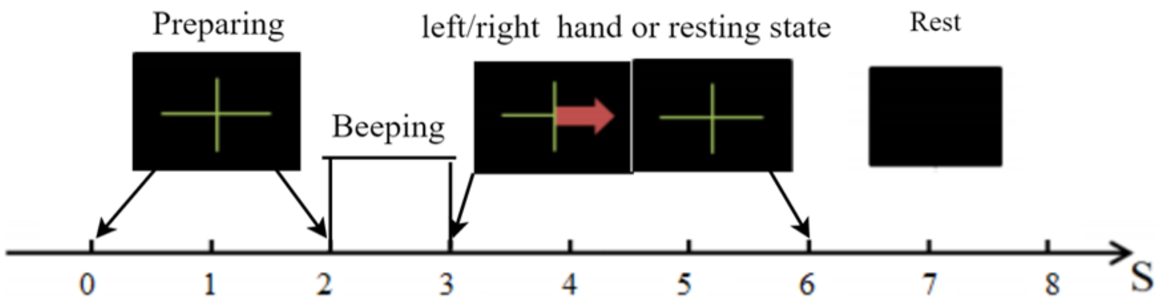


Figure 2.7.: The figure shows an example of the timing of one trial in a BCI calibration session, instructing the user to perform a mental task of the left/right, hand or resting state.

2.5.2 Advantages of BCI as a potential rehabilitation approach

The potential BCI as a rehabilitation approach for individuals with stroke has gained growing attention. There are several advantages that BCI offer as a rehabilitation tool, including:

- By using BCI, stroke patients can learn to control a computer or robotic device with their brain signals. This promotes the activation of the damaged motor cortex and the strengthening of neural connections [102]. The repetitive training and feedback provided by BCI can lead to brain plasticity and functional recovery in stroke patients [103]
- BCI can be used without invasive procedures, making them a safer and less painful option for stroke patients
- Studies have shown that, compared to other therapies, BCI can help chronic stroke patients achieve significant improvement in motor function, even

many years after the stroke [104].

- BCI can be used in remote or resource-limited settings, making rehabilitation more accessible to a wider population [37].
- BCI can provide real-time feedback to patients, allowing them to see their progress and encouraging them to continue with therapy.
- BCI technology can be applied in the initial phases of stroke rehabilitation, resulting in more favorable functional outcomes when compared to conventional therapy [105].

2.6 Studies using BCI for stroke rehabilitation

This section will discuss the clinical studies that used BCI for stroke rehabilitation. The clinical studies were categorized into randomized clinical trials (RCTs) or single clinical studies (i.e. study without a control group). In RCTs, stroke patients were randomly allocated to either receive BCI intervention or belong to the control group, which received either sham BCI or traditional rehabilitation.

2.6.1 Randomized clinical trails (RCTs)

Several studies have explored the use of BCI for stroke rehabilitation. For instance, a randomized clinical trial (RCT) conducted by [28] demonstrated significant improvement in motor function among 12 chronic stroke patients who underwent 20 sessions of ipsilesional BCI training to activate hand and arm orthoses. This improvement was compared to a control group of 12 patients who received sham BCI training, where orthosis movement was random and not related to the stroke patients' ipsilesional signals. A RCT reported by [106] showed that 10 stroke patients who performed fNIRS-based MI BCI coupled with visual feedback achieved significantly greater gain in motor function compared to the sham BCI group. A later RCT conducted by [35]compared changes in motor function among 11 chronic stroke patients who underwent MI BCI coupled with robot-assisted therapy (136 repetitions per session) with those of 15 chronic stroke patients who received conventional robot-assisted therapy (1040 repetitions per session). The study reported that 60% of chronic stroke patients in the MI-based BCI group achieved significantly greater improvements in motor function compared to the control group who underwent more repetitive and intensive conventional robot-assisted therapy. However, the study did not find statistically significant differences between the two groups overall.

The study presented in [29] aimed to explore the impact of combining Action Observation Training (AOT) with BCI to trigger FES on motor function recovery of the upper limb in stroke patients. Thirty stroke patients were randomly divided into two groups: an experimental group (n=15) received AOT combined with BCI-FES, while a control group (n=15) only received conventional therapy. The study found that the experimental group showed significantly greater improvement in motor function compared to the control group.

The study in [33] investigated the effect of transcranial direct current stimulation (tDCS) on a BCI system combined with the MIT-MANUS robot. 19 chronic stroke patients were randomly divided into two groups, a BCI group (n=10) and a control group (n=9). In the BCI group, brain stimulation with tDCS was applied for 20 minutes, while in the control group, sham tDCS was applied for only the first 30 seconds, followed by one hour of MI-based BCI with robotic feedback for both groups. After two weeks of intervention, no significant difference in motor function improvement was observed.

Another RCT study conducted by [35] investigated the effectiveness of MI BCI coupled with a haptic knob in upper limb stroke rehabilitation. Twenty-one chronic stroke patients were randomly allocated to BCI with the haptic knob (n=6), haptic knob alone (n=7) or standard arm therapy groups (n=8). The study revealed that the BCI group gained significantly more motor function improvement as compared to the standard arm therapy group.

The study by [30] explored the benefit of combining BCI with FES. 18 chronic stroke patients were randomly divided into two groups, a BCI group (n=8) received BCI combined with FES, while a sham BCI group (n=8) received sham feedback, where the FES activation was not related to the patient's brain activity. Both groups underwent an equal amount of FES, with one hour of two weekly sessions for five weeks. The results showed that the motor function in the BCI group significantly improved.

Another RCT conducted by [96] studied the effectiveness of MI BCI coupled with FES for the patients with severe upper limb impairment (n=8), compared to patients in control group who received only FES (n=7). The BCI group achieved a significant motor function improvement of the upper limbs . Furthermore, the event-related desynchronization (ERD) of the ipsilesional hemisphere in the BCI group was significantly induced as compared to the preintervention.

RCT conducted by [38] studied whether stroke patients with severe upper limb motor function could be get a benefit from ten BCI training sessions. Stroke patients in the BCI group (n = 36) performed MI BCI to trigger hand exoskeleton strapped to their affected hand, and the movement of hand exoskeleton. In a sham BCI group (n = 11), the movement of hand exoskeleton was not related to the patient's brain activity. The difference between two groups was not statistically significant.

Authors in [31] recently published the results of their RCT, reporting that the 14 chronic stroke patients who received EEG-based BCI coupled with FES achieved significantly more motor function improvements than the 13 chronic stroke patients in the sham BCI group. Moreover, the BCI group showed an increase in

the functional connectivity between the motor regions in the ipsilesional hemisphere which was significantly correlated with the motor function improvement.
In summary, these randomized controlled trials reported the efficacy of BCIs compared with other therapies for upper extremity stroke rehabilitation. Although the reported results are encouraging, significant differences exist in terms of motor recovery outcomes following stroke. Further research is needed to investigate the effectiveness of different BCI designs for upper extremity rehabilitation after stroke.

2.6.2 Single group clinical trails

As one of the first clinical trials, [107] found that stroke patients could successfully learn to control their ipsilesional sensorimotor rhythms using BCI. The clinical study presented by [108] measured the EEG during motor imagery in 29 patients. The study found that greater impairment was associated with greater ERD in the contralesional hemisphere. The study in [109] found that intention of movement, as defined by the attenuation in mu-rhythm (8-13 Hz), was detectable in post-stroke patients, and this signal was successfully used in 4 of 6 stroke patients to control a BCI coupled with FES. However, these clinical studies did not show motor function improvement as a result of BCI based rehabilitation.
These outcomes highlight the technical feasibility and potential of BCIs to detect and utilize brain signals associated with motor imagery in stroke patients. The study by [110] investigated the effectiveness of physical practice followed by mental practice using BCI coupled with hand exoskeleton in 4 chronic stroke patients. After six weeks (2 to 3 sessions/week) of the BCI intervention, the patients showed improvement in motor function recovery, the mood, increased motivation and decreased fatigue. The improvement in BCI performance was correlated with motor function recovery.

A recent clinical study conducted by [43] aimed to investigate the efficacy of combining BCI with FES in improving motor function after stroke. Fifty-one stroke patients participated in this study and underwent 25 BCI therapy sessions. The results demonstrated a significant improvement in the motor function of the affected arm, as well as a reduction in wrist and finger spasticity following the intervention.
In summary, these clinical studies highlight the potential of BCI technology to enhance functional outcomes and motivate patients during stroke rehabilitation. However, further research is needed to comprehensively understand both the advantages and limitations of implementing BCI in this context, as will be discussed in the next section.

2.7 Limitations and possible research directions of current BCI for stroke rehabilitation

Despite the promising results, the use of BCI technology for stroke rehabilitation is still in the early stages of development and study. There are several unanswered questions and further efforts are needed to improve the feasibility, acceptability, reliability, and validity of BCI for this application. This may include (but is not limited to):

- Conducting more RCT studies with a large number of patients to increase the validity of the BCI for upper limb stroke rehabilitation.
- It would be desirable to investigate the integration between FES and hand/arm orthosis to assess if a BCI that controls both of them can result in more significant motor function improvement [31].
- Improving the design of the BCI to make it suitable also for those patients

who were excluded from previous studies due to their inability to operate the BCI. Table 2.1 shows the percentage of patients who have been excluded from the previous clinical trial due to their inability to use BCI.

- Designing lighter and inexpensive BCI devices to increase the feasibility and acceptability of the technology.
- Design a remote BCI system for convenient, personalized, and adaptive therapy sessions from the comfort of home. Therefore, the cost of rehabilitation will be lower and travel will not be required, as opposed to in-person therapy.

Table 2.1.: The percentage of the excluded patients due to their inability to use BCI. CA refers to classification accuracy and np refers to number of patient

Study	np	Not meet BCI CA	% Excluded
[35]	23	6	26 %
[34]	30	11	36%
[33]	22	5	23%

- Different BCI designs, used in the existing clinical trials, reported different clinical outcomes. The mechanism and efficiency of BCI for stroke rehabilitation generally remains unclear, and it could be hard to conclude the more effective BCI paradigms for upper limb stroke rehabilitation.Therefore, it might be desirable to conduct a comprehensive meta-analysis to evaluate different aspects of the BCI design.

  In this Line, the next chapter of this thesis will present a comprehensive meta-analysis to evaluate the short-term and long-term efficacy of BCI for the hemiparetic stroke rehabilitation, as well as sub-groups meta-analysis to evaluate the efficacy of different aspects of the BCI design according to the type of performed mental tasks, applied neural classification features, and feedback mechanism given to patient.

3

Efficacy of Brain–Computer Interface and the Impact of Its Design Characteristics on Poststroke Upper-limb Rehabilitation: A Systematic Review and Meta-analysis of Randomized Controlled Trials

The findings of this chapter have been published in Clinical EEG and Neuroscience [111].

– Published, March 2021 –

3.1 Chapter Introduction

Recently, a number of randomized controlled trials (RCTs) have investigated the efficacy of the BCI for post stroke upper-limb rehabilitation, and compared the outcomes with those obtained from other existing therapies [28, 31, 112]. Despite the encouraging results in many of these RCTs, there is a significant variance in their reported BCI outcomes [31, 33, 35, 112]. This issue might be due to the heterogeneity among their BCI study designs [113], including differences in the performed mental practice, the extracted brain features, the type of feedback given to the patients, and the level of stroke chronicity in the participants. A meta-analysis conducted by Cervera et al. reported positive effects of the BCI on upper-limb stroke rehabilitation in a short-term [114]. Another meta-analysis conducted by Bai et al. considered the long-term efficacy of the BCI on upper-limb stroke rehabilitation [103].

However, given the considerable heterogeneity in the motor function improvement among the BCI RCTs, there is a need for an extensive meta-analysis to assess the impact of different BCI designs on the treatment efficacy. This chapter conducted a systematic review and meta-analysis of the short-term and long-term effects of BCI on upper-limb rehabilitation after stroke.

Importantly, we also study the impact of different BCI design characteristics on the efficacy of the post-stroke upper-limb rehabilitation. The findings of this meta-analysis aim to improve the future clinical trials by providing evidence-based information about different designs of the BCI used for rehabilitation.

3.2 Method

This chapter was conducted in accordance with the PRISMA check list for systematic review and meta-analysis [115]. PRISMA aims to help researchers effectively report the findings of systematic reviews and meta-analyses [116]. The PRISMA checklist contains 27 items, which should be reported to ensure transparency and completeness of the report. The 27 items are divided into 7 categories, including title, abstract, introduction, methods, results, discussion and funding. Using the keywords provided in Supplemental Appendix Table A.1, we systematically searched PubMed, PEDro and Cochrane Library for the studies that published up until 25 April 2020. Appendix Table A.1 provides the detailed electronic search strategy that we used. The identified studies were included in this meta-analysis only if they met the following inclusion criteria:

1. The study is written in English;
2. The study design is a randomized controlled trial of upper-limb BCI rehabilitation, in which the two groups (i.e. the experimental group and the control) are all stroke patients;
3. The study reported the results of upper limb Fugl-Mayer Assessment (FMA-UE) before and after the intervention; We chose the Fugl-Meyer Assessment, because it is the most commonly used outcome measure in the upper-limb BCI rehabilitation studies [117]. The FMA-UE is widely used to evaluate and measure the upper-limb motor function impairment in patients after the stroke [118].

The FMA-UE score is mainly in the range of a minimum 0 (hemiplegia) to a maximum of 66 (normal motor function). We excluded studies without a control group, studies with healthy subjects, studies with a feedback mechanism not combined with BCI or studies without Fugl-Meyer Assessment (e.g. to assess the changes in cortical activity).

We extracted the following details from each included studies: surname of the first author, year of the publication, aim of the study, brain imaging modality, number of participants, phase of the stroke (i.e. chronic or sub-acute), length and frequency of the interventions, outcome measures, type of performed mental practice during the BCI intervention (i.e. motor imagery or intention of movement), BCI feature extraction method, type of feedback, and length of follow-up assessments after the intervention. The corresponding investigators were contacted if the included studies lacked some details.

The Physiotherapy Evidence-Based Database (PEDro) scale is commonly used to measure the methodological quality of a clinical trial by considering 11 criteria (i.e. eligibility criteria Specified, randomly allocated, concealed allocation, baseline comparability, blinded subjects, blinded therapist, blinded assessor, Adequate follow-up , intention to treat analysis, between-group statistical comparison for at least one key outcome, point and variability measures) [119].

The PEDro score is a score ranging from 0 to 10, which represents the total number of criteria that have been satisfied in the clinical trial, excluding the eligibility criteria. A clinical trial with a score from 6 to 10 is considered as high quality, 4 to 5 as fair quality and less than or equal to 3 as poor quality. In this study, two reviewers independently applied the PEDro scale to assess the methodological quality of the included studies. In the case of disagreement, a third reviewer was consulted and an agreement reached.

We conducted the meta-analysis using the Comprehensive Meta-Analysis (CMA) version 3.0 software [120]. CMA is a tool to perform meta-analysis, create the forest plot, calculate effect sizes, and much more. We calculated the effect sizes for the pooled and individual studies using Hedge's equation with correction for small studies [121].

Due to considerable variations in characteristics of the included studies, random-effects models were used to estimate the pooled effect sizes and their 95% confidence intervals (CIs) (Additional details can be found in Appendix A.1). In addi-

tion, we performed subgroup analyses to investigate the impact of different BCI design characteristics (i.e. performed mental practice, extracted BCI features, type of the given BCI feedback and the stroke phase) on treatment efficacy. We used the Higgins' I^2 statistic to assess heterogeneity across the included studies [122].
Generally, I^2 greater than 50% could be considered as substantial heterogeneity. Finally, the probability of publication bias in our meta-analysis was assessed by plotting the funnel plot and applying Egger's regression test [123].

3.3 Results

3.3.1 Literature search and characteristics of the selected studies

Figure 3.1 shows the flowchart of the search strategy and the selection steps taken in this review. We initially identified 585 articles, 12 of which met the inclusion criteria. The study by Ang et al. [34] had two control groups, one control group used the standard arm therapy, and the second control group used the haptic knob. Thus, we combined the two control groups into a single control group as recommended by the Cochrane handbook for systematic reviews of interventions [124]. Table 3.1 provides the main characteristics of the included studies.
Appendix Table A.2 presents the PEDro scores for all of the twelve selected studies. It can be seen that according to the PEDro scores, none of the selected studies are considered to have low methodological quality. Appendix Table A.3 presents the mean and standard deviation of the changes in FMA-UE scores between the pre- and post-intervention in the selected studies, while the Appendix Table A.4 shows the mean and standard deviation of the changes in FMA-UE scores between the pre-intervention and the follow-up session.

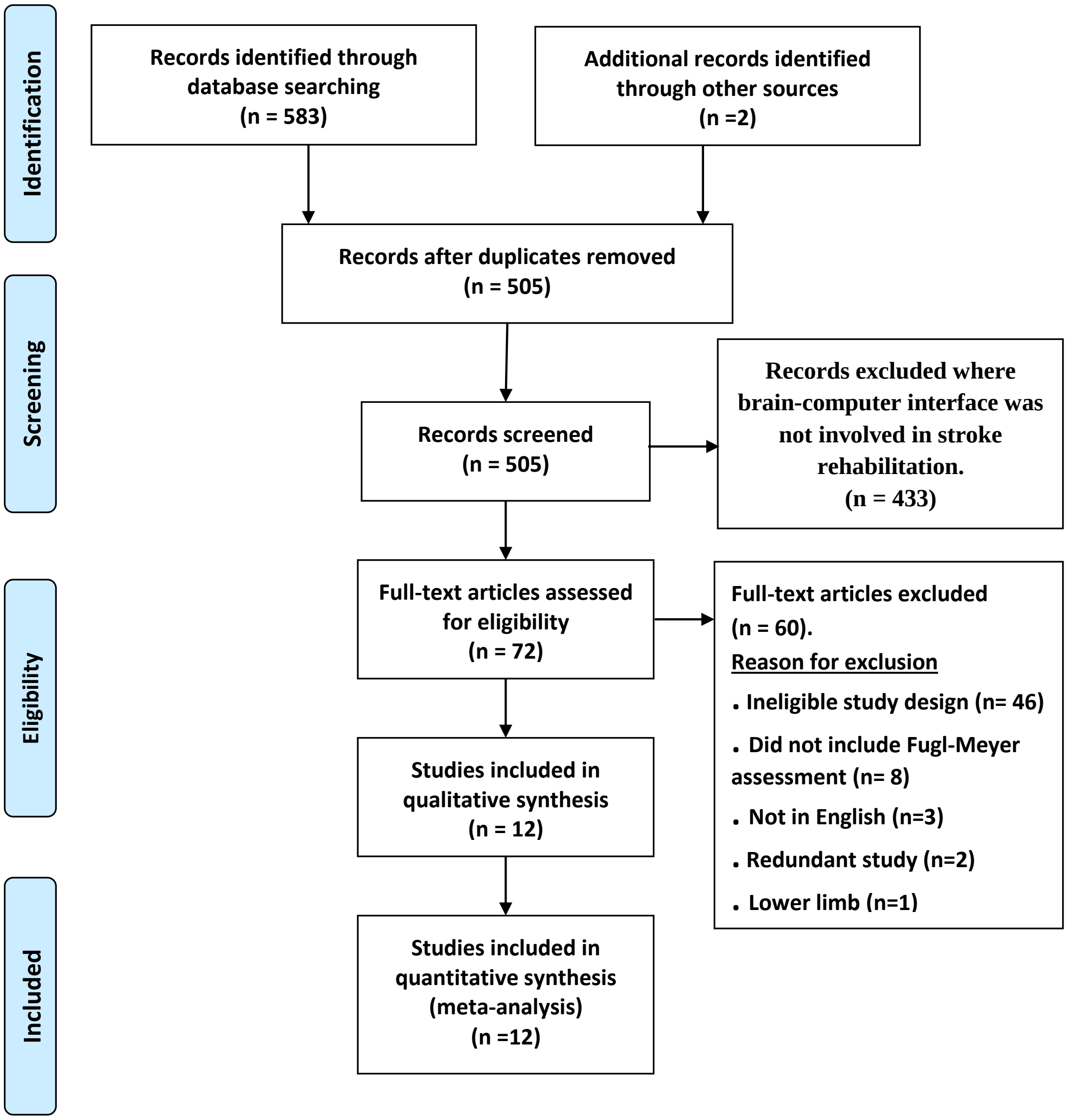


Figure 3.1.: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart illustrating the process for the selection of the included studies in this meta-analysis.

3.3.2 Short-term and long-term efficacy of BCI

The pooled results showed that, according to the short-term assessments immediately after finishing the intervention, the BCI is significantly more effective than the control interventions in post-stroke upper-limb rehabilitation (Hedge's

Table 3.1 Main Characteristics of the Included Studies.

Study	EG/CG	BCI modality	Experimental intervention	Control intervention	Intervention period	Feature	Stroke phase	MI/IM	Outcome measures	Follow-up (weeks)
Ang et al	6/8 ^{HK}/ 7^{SAT}	EEG	BCI-HK 1 h BCI + 30 min TAAM	HK:1 h HK + 30 min TAAM; SAT:1.5 h TAAM	6 weeks, 18 sessions	FBCSP	Chronic	MI	FMA-UE	24
Ang et al	11/14	EEG	BCI-MIT-Manus robot 1.5 h 136 repetitions	MIT-Manus robot 1.5 h 1040 repetitions	4 weeks, 12 sessions	FBCSP	Chronic	MI	FMA-UE	12
Ang et al.	10/9	EEG	20 min tDCS + 1 h BCI-MIT-Manus robot	20 min sham tDCS + 1 h sham BCI	2 weeks, 10 sessions	FBCSP	Chronic	MI	FMA-UE	4
Biasiucci et al	14/13	EEG	BCI-FES 1 h	Sham BCI-FES 1 h	5 weeks, 10 sessions	Band power	Chronic	IM	FMA-UE, ESS, MRC, MAS	36
Cheng et al	5/5	EEG	BCI-assisted soft robotic glove 90 min + 30 min SAT	Soft robotic glove 90 min + 30 min SAT	6 weeks, 18 sessions	FBCSP	Chronic	MI	FMA-UE, ARAT	24
Frolov et al	36/11	EEG	BCI-exoskeleton 30 min + SPT	Sham BCI 30 min	2 weeks, 10 sessions	Band power	Chronic	MI	FMA-UE, ARAT	N/A
Kim et al	15/15	EEG	BCI-FES 30 min + 30 min AOT	AOT 30 min	4 weeks, 12 sessions BCI. 20 sessions AOT	Band power	Chronic	IM	FMA-UE, MAL, MBI	N/A
Li et al	7ne;7nc	EEG	BCI-FES 1–1.5 h + CON	FES 20 min + CON	8 weeks, 24 sessions BCI/FES and 40 sessions CON	CSP	Subacute	MI	FMA-UE, ARAT	N/A
Mihara et al	10/10	fNIRS	BCI-visual feedback 20 min + 120 min NDT	Sham BCI 20 min + 120 min NDT	2 weeks, 6 sessions BCI/Sham, 14 sessions NDT	Band power	Subacute	MI	FMA-UE, ARAT, MAL	2
Pichiorri et al	14/14	EEG	BCI-virtual hand 1 h	MI, 1 h	4 weeks, 12 sessions	Band power	Subacute	MI	FMA-UE	N/A
Ramos-Murguialday et al	16/16	EEG	BCI-orthosis 1 h + 1 h BPT	Sham BCI-orthosis 1 h + 1 h BPT	4 weeks, 20 sessions	Band power	Chronic	IM	FMA-UE GAS, MAL	26
Wu et al	14/11	EEG	BCI-exoskeleton 1 h + 1 h routine training	Routine training 2 h	4 weeks, 20 sessions	Band power	Subacute	MI	FMA-UE ARAT, WMFT	N/A

Abbreviations: AOT, action observational training; ARAT, action research arm test; BCI, brain–computer Interface; BPT, behavioral physical therapy; CG, control group; CON, conventional therapy; CSP, common spatial pattern; EG, experimental group; EES, European stroke scale score; GAS, goal attainment scale; FBCSP, filter bank common spatial pattern; fNIRS, functional near-infrared spectroscopy; FES, functional electrical stimulation; FMA-UE, Fugl-Meyer assessment upper extremity; IM, intention of movement; HK, haptic knob; MAL, motor activity long; MAS, modified Ashworth scale; MBI, modified Barthel index; MI, motor imagery; MRC, medical research council; N/A, not available; NDT, neurodevelopmental treatment; SAT, standard activity therapy; SPT, standard physical therapy; TAAM, therapist-assisted arm mobilization; tDCS, transcranial direct-current stimulation; WMFT, Wolf motor function test.

g= 0.73; P=0.006) (Figure 3.2 A). In nine out of twelve studies, the BCI resulted in higher improvements in FMA-UE, compared to the control interventions (Ang et al. [125], Biasiucci et al.[31], Frolov et al. [38], Kim et al. [29], Li et al. [96], Mihara et al. [106], Pichiorri et al. [126], Ramous et al. [28] and Wu et al. [112]). The highest BCI intervention effect size was reported by Wu et al. [112] (Hedge's g =3.48; P<0.001). In six studies, namely Biasiucci et al. [31], Kim et al. [29], Mihara et al. [106], Pichiorri et al. [126], Ramos et al. [28] and Wu et al. [112], the effect size was significantly favoring BCI. There was substantial heterogeneity among the included studies (I^2 =77.12%; Q= 48.077; df=11; P= 0.000). There is no evidence that the short-term effects of BCI are subject to publication bias. As shown in Appendix Figure A.1, the included studies have a relatively symmetric distribution across the overall effect size in the funnel plot. Moreover, the P value for Egger's test is not significant (p= 0.3795).

The overall effect size, shown in Figure 3.2 B, indicates the effectiveness of the BCI intervention in long-term (Hedge's g=0.33; P=0.041) with no heterogeneity among the included studies (I^2= 0.000%; Q=5.839; df= 6; P= 0.442). Specifically, in five out of seven studies, the FMA-UE changes between the follow-up session and the pre-intervention was in favor of the BCI group.

The funnel plot of the long-term effect of BCI appears to be symmetric (see Appendix Figure A.2), and there is no evidence of publication using the Egger's test (P = 0.541).

3.3.3 Chronic versus sub-acute

Eight studies recruited stroke patients in the chronic phase (>6 months from stroke onset) [28, 29, 31, 33, 35, 38, 125, 127], and the remaining four studies recruited stroke patients in the sub-acute phase (1–6 months from stroke onset)

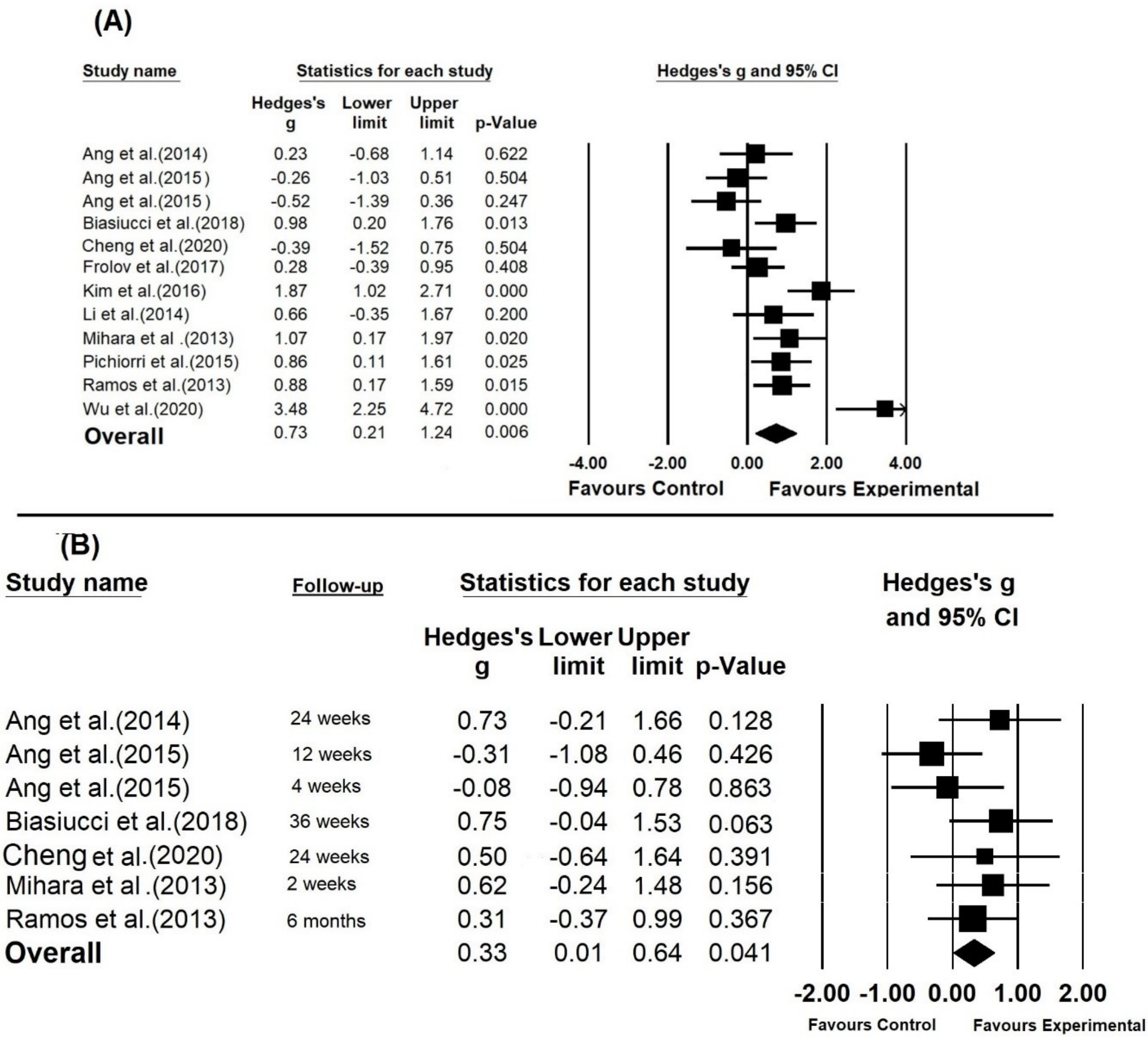


Figure 3.2.: Evaluating effects of brain–computer interface, compared to control interventions, in improving upper-limb motor functions after stroke: (A) assessed immediately after finishing the intervention and (B) assessed in the follow-up session a number of weeks after finishing the intervention.

[96, 106, 112, 126]. The pooled effect size of BCI was higher for the patients in the sub-acute phase than those in the chronic group (Hedge's g = 1.45; P= 0.008 versus Hedge's g =0.41; P= 0.138) (Figure 3.3 A).

The observed effect sizes tended to be significantly different between the two subgroups (P =0.09).

Furthermore, still a substantial heterogeneity was observed between the studies in sub-acute phase (I^2 = 80.17%; Q= 15.128; df=3; P = 0.002) as well as in the chronic phase (I^2 = 71.634%; Q= 24.577; df= 7; P = 0.001).

3.3.4 Motor imagery (MI) versus intention of movement (IM)

In the included studies, the performed BCI mental practices were different (Figure 3.3 B). Nine studies instructed the BCI group to imagine the movement of the affected hand [33, 35, 38, 96, 106, 112, 125–127], whereas three studies asked the BCI group to attempt moving the affected hand [28, 29, 31].

The effect size on motor function recovery was higher for the studies using the intention of movement (Hedge's g= 1.21; P< 0.001) compared with those using the motor imagery (Hedge's g= 0.55; P =0.089). However, the difference between the two subgroups was not statistically significant (P =0.135).

The heterogeneity among the studies using the intention of movement was moderate (I^2= 42.38%; Q= 3.471; df= 2; P= 0.176), whereas there was a substantial heterogeneity among the motor imagery studies (I^2 =78.348%; Q=37.01; df= 8; P= 0.000).

3.3.5 BCI classification features

The included studies were also different in BCI features that they used. Seven studies used the band power features to detect movement-related brain patterns in BCI [28, 29, 31, 38, 106, 112, 126]. The CSP features were used only in one study [96] and the FBCSP features were used in four studies [35, 125, 127, 128].

The group of studies that used band power features had the highest significant effect size on motor function recovery in favor of the BCI intervention (Hedge's g=1.25; P<0.001) (Figure 3.4), with substantial heterogeneity among the studies (I^2 = 75.208%; Q=24.201; df= 6; P= 0.000).

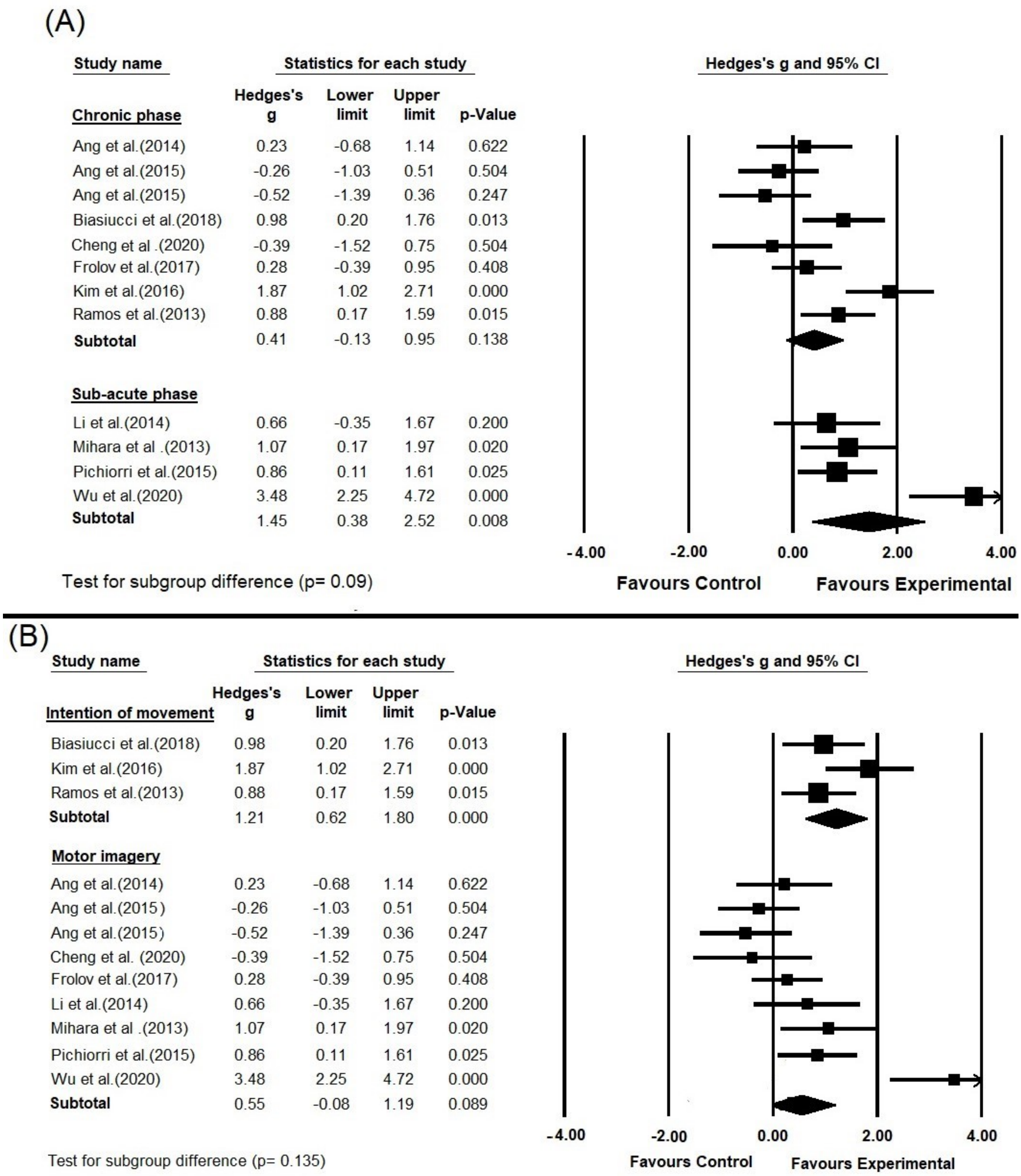
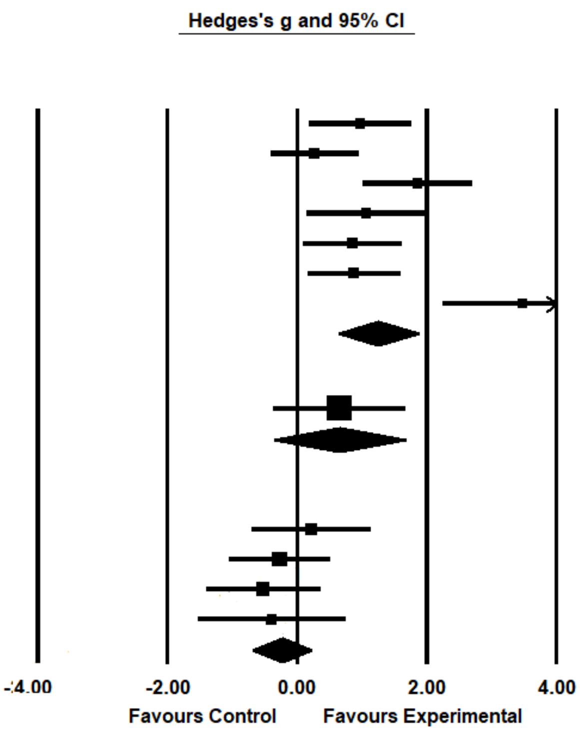


Figure 3.3.: (A) A subgroup meta-analysis comparing the efficacy of brain–computer interface in improving upper-limb motor functions, between 2 different phases of stroke. (B) A subgroup meta-analysis comparing the efficacy of brain–computer interfaces with different mental practices on poststroke upper-limb motor recovery; (ie, motor imagery vs intention of movement).

Conversely, the effect size on motor function recovery was in favor of the control group in the studies using the FBCSP features in the BCI intervention (Hedge's g =-0.23; P=0.315) with no heterogeneity. The difference between the studies with the band power features and the studies with the FBCSP features was statistically significant (P <0.001). Only one study used the CSP features in their BCI model, yielding the effect size in favor of the BCI group (Hedge's g =0.66; P =0.2).

Study name	Statistics for each study			
	Hedges's g	Lower limit	Upper limit	p-Value
Band power				
Biasiucci et al.(2018)	0.98	0.20	1.76	0.013
Frolov et al.(2017)	0.28	-0.39	0.95	0.408
Kim et al.(2016)	1.87	1.02	2.71	0.000
Mihara et al .(2013)	1.07	0.17	1.97	0.020
Pichiorri et al.(2015)	0.86	0.11	1.61	0.025
Ramos et al.(2013)	0.88	0.17	1.59	0.015
Wu et al.(2020)	3.48	2.25	4.72	0.000
Subtotal	1.25	0.63	1.87	0.000
Common spatial pattern (CSP)				
Li et al.(2014)	0.66	-0.35	1.67	0.200
Subtotal	0.66	-0.35	1.67	0.200
Filter bank common spatial pattern (FBCSP)				
Ang et al.(2014)	0.23	-0.68	1.14	0.622
Ang et al.(2015)	-0.26	-1.03	0.51	0.504
Ang et al.(2015b)	-0.52	-1.39	0.36	0.247
Cheng et al. (2020)	-0.39	-1.52	0.75	0.504
Subtotal	-0.23	-0.68	0.22	0.315



Test for subgroup difference between band power and filter bank common spatial pattern (p< 0.001)

Figure 3.4.: A subgroup meta-analysis comparing the efficacy of brain–computer interface, grouped based on different classification features, on poststroke upper-limb motor recovery.

3.3.6 Type of BCI feedback

The type of BCI feedback used to move the affected hand was different across the studies. As can be seen in Figure 3.5, functional electrical stimulation (FES) was used in three studies [29, 31, 96]. A hand exoskeleton robot was used in two studies [38, 112]. The MIT-MANUS robot was used in tow studies [33, 35], and haptic knob and orthosis (hand and arm) robot was used in one each [28, 125]. One study provided only visual feedback to the patients [106]. Finally, the study conducted by Pichiorri et al. used a virtual hand to provide the BCI feedback to the patients [126]. Compared to the control interventions, the highest statistically significant effect size on upper extremity recovery was obtained by the group of studies that used FES as the BCI feedback (Hedge's g =1.2; P =0.001), with moderate heterogeneity among the studies (I^2 = 47.369%; Q=3.8; df= 2; P= 0.15).

However, the effect size of the group studies with the FES-based feedback was not significantly higher than the effect sizes of the other groups of studies with the other types of BCI feedback.

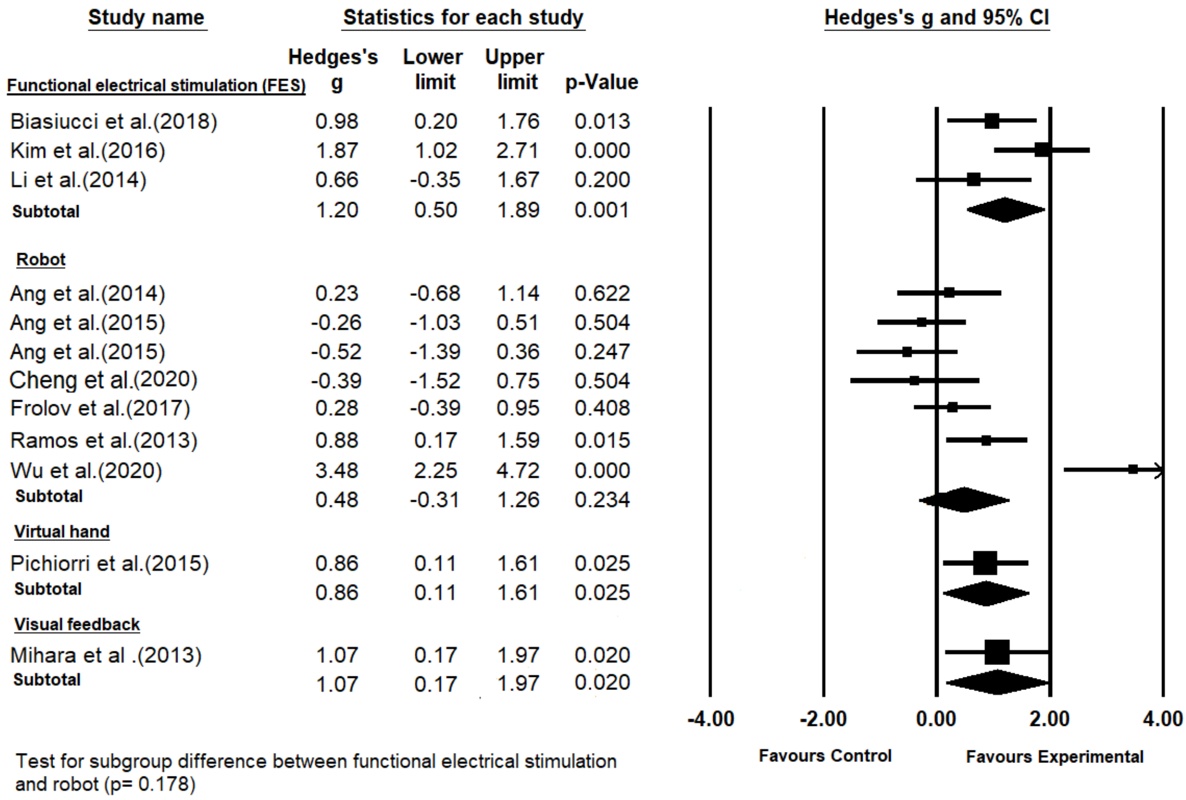


Figure 3.5.: A subgroup meta-analysis comparing the efficacy of brain–computer interface, grouped based on different types of feedbacks, on poststroke upper-limb recovery.

3.4 Discussion

This study was conducted according to the recommendations of the PRISMA checklist for meta-analyses and systematic reviews [115]. Our meta-analysis studied changes in the FMA-UE scores between pre- and post-intervention, and showed that BCI had a significantly higher effect size in improving upper extremity functions following stroke, when compared with control therapies. These findings are consistent with the results of the previous meta-analysis conducted by Cervera et al.[114], and support the short-term efficacy of BCI. Importantly, our study analysed 12 randomized controlled trials involving 295 stroke patients, while Cervera et al. study covered 9 randomized controlled trials with 235 stroke patients.

We also analyzed the results of 7 out of 12 included studies that reported the FMA-UE scores of the patients in a follow up session held a number of weeks after the cession of the intervention. Our results showed that the BCI effects in restoring upper extremity functions are persistent over long-term with a pooled effect size significantly better than the control interventions. As an example, the upper-limb improvements were almost maintained at 36 weeks after the intervention in the study conducted by Biasiucci et al. [31].

However, the recent meta-analysis conducted by Bai et al. [103] did not observe long-term efficacy of BCI compared to conventional therapies. The reason might be because they considered a smaller number of randomized clinical trials (5 studies). In addition, we combined the two control groups in the study conducted by Ang el al. [34] to create a single control group, while Bai et al.[103] selected the haptic knob group and excluded the standard arm therapy group. Interestingly, the most recent randomized controlled trial, conducted by Wu et al. showed the highest effect size in improving upper extremity functions in favour of BCI (i.e. g =3.48) [112]. As can be seen in Figure 3A, the BCI effect size of this study is much larger than the effect sizes of the other included studies.

In this study, unlike the other studies, the motor imagery instruction was given to the patients by displaying a video of a hand using different tools. Then the patients were asked to repeat the presented hand movement using mental imagery. The authors emphasized that the given instruction played an important role in the observed motor function recovery, possibly by linking the brain's visual and motor system.

Compared with conventional therapies, our subgroup meta-analysis showed that for subacute and chronic patients, BCI is more effective in improving upper limb function (see Figure 4A). Our results indicated that participants who engaged in intention or attempted movement of the impaired hand, often followed by actual movement when possible, achieved a higher overall effect size in favor of BCI use compared to those who performed only motor imagery, although this difference was not statistically significant. We propose that the act of intending to move, as opposed to merely imagining the movement, likely leads to higher activity in neural circuits and enhances patient engagement and attention [129]. This hypothesis is supported by previous research which shows that intending and attempting movements can stimulate neural circuits more robustly than motor imagery alone, resulting in better rehabilitation outcomes. For instance, Blokland et al. [130] demonstrated that BCI systems focusing on the intention of movement showed significantly higher accuracy compared to those relying solely on motor imagery. Additionally, for healthy participants, the brain's spectral responses and BCI performance during movement intention and execution were more similar compared to those during motor imagery. This suggests that intending or attempting to move can engage the brain's motor areas more effectively, potentially leading to improved motor recovery. Moreover, engaging in attempted movements may provide sensory feedback, which further stimulates neural plasticity and reinforces motor learning pathways. This dual engagement of motor and sensory pathways could contribute to a more comprehensive rehabilitation process, as highlighted by studies such as Birbaumer et al. and Grefkes and Fink, which noted greater activation in motor-related brain areas during active movement tasks, facilitating neural plasticity and motor functional recovery [131, 132]. Considering these findings, future BCI-based stroke rehabilitation studies should focus more on the intention or attempted movement of impaired limbs rather than relying solely on motor imagery to achieve more significant therapeutic outcomes. Further research is needed to confirm these observations and explore the underlying mechanisms in greater detail. Our subgroup meta-analysis grouped the included studies according to the BCI features used, further revealing that the use of band power features yielded the highest effect size on favour of BCI compared to the control interventions. Indeed, the BCI studies using the band power features achieved a significantly greater upper-limb motor function recovery than those using the FBCSP features ($P < 0.001$). Previous studies on healthy and stroke participants suggested that FBCSP could lead to a higher BCI accuracy than the band power features. In addition, some studies have reported that there is a correlation between the BCI accuracy and the motor function improvement after a BCI intervention [39, 129].

Thus, someone may initially assume that using FBCSP should produce a higher BCI effect size on motor recovery. However, the long term effectiveness of BCI for stroke rehabilitation greatly involves human learning. The results of our meta-analysis suggest that most-likely in long-term the use of band power features help patients better learn to self-regulate their brain patterns, leading more functional recovery and inducing neuroplasticity as compared to more complex features such as FBCSP. In FBCSP, the patients may not easily find a connection between their mental practice and what they observe as the output BCI. The randomized control trials that used BCI to trigger FES had the largest significant effect size in restoring upper-limb function. This improvement may be due to the positive impact of FES on the cortical excitability as reported by several studies [133, 134].

In the study conducted by Ang et al. [35], the effect size was in favour of the control group. This may be due to the relatively small number of training repetitions in experimental group compared to the control group (136 versus 1040 repetition). In addition to the number of training repetitions, the use of motor imagery and FBCSP may have contributed in the negative results, as discussed in this study. Another study by the same research group also showed an effect size in favour of the control group [45]. This finding might be because of the short period of the rehabilitation intervention (2 weeks). Interestingly, this study reported a slight improvement in the BCI outcomes at the follow-up session held 4 weeks post-intervention. However, it would be difficult to distinguish if this observed slight improvement was as a result of the BCI intervention or the transcranial direct current stimulation (tDCS). Typically, a longer intervention, such as six weeks of rehabilitation with three sessions per week is recommended [36].

3.5 Limitations

In this meta-analysis, we observed large variations in the BCI intervention effect sizes across the included clinical trials. As discussed previously, these variations can be potentially due to differences in the BCI design including differences in the BCI feedback, performed mental practices, extracted classification features, and the phase of the stroke in the participants, among others. This finding further confirms that there is a need to optimize the BCI design for upper limb stroke rehabilitation in order to maximize the potential motor function improvement in patients. Only twelve randomized clinical trials (295 patients) were available to analyze in this study. Hence, more studies with a larger number of patients are required to increase the reliability and generalizability of the results.

Moreover, in order to increase the reliability of sub-group meta analyses, it has been recommended to have at least five clinical trials in each sub-group [135]. In some of our sub-group analyses, this condition could not be met. Moreover, we did not consider the variations among the included clinical trials in terms of the intensity of BCI intervention (see Table 3.1).

3.6 Conclusion

This chapter showed that BCI has significant immediate and long-term effects in improving upper-limb motor functions after stroke, compared to conventional therapies. Our results support using intention of movement of the impaired hand as the BCI mental practice, the band power features as the BCI classification features and functional electrical stimulation as the BCI feedback in future BCI-based stroke rehabilitation studies.

It is important to note that in many BCI-based studies, the activation of the ipsilesional hemisphere was considered a key factor required for motor recovery after stroke. However, emerging evidence suggests that the contralesional hemisphere also plays a role in motor function rehabilitation. Therefore, the next chapter is going to investigate the effectiveness of the BCI in detecting motor imagery of the affected hand from contralesional hemisphere.

4

Exploring the Ability of Stroke Survivors in Using the Contralesional Hemisphere to Control a Brain-computer Interface

The findings of this chapter have been published in Scientific Reports [68].

– Published, Sept 2022 –

4.1 Chapter Introduction

In several BCI clinical studies, the provided neurofeedback was based on the activity of the ipsilesional motor cortex [64, 105, 136]. These studies are aligned with functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) studies, confirming that enhancing the excitability of the ipsilesional motor cortex can play an important role in motor recovery after stroke [137]. On the other hand, other studies reported that enhancing the excitability of the contralesional side appears to play a significant role in motor recovery for a subset of stroke patients [63, 65, 138]. Similarly, Kaiser et al. [139] reported that during motor imagery of the impaired hand, more impaired patients showed higher event-related desynchronizations (ERDs) (i.e. EEG signature of motor tasks) in the contralesional hemisphere when compared with less impaired patients. Antelis et al. [140] found similar outcomes in stroke patients when they attempted and executed a hand movement. Interestingly, a very recent study demonstrated that for stroke users encountering BCI deficiency, i.e. those with poor conventional BCI accuracy, neuronal modulation was significantly greater in the contralesional hemisphere compared to the ipsilesional hemisphere [141].

Hence, we hypothesize that for some stroke patients, EEG signals from the contralesional hemisphere may outperform EEG signals from the ipsilesional hemisphere in terms of BCI performance. Physiologically, as the contralesional hemisphere is usually unaffected by stroke, it may implied that many stroke patients should be able to generate brain signals from the contralesional hemisphere in response to imagined or attempted movement of the affected hand [142]. Furthermore, a previous study used EEG signals from the contralesional hemisphere to successfully control a BCI [143]. However, this study was limited to only 10 stroke patients, and the final results were not compared with the results of a conventional BCI system that uses ipsilesional signals. More research is needed to fully understand the effects of other confounding variables that may affect the cortical activation patterns and BCI performance in stroke patients, including lesion location and size, and time since stroke.

In short, this chapter aims to address the following questions:

- Are the stroke patients able to meaningfully operate a BCI-based rehabilitation system using EEG signals from only the contralesional hemisphere?
- Is there a difference in the performance of stroke patients in controlling BCI using EEG from the contralesional hemisphere when compared to using EEG from the ipsilesional hemisphere or even from both hemispheres and how much is this different?
- Are there any relationships between the BCI performance and the patient's demographic data including Fugl-Meyer assessment score and time since stroke?

In this study, EEG signals of 136 stroke patients performing motor imagery of their impaired hands and their respective BCI features were extracted from channels covering either the ipsilesional, contralesional or both hemispheres using the common spatial patterns (CSP) algorithm [97], the filter bank common spatial patterns (FBCSP) algorithm [98], and the band power (BP) feature extraction algorithm [144]. In order to reduce the dimensionality of the features, we only used the most discriminative ones by applying the mutual information-based best individual feature (MIBIF) algorithm for feature selection. Next, the selected features were classified using the naive Bayesian Parzen window (NBPW) classifier [145]. The above mentioned feature extraction and classification algorithms have been commonly used in previous BCI-based stroke rehabilitation clinical trials [44, 146, 147]. Finally, the average 10-fold cross validation outcomes of the three types of BCI (i.e. ipsilesional, contralesional and bilateral BCI) were statistically analyzed in terms of BCI accuracy, as well as the impact of the motor impairment and post-stroke time on the BCI performance. We hope that the results of this study will contribute to a deeper understanding of how to promote personalized modulation of neural signals to enhance neuroplasticity, thereby benefiting the stroke patients. It should be noted that the EEG data utilized in this chapter was obtained from four separate clinical trials conducted by other researchers [44–47]. This data was obtained through collaboration with the researchers who conducted these trials.

4.2 MATERIALS AND METHODS

4.2.1 Datasets description

Participants

We analyzed the EEG datasets recorded from 136 stroke patients during the BCI screening sessions of four clinical trials [44–47]. Among the 136 participants, 17 were in subacute phase (3.32 $\pm$ 1.5 months from stroke onset) and 119 in chronic phase (23.68 $\pm$ 17.72 months from stroke onset). Participants were 52.81 $\pm$ 11.36 years old, on average Fugl-Meyer score was 28.64$\pm$12.92.
These four clinical trials were carried out from 1 January 2011, to 30 September 2017 with ethics approval from the institution's Domain Specific Review Board, National Healthcare Group, Singapore. All four clinical trials are registered on ClinicalTrials.gov as: NCT00955838 [44], NCT01897025 [45], NCT01287975 [46], and NCT02765334 [47]. The clinical trial in [44] investigated the efficacy of the BCI system coupled with the MIT-Manus robotic feedback on upper-limb motor function improvement, whereas the clinical trial in [45] studied the possible benefits of using transcranial direct current stimulation (tDCS) in combination with

the BCI and robotic feedback to improve the motor function. The purpose of the clinical trial described in [46] was to observe whether the BCI combined with the haptic knob robot can enhance the arm rehabilitation of stroke patients, whereas the effectiveness of BCI with visual feedback for upper-limb stroke recovery as well as the impacts of mental fatigue on BCI performance were investigated in [47].

The participants participating were between 21 and 70 years old with the following inclusion criteria:

1) Participants had their first cortical and sub-cortical stroke, with a Fugl-Meyer score ranging from mild to severe impairment of upper extremity function.

2) Participants could understand the verbal instructions, and achieved a score higher than 6 out of 10 in the abbreviated mental test.

3) Participants did not suffer from any medical instability, epilepsy, severe depression, skin problems that could get worse due to wearing the EEG cap, severe spasticity in any of the elbow, finger, shoulder or wrist as assessed by the modified Ashworth scale (score > 2), or severe vision problems.

Motor imagery-based BCI paradigm

All participants first attended a motor imagery based BCI screening session without feedback. During the screening session, the participants were instructed to perform motor imagery of their affected arm and hand. The BCI screening session consists of 4 runs and each run consists of 20 trials of the motor imagery task and 20 trials of the idle state in random order. After each run, a 2 minute break was given to the participant. On average, each trial took 12 seconds and each run took about 8 minutes. Figure. 4.1 illustrates the timing of one trial. A total of 160 trials were collected in each session. The BCI screening session lasted about an hour, including the EEG cap setting.

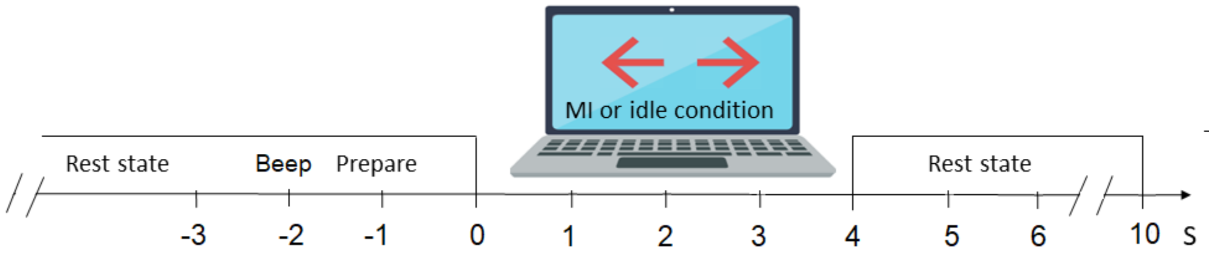


Figure 4.1.: The timing of one trial in the BCI screening session, instructing the patient to perform either motor imagery of stroke-affected hand or idle task.

EEG signal acquisition

For the first three clinical trials [44–46], the Neuroscan Nuamps EEG amplifier with unipolar Ag/AgCl electrode channels was used to collect EEG data from 27 channels, which were referenced to the nasion. The collected EEG data was digitally sampled at the frequency of 250 Hz with the resolution of 22 bits and the voltage range of $\pm$130 mV. For the fourth clinical trial [47], EEG data was collected using the Neurostyle EEG amplifier with 24 unipolar Ag/AgCl electrode channels referenced to the FPz. The EEG was digitally sampled at 256Hz with a resolution of 24 bits for voltage ranges of $\pm$300mV.

4.2.2 BCI classification models

Figure. 4.2 shows all the procedures required to training and evaluating the BCI models.

Preprocessing and BCI feature extraction

In order to calculate the features, we selected a specific channel set for each type of BCI model (i.e. contralesional, ipsilesional or bilateral BCI):

- Channels that cover either the left or right hemisphere: (FC3, FCz, T7, C3, Cz, CP3, CPz, P3, Pz; or FCz, FC4, Cz, C4, T8, CPz, CP4, Pz, P4). Depending

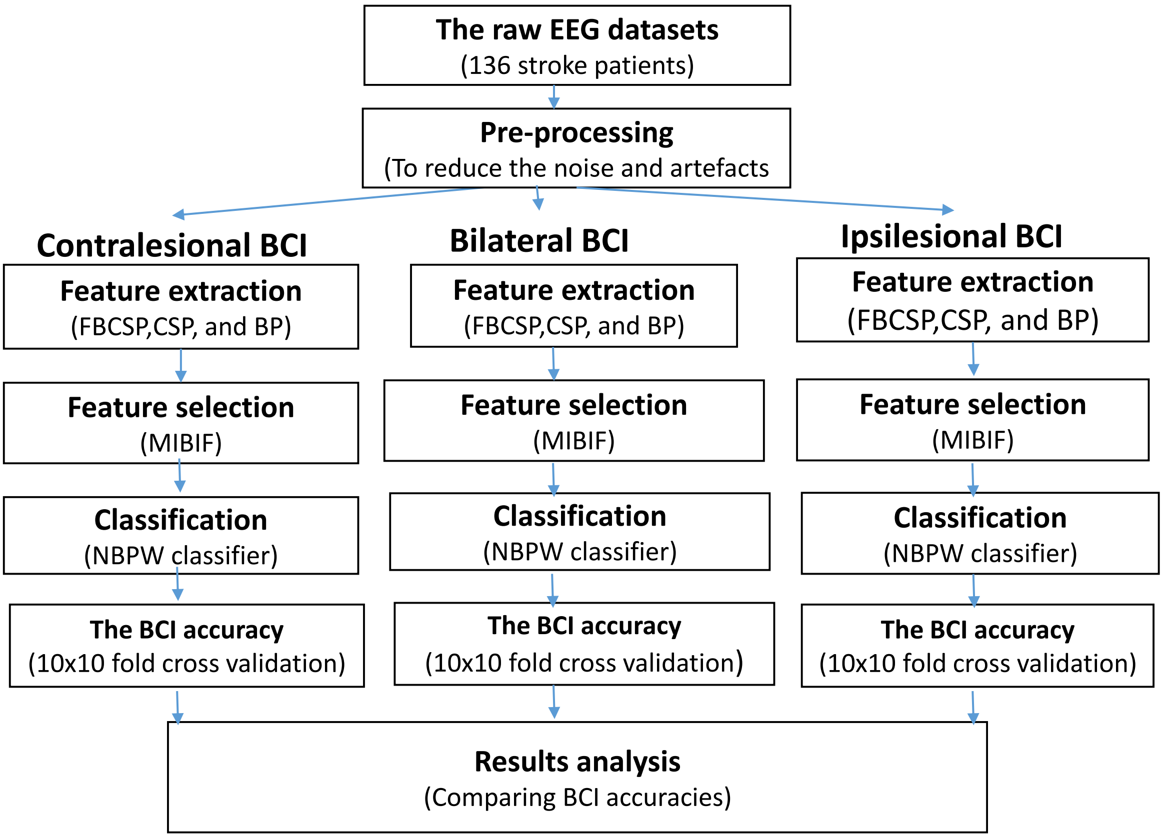


Figure 4.2.: Flowchart presenting the steps taken for training and evaluating the BCI models. Abbreviations: BP, band power; CSP, common spatial patterns; FBCSP, filter bank common spatial patterns; MIBIF, mutual information-based best individual feature selection; NBPW, Naive Bayesian Parzen window.

on the location of the lesion, they would be called either ipsilesional or contralesional channels.

- Bilateral channels: (FC3, FCz, T7, C3, Cz, CP3, CPz, P3, Pz; FC4, C4, T8, CP4, , P4).

The channels of interests are shown in Figure 4.3. In this study, we used the three most commonly used feature extraction algorithms in the BCI-based stroke rehabilitation, namely common spatial patterns (CSP), filter bank common spatial patterns (FBCSP), and band power features (BP) [44, 105, 146]. When using CSP and BP, we first employed a zero-phase band-pass filter from 8 to 30 Hz in order to clean the raw EEG signal from high-frequency noise and low-frequency artifacts. This frequency band has been selected because it contains the mu (8-12 Hz) and beta (13-30 Hz) rhythms, which are well associated with motor imagery and actual movement [148]. For the FBCSP, we employed a filter bank with nine band-pass filters to partition the EEG dataset into nine frequency bands (4-8 Hz, 8-12 Hz,..., and 36-40 Hz) [98]. Four seconds motor imagery and idle class EEG data were extracted after the visual cue for CSP, FBCSP and BP feature extraction. We also extracted 1.5 seconds of EEG during the preparation period, before the visual cue, as the baseline reference for the BP feature extraction. More detailed information about these feature extraction methods can be found in the subsequent sections. This study was performed without any artifact rejection.

Common spatial patterns (CSP) The CSP algorithm has been commonly used in classification of multi-channel EEG signals, recorded during motor imagery [97]. The main concept of CSP is to weight the EEG channels, such that the variance of band-pass filtered EEG signals is maximized in one class and minimized in the other [97]. In this study, the first 2 rows and the last two rows of the CSP matrix were used for spatially filtering the EEG signals. After that, the normalized log variance of the spatially filtered EEG signals were used as the input features for the classifier. Hence, 4 CSP features were extracted in total.

Filter bank common spatial patterns (FBCSP) The CSP method can successfully design the optimal spatial filters for distinguishing the two classes of EEG signals in motor imagery-based BCI [149]. However, the efficacy of this method is dependent on its operating frequency band due to the large variability between users [98]. The FBCSP algorithm has been introduced to solve this problem by using a filter bank to filter the EEG data into 9 frequency bands (i.e. 4-8 Hz, 8-12 Hz, 12-

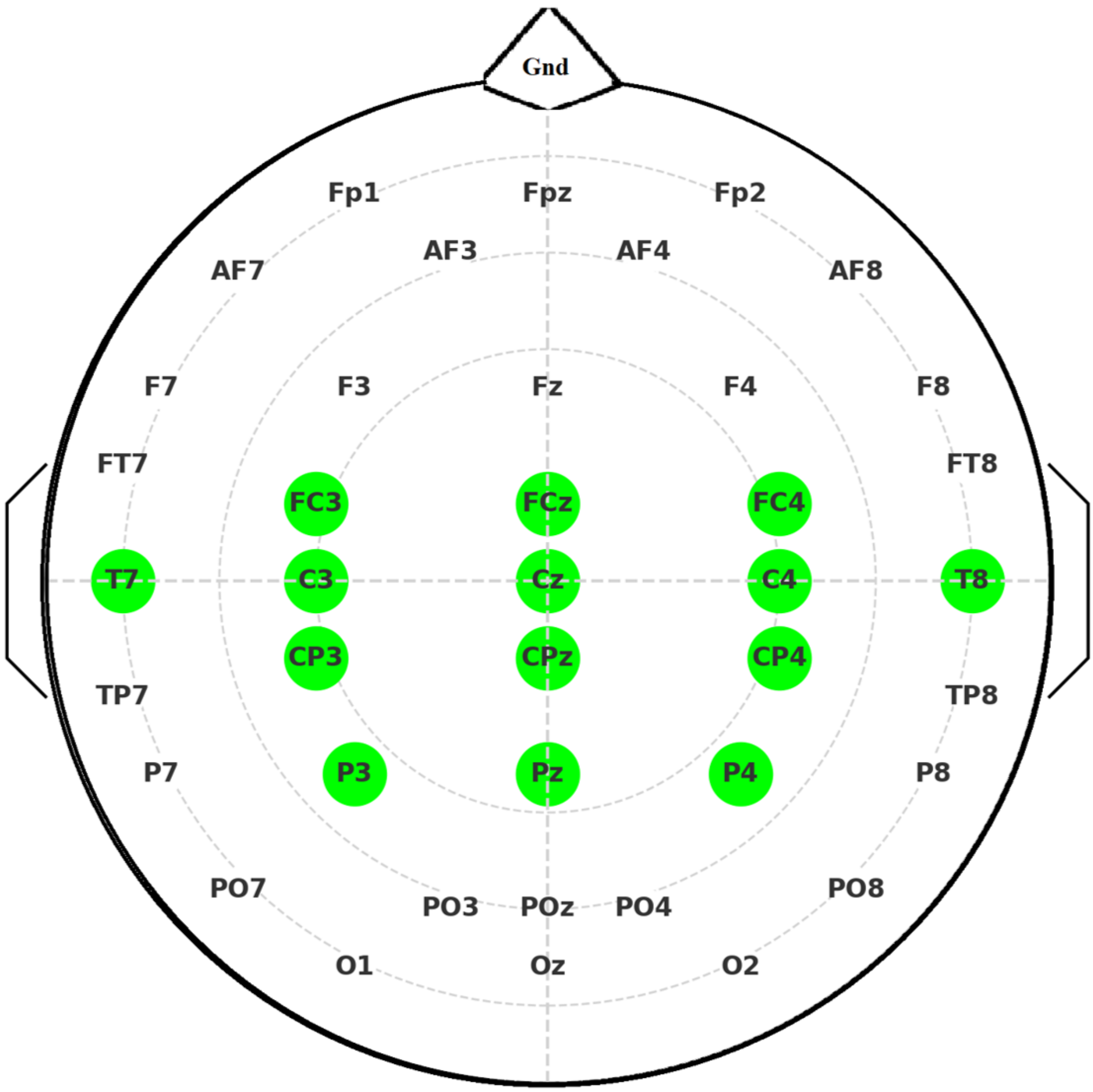


Figure 4.3.: A scalp map showing the 10-20 international electrode map for EEG. The green color indicates the position of the channels that have been used in this study.

16 Hz, ... and 36-40 Hz) [98]. Next, for each frequency band, the band-specific CSP filters are calculated and applied to the corresponding band-passed EEG signals. In this study, for each band, 4 CSP features were extracted using the first and the last two CSP filters. Thus, a total of 36 FBCSP features were extracted.

Band power features (BP) The motor imagery and intention of movement can change ongoing brain waves in a form called event-related desynchronization/synchronization (ERD/ERS) [150]. ERD/ERS is characterized by suppression and enhancement of the power of sensorimotor rhythms, respectively, in the frequency range [8-30 Hz] [100].

In the present study, the BP features measure the average ERD/ERS changes relative to the baseline, as suggested by [151]. After band-pass filtering the EEG signals from 8 to 30 Hz, the BP feature of the i^{th} channel from the j^{th} trial, $\mathbf{BP}(i,j)$, was calculated as

$$\mathbf{BP}(i,j) = \mathbf{log}\left(\frac{\mathbf{T}(i,j) - \mathbf{B}(i,j)}{\mathbf{B}(i,j)} \times 100\right), \quad (4.1)$$

where $\mathbf{T}(i,j)$ denotes the average power of the channel i at the trial j when performing the task (i.e. 4 seconds EEG signals immediately after the cue). Similarly, $\mathbf{B}(i,j)$ denotes the average power of the channel i at the trial j during the preparation period (i.e. 1.5 seconds before the cue).

Feature selection

In order to select a more discriminative feature subset from the extracted features, we employed the mutual information-based best individual feature (MIBIF) algorithm based on the filtering feature selection approach [145]. MIBIF calculates the mutual information between each feature and the corresponding class labels, and arranges them in ascending order. Next, the top 4 features with the highest mutual information are selected. In the case of CSP, feature selection was not used because there were only 4 CSP features extracted. Further information about MIBIF can be found in [152].

Classification and validation

In this step, we choose the Naïve Bayesian Parzen Window (NBPW) classifier, which is known for its relatively fast classification capabilities [98, 145, 153]. Different classification algorithms can be employed; however, research by Ang et al. indicated that the NBPW classifier showed superior performance in offline BCI accuracy [98].

As described in [154], in our study, we employed a 10×10-fold cross-validation technique to ensure a robust evaluation of the classifier outcomes. Specifically, for each patient, we conducted 10 separate runs, where in each run, the 160 trials were randomly divided into 10 portions. During each run, we performed 10-fold cross-validation by using nine portions for training and one for testing, iterating this process such that each portion served as the test set exactly once. This procedure was repeated 10 times, each with a new random split of the data, providing a comprehensive assessment by averaging the results of these multiple cross-validation processes. This approach differs from the standard 10-fold cross-validation, which typically involves a single random division into folds. Such an enhanced approach to cross-validation is supported by findings in the literature, which suggest that repeated cross-validation and multiple random splits can provide more reliable performance [155, 156].

4.2.3 Visualization of cortical activity during motor imagery

Event-related synchronization/desynchronization (ERS/ERD) was used to visualize the cortical activation during motor imagery. The grand average time-frequency maps and the grand average ERD/ERS plots were calculated for the ipsilesional and the contralesional hemisphere separately, at either C3 or C4, by pooling the motor imagery trials of all patients. Time-frequency maps are commonly used to visualize the changes in the spectral power of different frequency bands in response to a stimulus across the time [157]. The time-frequency maps were plotted by calculating the power spectrum within a sliding time window and then averaging results across trials. The baseline period for time-frequency maps is 1.5 second before the cue.

To obtain the ERD/ERS plots, the relative change in the relative power with respect to the average power of the preparation period was calculated from 8 to 30 Hz, as presented in [144]. The grand average ERD/ERS plots were presented in time intervals from -2 to 4 seconds relative to the onset of the cue, with baseline of 1.5 second before the cue (i.e. preparation period).

4.2.4 Statistical Analysis

We analyzed the data using IBM SPSS Statistics for Windows, released in 2019, version 26.0. In this study, the classification accuracy of the BCI types were compared across the three feature extraction methods using the Wilcoxon signed rank test. Since our classification accuracy comes from 4 different datasets, we used this non-parametric test [158].

The 99% confidence of the chance performance for 160 trials is around 60% when using the inverse binomial distribution function [154]. Hence, any participant who has a BCI accuracy of less than 60% is considered to be performing at a chance level. We selected 80% as the other threshold, because in several

BCI studies participants with above 80% BCI accuracy were considered as BCI high performers [159].

We also calculated the correlation between the classification results and the Fugl-Meyer scores as well as the time since stroke for each feature extraction method and each BCI type. Correlation analysis was conducted with Kendall's Tau correlation, which is a non-parametric method [160]. The significant level was set to $p = 0.05$ for all the analyses.

4.3 Results

4.3.1 ERD/ERS in contralesional and ipsilesional hemisphere

The time-frequency maps with the ERD/ERS patterns during motor imagery in the contralesional and ipsilesional hemisphere are shown in Figure 4.4. We observed that the ERD/ERS phenomenon occurs in both the contralesional and ipsilesional hemispheres. On average, the ipsilesional hemisphere had slightly higher ERD than the contralesional hemisphere, mostly in the beta band. However, the contralesional hemisphere generated a stronger grand average ERS, mostly in the mu-rhythm, compared to ipsilesional hemisphere. The mu rhythm refers to a specific frequency band of brain waves, typically ranging between 8 and 13 Hz [161]. It is prominently observed over the sensorimotor cortex. Figure 4.5 shows the grand average power changes in ERD/ERS in the contralesional and ipsilesional hemisphere. It can be observed that during motor imagery there is a relative power decrease (ERD) after onset of motor imagery ($t = 0$), followed by an increase in the power (ERS) in both hemispheres. The grand average ERD has a slightly lower amplitude in the ipsilesional hemisphere than in the contralesional hemisphere. However, as compared to the ipsilesional hemisphere, the contralesional hemisphere showed a higher amplitude of ERS. Importantly, comparing different time-intervals as well as performing point-to-point comparisons, we did not observe any statistically significant difference between the ERD/ERS of the ipsilesional or contralesional hemispheres over the time range of [0, 4] s (p>0.05, Wilcoxon signed-rank test).

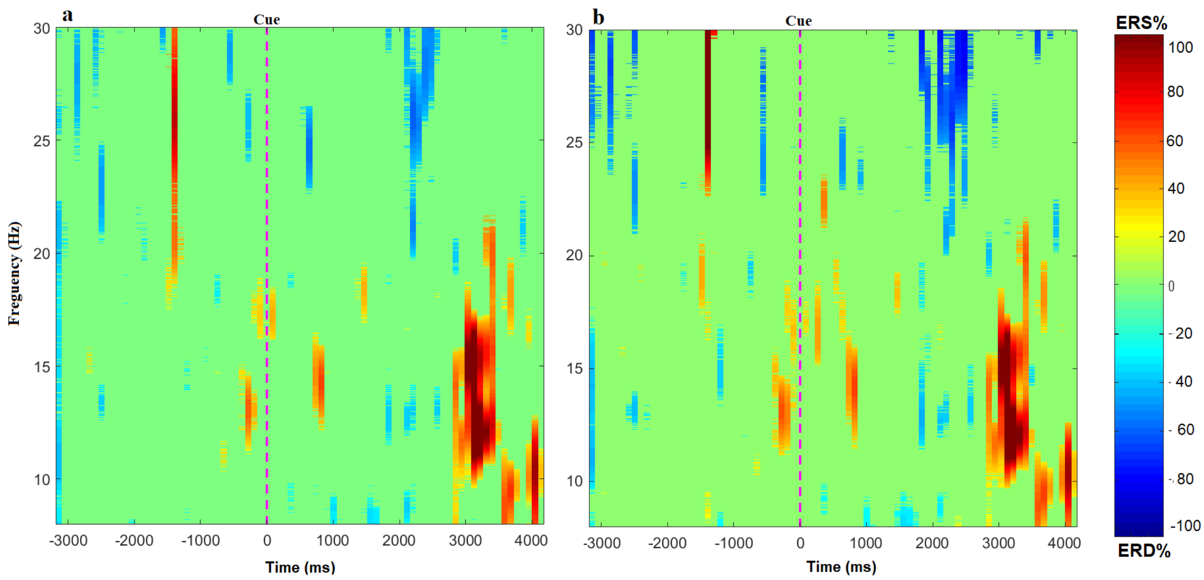


Figure 4.4.: Time-frequency representation shows the grand average of event-related (de)synchronization (ERD/ERS). a, The ERD/ERS in the contralesional hemisphere. b, The ERD/ERS in ipsilesional hemisphere. ERD is indicated by the blue colors, whereas ERS is indicated by the red colors.

4.3.2 Comparing classification results of contralesional, ipsilesional and bilateral BCI types

Figure 4.6 and Table 4.1 compare the 10×10-fold cross-validation results of the three types of BCI (i.e. bilateral, contralesional or ipsilesional channels) obtained from 136 stroke patients, using either FBCSP, CSP or BP features. Overall, the use of the bilateral channels with FBCSP features yielded the highest BCI performance, which was significantly better than the ipsilesional and contralesional BCI performance using FBCSP and CSP ($P < 0.001$). However, it was not significantly better than the contralesional BCI with BP features ($p > 0.05$). The results

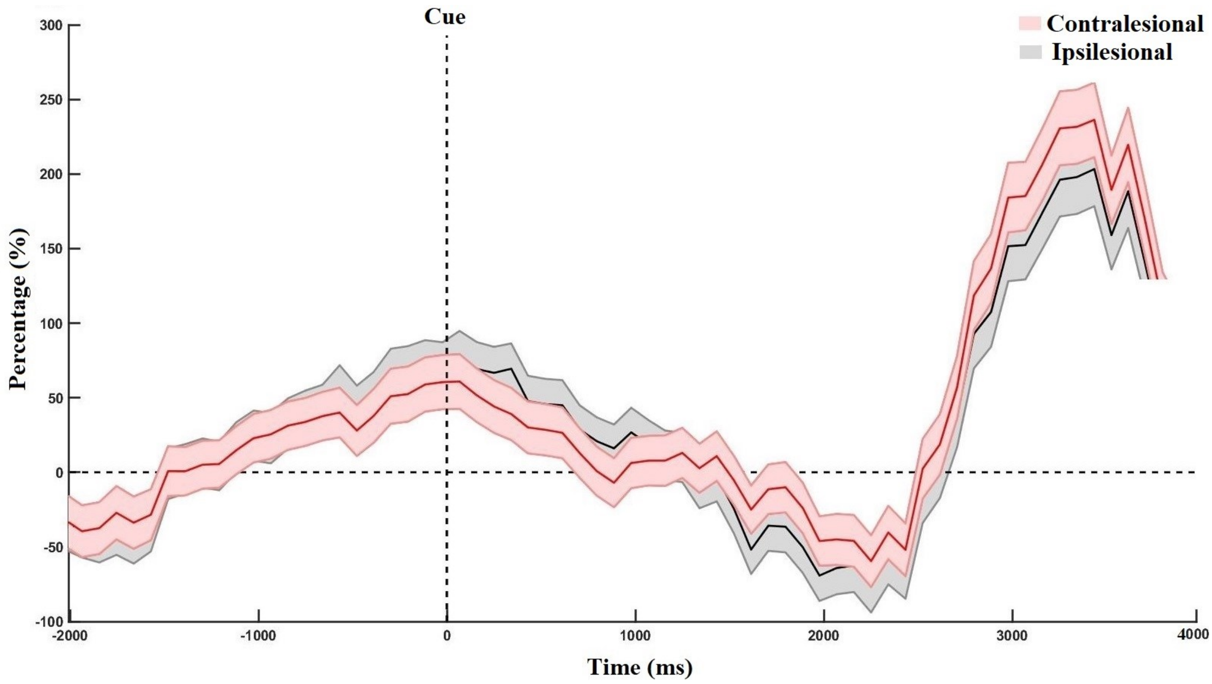


Figure 4.5.: The grand average power change in event-related (de)synchronization (ERD/ERS) in contralesional and ipsilesional hemispheres during motor imagery (i.e. from 0 to 4 second), relative to the resting baseline 1.5 seconds before the cue.

also showed that, on average, the contralesional BCI performed slightly better than the ipsilesional BCI. Importantly, when using FBCSP and BP feature, there was no statistically significant difference in the stroke patients' performance in controlling BCI using the ipsilesional hemisphere compared to the one using the contralesional hemisphere.

Table 4.1.: Comparison of the average 10×10 fold cross-validation BCI accuracies between the three types of BCI (bilateral, contralesional or ipsilesional channels), obtained using three different BCI feature extraction methods.

Feature Extraction	Bilateral Acc. $(Mean \pm SD)$	Contralesional Acc. $(Mean \pm SD)$	Ipsilesional Acc. $(Mean \pm SD)$	Bilateral vs Cont. (p-value)	Bilateral vs Ipsi. (p-value)	Cont. vs Ipsi. (p-value)
FBCSP	74.8 ± 13.02	71.23 ± 11.44	70.7 ± 12.66	< 0.001	< 0.001	0.62
CSP	69.05 ± 12.59	65.87 ± 12.10	64.01 ± 12.65	< 0.001	< 0.001	0.029
BP	74.01 ± 6.9	72.52 ± 9.06	71.99 ± 9.65	0.18	0.017	0.641

Abbreviation: Acc., Accuracy, Cont., contralesional; Ipsi., ipsilesional; SD, standard deviation; vs, versus.

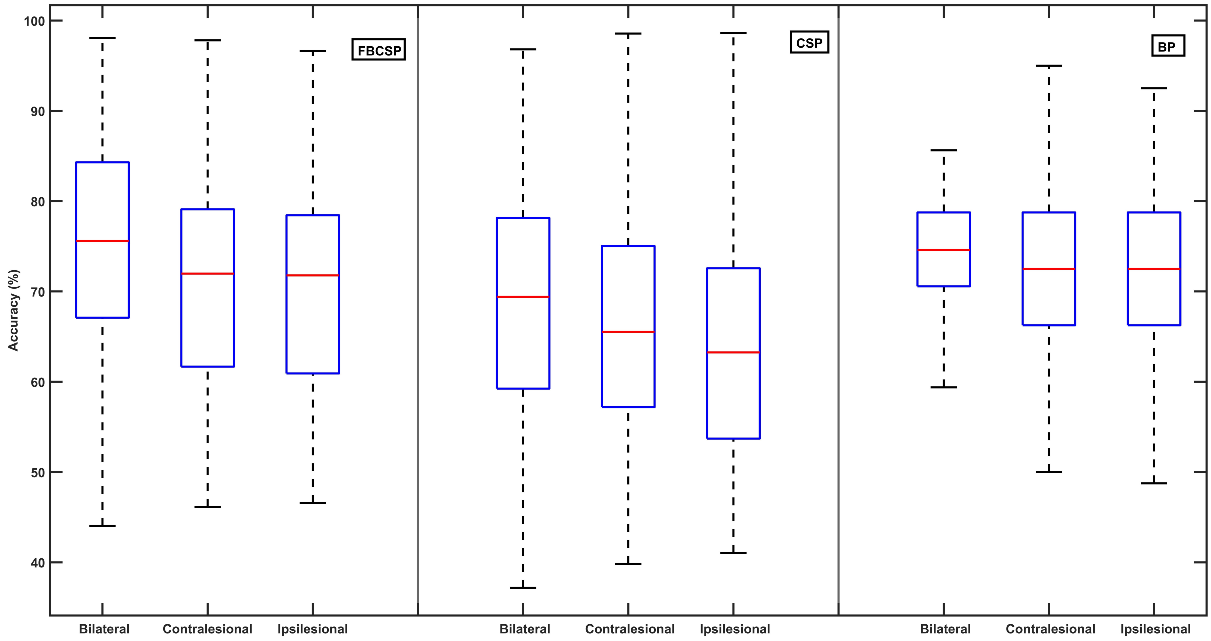


Figure 4.6.: The box-plot shows average cross-validation BCI accuracy of 136 stroke patients using either bilateral channels that cover both hemisphere, contralesional or ipsilesional channels. The y axis represents the BCI accuracy resulted from 10×10-fold cross-validations, and the x axis represents the three types of BCI accurcies using either FBCSP, CSP or BP as feature extraction.

Table 4.2 shows that the overall number of patients who did not achieve an average BCI accuracy above 60% using the contralesional hemisphere was less than the number of patients who failed to achieve an average BCI accuracy above of 60% using the ipsilesional BCI. Interestingly, when we look at the scatter plots in Fig. 4.7, it can be observed that the contralesional BCI yielded a better classification accuracy than the ipsilesional BCI for those with the the ipsilesional BCI accuracy less than 60% ($p < 0.05$ for all three feature extraction methods obtained using Wilcoxon signed-rank test). On the contrary, those with the ipsilesional BCI accuracy greater than 80% achieved lower accuracy using the contralesional BCI ($p < 0.05$ for BP, FBCSP and $p = 0.09$ for CSP, obtained using Wilcoxon signed-rank test). Table 4.3 provides more details on the corresponding statistical results.

4.3.3 Impact of Post-stroke Sensorimotor Impairments and the time since Stroke on BCI Performance

We did not observe a significant correlation between the ability of stroke patients to use contralesional, ipsilesional or bilateral hemispheres to operate BCI and their Fugl-Meyer score (Table 4.4). That being said, we observed significant difference between the Fugl-Meyer scores of those with average ipsilesional BCI accuracy less than 60% and the Fugl-Meyer scores of those with ipsilesional BCI accuracy higher than 80%. From Table 4.5, we observe that those with the ipsilesional BCI accuracy below 60% had significantly higher motor impairments, measured using Fugl-Meyer assessment, than those with the ipsilesional BCI accuracy above 80% ($p < 0.05$, Wilcoxon signed-rank test).

Regarding the impact of stroke duration on BCI Performance, we did not observe any significant correlation between the accuracy of detecting motor imagery using either, contralesional, ipsilesional, or bilateral hemisphere and the time since stroke (see Table 4.6). Furthermore, no significant difference was found in the time following stroke of patients with the ipsilesional BCI accuracy below 60%, and those with the ipsilesional BCI accuracy above 80% ($p > 0.05$, Wilcoxon signed-rank test).

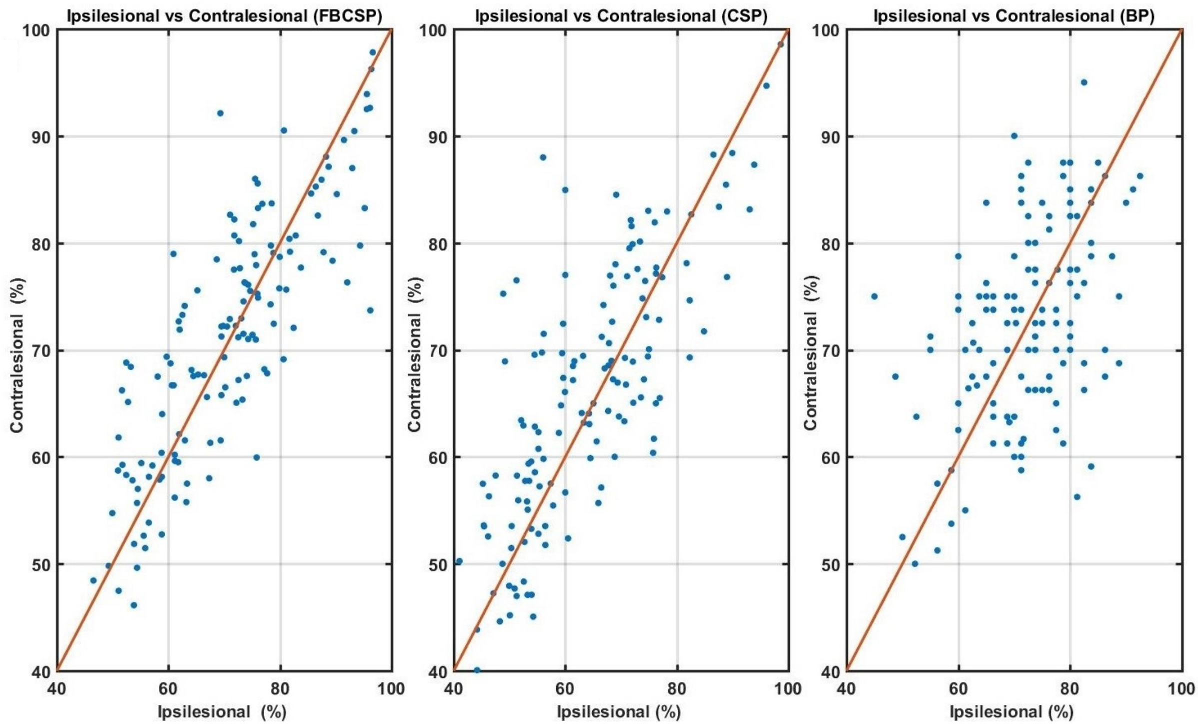


Figure 4.7.: Scatter plots comparing the average cross validation accuracy of contralesional and ipsilesional BCIs using different feature extraction algorithms (FBCSP, CSP, and BP). The blue dots represent the average BCI accuracy for each stroke patient.

Table 4.2.: Percentage of the patients with the average BCI accuracy (bilateral channels, contralesional, or ipsilesional) less than 60% using different BCI feature extraction methods.

Feature extraction	Contralesional Below 60%	Ipsilesional Below 60%	Bilateral Below 60%
FBCSP	15.6%	22.79%	13.76%
CSP	28.1%	42.64%	34.1%
BP	7.1%	8.82%	6.6%

Table 4.3.: Comparison of the average 10×10 fold cross-validation accuracy of the ipsilesional and contralesional BCI for those with ipsilesional BCI accuracy below 60% and those with the ipsilesional BCI accuracy above 80%, obtained using three different BCI feature extraction methods.

Feature Extraction	Ipsilesional Acc.<60%			Ipsilesional Acc.>80%		
	Ipsilesional $(Mean \pm SD)$	Contralesional $(Mean \pm SD)$	p-value	Ipsilesional $(Mean \pm SD)$	Contralesional $(Mean \pm SD)$	p-value
FBCSP	54.37 ± 3.29	57.74 ± 6.51	0.02	89.01 ± 5.55	83.92 ± 7.33	$3.8 \times 10^{-}5$
CSP	52.32 ± 4.65	57.34 ± 9.57	$5.05 \times 10^{-}5$	$88.52\pm$ 5.65	$82.62\pm$ 8.55	0.002
BP	52.27 ± 5.91	61.35 ± 8.55	0.05	85.05 ± 3.36	77.08 ± 9.58	$7.79 \times 10^{-}4$

Abbreviation: Acc., Accuracy, SD, standard deviation.

Table 4.4.: Correlation between the Fugl-Meyer scores of the patients and their BCI accuracies obtained using either contralesional, ipsilesional, or bilateral channels using three different BCI feature extraction methods.

Feature extraction	Contralesional channels		Ipsilesional channels		bilateral channels	
	Kendall's Tau	p-value	Kendall's Tau	p-value	Kendall's Tau	p-value
FBCSP	0.057	0.415	0.09	0.199	0.089	0.211
CSP	0.042	0.551	0.093	0.181	0.115	0.92
BP	0.055	0.429	0.1	0.15	0.23	0.67

Table 4.5.: Comparison of the Fugl-Meyer scores between those with the ipsilesional BCI accuracy below 60% and those with the ipsilesional BCI accuracy over 80%, obtained using three different BCI feature extraction methods.

	Ipsilesional Acc.<60%	Ipsilesional Acc. >80%	
Feature Extraction	FMA score	FMA score	p-value
FBCSP	16.28 ± 16.16	29.57 ± 13.84	0.016
CSP	18.68 ± 14.24	32.54 ± 15.88	0.015
BP	19.77 ± 10.96	30.33 ± 13.69	0.047

Abbreviation: FMA, Fugl-Meyer Assessment; Acc., Accuracy.

Table 4.6.: Correlation between the time since stroke and the obtained BCI accuracy using contralesional, ipsilesional, or bilateral channels with three different BCI feature extraction methods.

Feature extraction	Contralesional channels		Ipsilesional channels		Bilateral channels	
	Kendall's Tau	p-value	Kendall's Tau	p-value	Kendall's Tau	p-value
FBCSP	-0.03	0.691	0.022	0.771	-0.014	0.85
CSP	-0.009	0.897	0.086	0.252	-0.046	0.542
BP	0.1	0.19	-0.037	0.622	0.09	0.431

4.4 Discussion

Many studies showed that in a healthy human, movement of the hand leads to an increased activation in the contralateral motor cortex and a decrease in activation of the ipsilateral motor cortex when compared to the resting state[59]. Although the capacity of modulating ipsilesional brain activity reduces where the damage on the ipsilesional hemisphere is more severe [162], several BCI clinical studies have shown that many stroke patients are still able to control BCI using EEG signals recorded over the ipsilesional hemisphere[64, 136]. Furthermore, a functional imaging study indicated that the ipsilesional hemisphere participated during the motor tasks [163]. This might be because surviving neurons in the ipsilesional cortex are activated during motor tasks [164].
Interestingly, after stroke undamaged parts of the brain play an adaptive compensatory role, such that movement of the stroke-affected hand may cause an increase in activation of the contralesional motor cortex [165]. Motor attempts and motor imagery are commonly used for stroke recovery using BCI. Brain activation vary among different motor tasks. Tasks involving motor imagery, increased motor impairment was reported to be associated with stronger ERD in the contralesional hemisphere [166]. However, the tasks involving motor attempt ,were associated with higher hemispheric asymmetry in ERS [166]. Nevertheless, people who make good recovery in hand function after a stroke often show

relatively normal task-related brain activation in both hemispheres when performing these motor tasks [167].

It is important to mention that motor execution and motor imagery are complex tasks, involving changes in activity of different parts of the brain including prefrontal, sensory and motor cortex[168]. Prefrontal cortex plays an important role in preparation and planning of movement[169]. Similarly, it is shown that the parietal cortex is involved in high-level cognitive aspects of action control [170]. Stroke often induces widespread brain functional changes and connectivity alterations (Appendix Figure B.1 presents examples of the inter-subject variability in brain activation during motor imagery for six stroke patients) [60]. Recent studies observed that motor function recovery in stroke involves not only the corticospinal system but also prefrontal and precortex [168, 169]. Thus, the most desirable BCI system for rehabilitation may require the use of a combination of brain signals from the frontal, central and parietal cortex as the BCI control signal.

This study investigated the ability of stroke patients to control the BCI using EEG activity of the contralesional hemisphere. Our results suggest that ERD/ERS phenomenon does occur in both the contralesional and ipsilesional hemispheres. This is further confirming the findings of Antelis et al. [140], which suggest that the contralesional hemisphere is also involved during the motor imagery of the affected hand.

In addition, the present study finds that the majority of stroke patients are able to operate the BCI using either their contralesional or ipsilesional hemisphere. By comparing the BCI accuracy obtained from the contralesional and ipsilesional hemisphere, we found that patients with the ipsilesional BCI accuracy less than 60% had significantly more motor impairment compared to those with the ipsilesional BCI accuracy greater than 80%. Interestingly, those who achieved the ipsilesional BCI accuracy below 60% achieved a significantly higher contralesional BCI accuracy. Conversely, those who achieved the ipsilesional BCI accuracy greater than 80% had a significantly lower contralesional BCI accuracy. These findings are consistent with previous studies, which indicated that more impaired patients had stronger neural modulations in the contralesional hemisphere than less impaired patients during motor imagery of the affected hand [139–141].

4.5 Conclusion

This chapter seems to suggest that the use of ipsilesional BCI may lead to a lower BCI accuracy in those patients with severe impairment which offers the use of contralesional BCI as a viable alternative. That being said, future works may include randomized control clinical studies comparing the effects of contralesional and ipsilesional BCI on improving motor function after stroke.

It is important to mention that BCI-based upper limb stroke rehabilitation also faces several challenges. The equipment used is bulky, expensive, and technically complex, requiring precise placement of numerous electrodes. As a result, it is mainly confined to hospitals or labs, which can be difficult for stroke patients with mobility problems who need frequent rehabilitation visits.

Moreover, the calibration process before each use can be time-consuming, often taking up to 20 minutes. These factors collectively hinder the widespread adoption of BCI-based rehabilitation technology in real-world settings. Therefore, the next chapter is going to address these challenges by developing a novel telerehabilitation system, called Tele BCI-FES, that combines BCI and FES technologies for the rehabilitation of upper limb function after a stroke.

The proposed system is portable and offers patients the ability to receive therapy remotely from their homes while still providing supervised therapy and the ability to make adjustments in real-time. Finally, the feasibility and acceptability of the proposed system are validated by conducting a clinical trial.

5

A clinical trial evaluating the acceptability and feasibility of brain-computer interface for upper-limb telerehabilitation after stroke

5.1 Chapter Introduction

Among 1.2 million stroke survivors in the UK, 77% experience upper limb weakness, of which 66% experience weakness beyond 6 months [171]. Upper limb motor impairments are common among stroke survivors and are associated with an increased risk of falling, dependency on care, and reduced quality of life [4, 172]. The annual financial burden of the stroke in the UK is around £25.6 bn, and that amount is predicted to increase significantly over the next 20 years [173, 174]. Therefore, there is an urgent need to develop a more effective and efficient rehabilitation techniques in order to reduce the disabling effects of stroke. Currently, available rehabilitation methods focus on assisting in recovery within the first few months after the stroke. These methods include the use of constraint induced movement therapy and functional electrical stimulation (FES)-based therapies as well as robotic based therapies [37, 94]. These therapies are mostly passive, requiring little to no effort from the patient themselves, and/or require intensive intervention from therapists.

Brain-computer interface (BCI) can be combined with available therapies to make them active where the movement of the impaired limb is directed by the patient's thoughts [111]. This active participation enhances neuroplasticity in stroke patients [90]. Recent clinical trials, including our meta-analysis, showed the superior efficacy of BCI in improving upper-limb motor function compared to other traditional rehabilitation approaches, for both patients in sub-acute and chronic stroke patients [105, 111].

Although the results from these studies are promising there are still a number of limitations with the technology. One primary issue is that the equipment used for BCI based rehabilitation is bulky, expensive, technically complex, and requires careful placement of numerous electrodes. As a result, the BCI based rehabilitation process is currently limited to hospitals or labs due to these hardware constraints, which can also create additional challenges. The need to travel frequently to the hospital for receiving rehabilitation can be challenging for stroke patients with mobility problems. Another issue that limits the real-world application of this technology is the calibration time required by a BCI for training before each use [175]. In some cases, it can take up to 20 minutes to calibrate the BCI before rehabilitation starts [41].

Therefore, the objective of this study is to develop a novel BCI system that is both feasible and appealing for stroke survivors to utilize in home-based rehabilitation. To achieve this, a novel portable BCI system has been developed, specifically designed for stroke rehabilitation. This system enables patients to conveniently use it in the comfort of their own homes while receiving remote supervision through the internet when required.

The BCI system classifies the EEG signals collected from the patient and identifies when the patient is attempting to move their weakened hand or staying still. When the BCI detects EEG signals associated with attempted movement, it activates a functional electrical stimulation system to provide assistance with the movement.

In short, the study objectives are:

- To assess if the patients can use the Tele BCI-FES system at home for post-stroke upper limb rehabilitation.
- To assess the patient's perspective about the use of the Tele BCI-FES device for home-based arm rehabilitation

The data from this study will be utilized to enhance the design of the Tele BCI-FES system and facilitate a larger clinical study.

5.2 Methods and Materials

5.2.1 Tele BCI-FES System Design

To complete this study it was necessary to create a novel system of hardware and software that was portable and easy to set up so that the participants could set it up at their homes. All attempts were made to ensure that the device is very user-friendly. Multiple Patient Public Involvement (PPI) sessions were conducted with individuals undergoing upper limb rehabilitation after a stroke. These sessions were aimed at gathering valuable feedback and suggestions from the patients themselves regarding the necessary improvements for the system. The final Tele BCI-FES components are shown in Figures 5.1 and 5.2.

During the experiment, a Dell laptop model Latitude 5420 was used as the platform for presenting instructions and providing feedback to the participant. The laptop had remote access and remote control computer software installed, which enabled the patient to communicate with the physiotherapist and/or researcher during the rehabilitation session. This software also allowed the researcher and/or physiotherapist to monitor the quality of the signals recorded from Tele BCI-FES and make adjustments to the parameters of Tele BCI-FES if necessary. Furthermore, the laptop was utilized for preprocessing and classifying the EEG signals collected by the EEG system. The selected EEG system for data collection was the Neuroelectrics ENOBIO 8, which captured signals from eight channels using gel-filled electrodes that were secured within a cap. This EEG system was selected for its compact size, ease of set up and adaptability, with the location of the electrodes being personalized for each of the participants. The FES device was the Odstock OML XL pace unit which is currently used by the NHS England and is recommended by the National Institute for Health and Care Excellence (NICE). To facilitate communication between the laptop and the FES stimulator, a control box was designed and created. The control box incorporates an Arduino programmed to replicate the signal typically transmitted to the FES through a foot switch. By replicating this signal, the laptop can safely activate the FES.

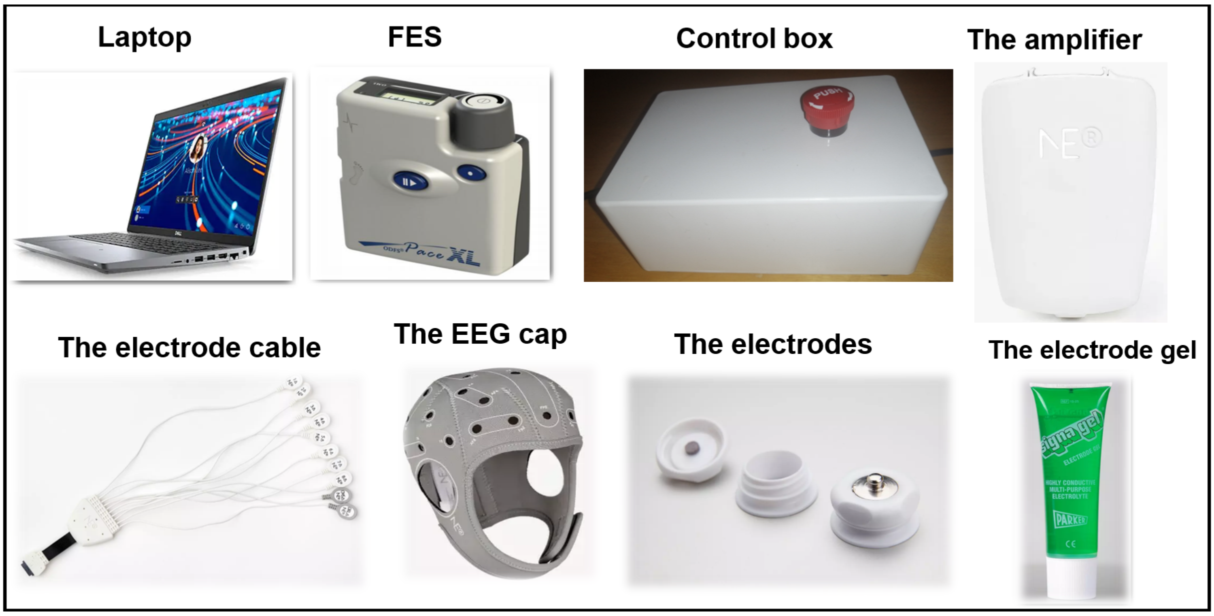


Figure 5.1.: This figure shows the Tele BCI-FES equipment that the participants used at home which included a latitude 5420 dell laptop, an Odstock ODFS® Pace XL FES unit, a control box, an ENOBIO8 EEG amplifier with Electrode lead, EEG cap with electrodes and a bottle of electrode gel used during the study.

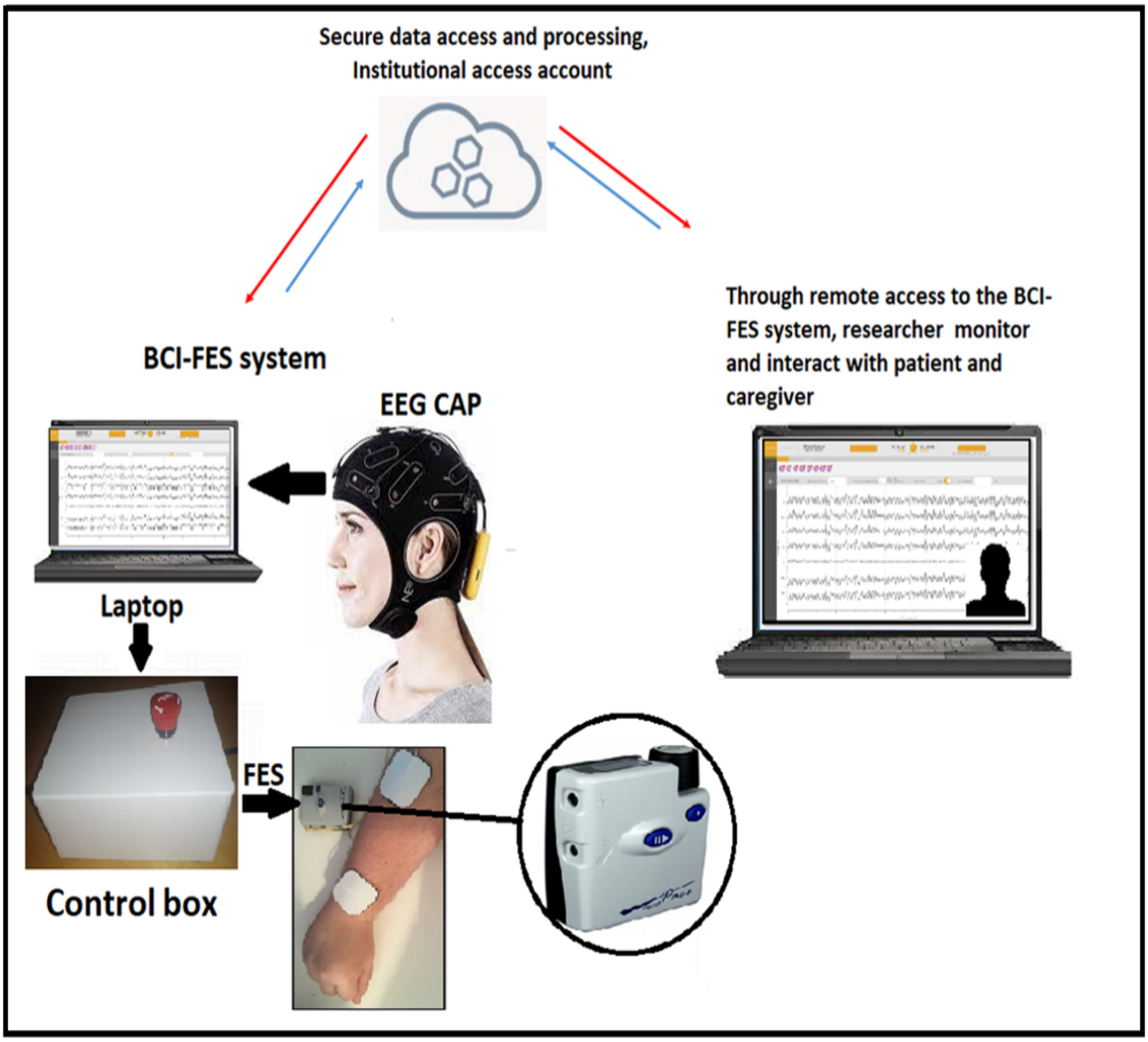


Figure 5.2.: The proposed Tele BCI-FES system for upper-limb stroke rehabilitation. The control box is equipped with an emergency button that instantly halts the system in case of any emergencies. Additionally, an Arduino board is used in the control box to receive commands from the laptop and send them to activate the FES device.

5.2.2 Tele BCI-FES single-arm clinical trial Design

Ethics statement and consent to participate

Ethics committee approval for this study was obtained from the NHS North of Scotland Research Ethics Service (REC reference: 22/NS/0018 and IRAS project ID: 305929). We applied to the Scottish ethics committee because the earliest available slot was there, allowing us to begin our research without unnecessary delays. This clinical study is registered at clinicaltrials.gov under the study identifier (NCT05215522) and registered with the ISRCTN registry (ISRCTN42991002). Every participant in the study provided written consent to participate after receiving comprehensive information about the research.

Inclusion and exclusion criteria

The study involved participants aged 18 and older who had experienced an ischemic or hemorrhagic stroke at least 6 months ago. These participants had residual arm weakness resulting from the stroke, affecting their ability to perform daily activities. Other inclusion criteria were a Fugl-Meyer score of upper limb less than 45, Cognitive and linguistic capacities to comprehend and take part in the study procedure, and having a caregiver who is willing to help deliver the Tele BCI-FES intervention. Furthermore, we included only participants capable of remaining seated for one hour with or without support, and those able to provide consent and understand instructions.

The exclusion criteria for selecting participants were as follows: Cognitive limitations that could hinder the capacity to adhere to the experimental protocol or give informed consent; dermatological, rheumatologic or orthopaedic illnesses of the affected arm interfering with movement of the elbow, history of epilepsy, having pacemaker or any other electrical implanted devices, pregnancy, severe dystonia/spasm. Moreover, those who were unable to perform the baseline assessments or achieve a baseline BCI accuracy below the chance level (i.e. 58%) were excluded from the study. Participants were also excluded if they previously participated in other upper limb rehabilitation studies.

Screening session

The clinical team distributed the patient information sheet to stroke patients attending the outpatient or Functional Electrical Stimulation clinic at Sheffield Teaching Hospitals. Patients who expressed interest in participating and provided consent underwent an eligibility screening process. Eligible patients were then invited to the University of Sheffield for their initial visit, where their eligibility was re-assessed and functional assessments were conducted. The optimal electrode location and stimulation intensity for the FES were determined for each participant. Finally, the BCI system was explained to them, and a calibration session with the BCI system was conducted.

BCI calibration: In the BCI calibration session, participants were instructed on how to set up and clean the EEG system. In addition, EEG signals were collected from the participants to assess the system's accuracy. During BCI calibration, 20 channels were used to collect EEG signals, as shown in figure 5.3.

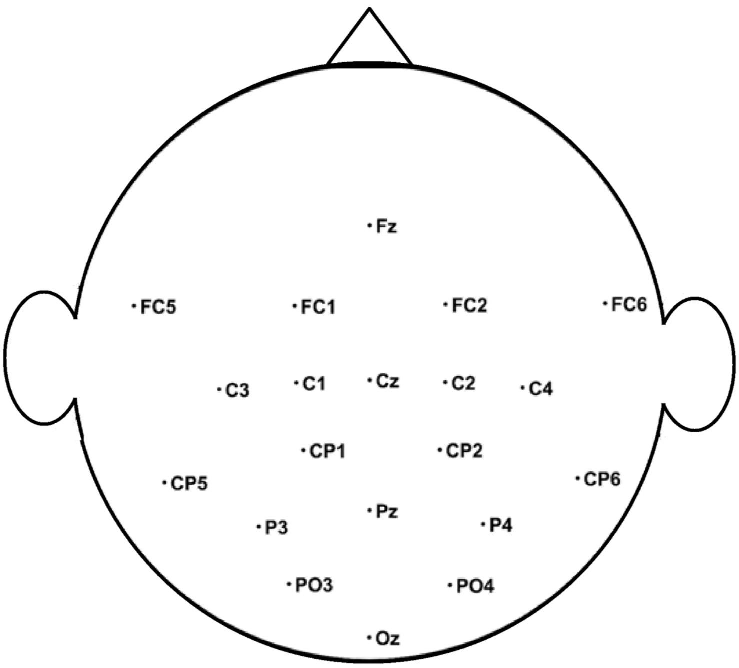


Figure 5.3.: The figure shows the position of 20 channels that were used for BCI calibration session.

The participants were instructed to attempt to extend their weakened hand with their fingers and wrist upwards so that the palm was facing forward and the fingers upwards. Those unable to produce any movement were asked to try to focus on this movement and imagine their hand moving. The BCI calibration session consisted of 5 runs, where each run had 11 trials of the attempt movement task and 11 trials of the staying still in random order. As shown in figure 5.4, for runs one to four each trial lasted 10 seconds, consisting of a two-second ready period following a beep, four seconds of either attempted movement or staying still, and four seconds of rest. On the fifth run, the FES was activated for the trials that the participants attempted to move their weakened hands, increasing the trial length to 18 seconds. Indeed, the fifth run gave the participants the chance to familiarize themselves with the FES activation. After each run, a break was given to the participants. On average, the BCI calibration session lasted about an hour, including the cap set up, demonstration of the equipment, collection of the EEG, and breaks.

After the EEG was collected it was used to train the BCI model and evaluate the participant's ability to control the BCI. The extracted EEG data were filtered using a zero-phase band-pass filter from 8 to 13 Hz. Zero-phase filter was used in EEG data filtering to prevent phase distortion, ensuring the accurate temporal representation of neural events [176]. Then the BCI features were extracted using a common spatial patterns (CSP) algorithm. Next, the extracted features were classified using a linear discriminant analysis (LDA) classier. LDA was chosen for our Tele-BCI-FES system due to its frequent use in BCI based rehabilitation, as it is more suitable for online BCI intervention with reduced computational costs during the calibration and validation stages [42, 43, 177].

The classifier outcomes were objectively evaluated using 10 runs $\times$ 10-fold cross-validation.

Following the classification of the EEG data from 20 channels, the best eight electrodes were obtained. Participants with a BCI classification accuracy greater than 58% were then offered a 3-week home-based rehabilitation using Tele BCI-FES system.

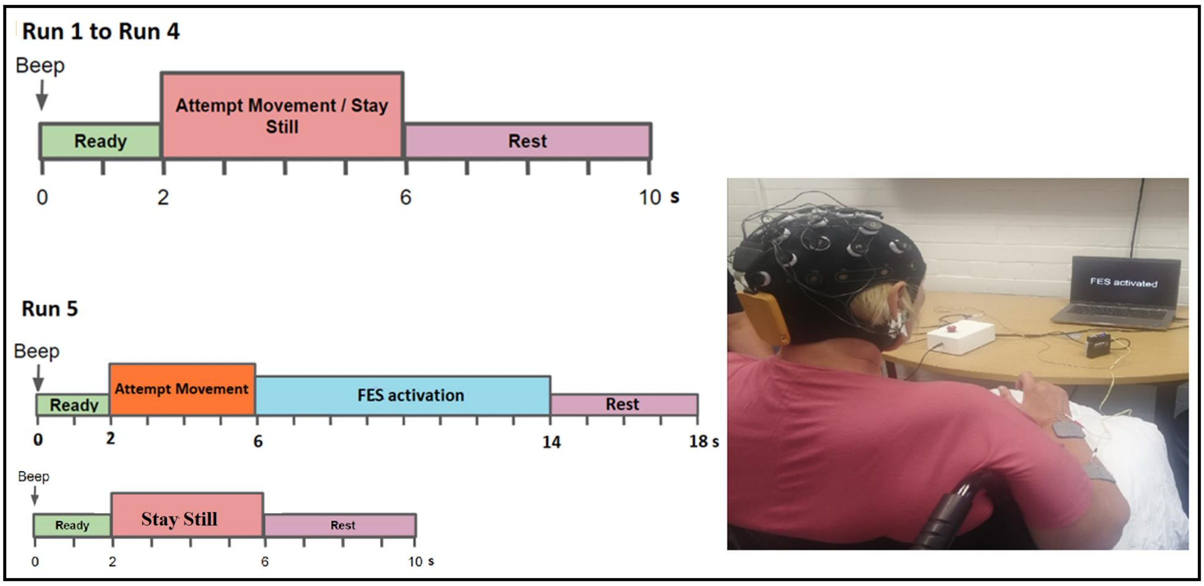


Figure 5.4.: Timing of the trials for the 5 runs of the BCI calibration session. The FES activates to produce hand movement when the participant is instructed to try to move their weakened hand during the final run (i.e, run 5).

Home sessions

Enrolled participants were provided with a Tele-BCI FES system at the end of the screening session to take home with them. This kit included all the BCI and FES equipment required to conduct the intervention at home, as shown in figure 5.1. In addition to the equipment, the participant was given instructions on the set-up of the EEG and FES, investigator contact details, a remote meeting schedule, and a custom EEG electrode location map.

Throughout this study, 10 remote sessions, each lasting one hour were scheduled. The first one was for practicing and making sure the participant and their caregiver are comfortable in setting up and using the Tele BCI-FES system. The next 9 sessions (3 sessions per week) consisted of 10 minutes of preparation (instructions, setup/calibration time), 40 minutes of Tele BCI-FES rehabilitation, a

5-minute patient interview on their experience with the session, and a 5-minute interview on experiencing any adverse effects and general health check.

During the home sessions, participants, with the assistance of their carer and remote guidance from the researchers, completed the system setup, which involved the following steps:

- Powering on the laptop.
- Connecting the EEG amplifier and control box to the laptop.
- Connecting the FES to the control box.
- Applying the FES electrodes to the arm with the guidance of a remote physiotherapist.
- Placing the electrodes in the EEG cap.
- Applying the provided gel to the electrodes and wearing the EEG cap.

The setup process was initially demonstrated during the screening session. Once the laptop was turned on, the researcher/physiotherapist were available remotely to provide guidance and support with the setup. Using the Team Viewer, a remote access software, the researcher was able to remotely access and control the laptop to configure the necessary software and initiate a video call. Before proceeding with the Tele BCI-FES intervention, a brief checklist was completed to ensure the participant had not experienced any adverse reactions since the previous session and was comfortable continuing with the study.

After ensuring the proper setup and connection of the system, the participant engaged in a remote rehabilitation session under the remote supervision of the physiotherapist. During this session, the FES was activated by the BCI whenever an attempted movement was detected. The home rehabilitation session lasted approximately 45 minutes, consisting of five runs. Each run mirrored the structure of the fifth run from the screening session, followed by a break.At the end of each home session, the participant was asked to fill a brief quantitative questionnaire to report their perception of the Tele BCI-FES system at that session. Please see section 5.2.3 for more details.

Final Assessment Session

After completing the home sessions, participants and their carers were invited to the University of Sheffield for a comprehensive post-assessment. This assessment included repeating the motor function evaluations conducted at screening to quantitatively measure the extent of hand function improvement achieved after the Tele-BCI-FES interventions. Following the post-assessment, in-depth qualitative interviews were conducted with participants and their carers. The interviews aimed to explore their experiences and perceptions regarding the use of the Tele-BCI-FES system.

5.2.3 Primary Outcomes

Recruitment and retention rates

Recruitment and retention rates were calculated to evaluate the success of the study in attracting and retaining participants [178]. The recruitment rate indicates the percentage of individuals who were approached to participate in the study and agreed to do so, while the retention rate represents the proportion of participants who completed the study in relation to the initial number of participants who enrolled. Study completion was considered as completing at least seven out of nine Tele BCI-FES home sessions.

Patients' participation rate

Patients' participation rate in the remote therapy sessions was assessed through the number of sessions they agreed to attend within a set period and using Pittsburgh Rehabilitation Participation Scale (PRPS) [179]. PRPS is scored on a 6-point scale that takes into account the patient's engagement in therapy (1: none- patient refused entire session to 6: excellent- patient participated in all activities of the session). This score was provided by the researcher and physiotherapist at the end of each session.

Participants Perception on adoption of technology

In order to evaluate the system's feasibility and acceptability, cumulative questionnaires were collected after each session. A in-depth final questionnaire was conducted face to face when the participants returned to have their final functional assessment. The questionnaires specifically focused on the participants' and carers' experiences during the session, including the setup process, adherence to instructions, quality of supervision, and perceived effectiveness of the rehabilitation session. The participant and carer were asked to rate these experiences on a scale of 1 to 5 (where 1 is very difficult, 2 difficult, 3 normal, 4 easy, and 5 very easy), the patient answered the following questions:

1. How difficult or easy did the carer find the Tele BCI-FES equipment setup?
2. How difficult or easy was to communicate with the remote connection system?
3. How difficult or easy did you find the use of the Tele BCI-FES device for rehabilitation?

4. How easy or difficult did you find wearing the Tele BCI-FES equipment?

The participants were also asked if they would recommend the Tele BCI-FES system to other patients with stroke. In addition, they were asked whether there is anything about the Tele BCI-FES system that they believe needs to be improved.

5.2.4 Secondary Outcomes (Functional Assessment)

We conducted the functional assessments both before and after the Tele BCI-FES intervention, using the upper extremity section of the Fugl-Meyer assessment (FMA_UE) [180]. This assessment assigns a numerical score to a patient's motor function and can be used to measure changes in their motor function and to evaluate the effectiveness of the intervention. The FMA_UE score ranges from 0 to 66, with lower scores indicating greater impairment in upper limb function.
The Leeds Arm Spasticity Impact Scale (LASIS) were also employed to assess passive arm function in subjects who had spasticity and little to no active upper extremity movement [181, 182]. The LASIS consists of 12 items that assess passive and low-level active function. Items are evaluated from 0 to 4 (0 indicates no difficulty; 1 indicates slight difficulty; 2 indicates a moderate level of difficulty; 3 indicates extreme difficulty; and 4 indicates an inability to carry out the activity). It may be worth mentioning that in our selection of LASIS) as functional assessment tool over the Modified Ashworth Scale (MAS), we considered the LASIS's ability to comprehensively evaluate the impact of spasticity on daily functional tasks [182, 183]. While the MAS is widely used for assessing abnormal tone and resistance to passive movements in patients with neurological conditions, it does not provide a complete view of how spasticity affects daily activities [184, 185].
Finally, the Numerical Rating Scale (NRS) was completed by each participant. On a scale of 0 (no pain) to 10 (severe pain), participants were asked to rate their level of pain using NRS scale [186].

5.2.5 Statistical Analysis

In this study, we used a paired one-tailed t-test to assess the significance of changes in outcome measures between the post-intervention and the screening session. The rationale for choosing a one-tailed test over a two-tailed test was based on our specific research hypothesis, which aims to explore the effectiveness of the proposed system in improving upper extremity recovery. Since our hypothesis predicted a directional improvement (i.e., post-intervention scores would be higher than the screening scores), a one-tailed test is appropriate for detecting this specific directional effect with greater statistical power [187]. Data analysis was carried out using MATLAB, with a significance level of $p = 0.05$. Based on the inverse binomial distribution function, a chance performance of 110 calibration BCI trials has a 99% confidence level of approximately 58%. Therefore, participants with a BCI accuracy of less than 58% in the calibration session were considered to be at chance level and were excluded from the study [154].

5.3 Results

Figure 5.5 presents a flow chart of the Tele BCI-FES study, from enrollment to analysis.

5.3.1 Participant Characteristics

Nine participants attended the screening session and had their eligibility for participation assessed. Eight of these participants continued to complete the home sessions while one participant was excluded from the study because their BCI accuracy was below the chance level. Seven participants completed the

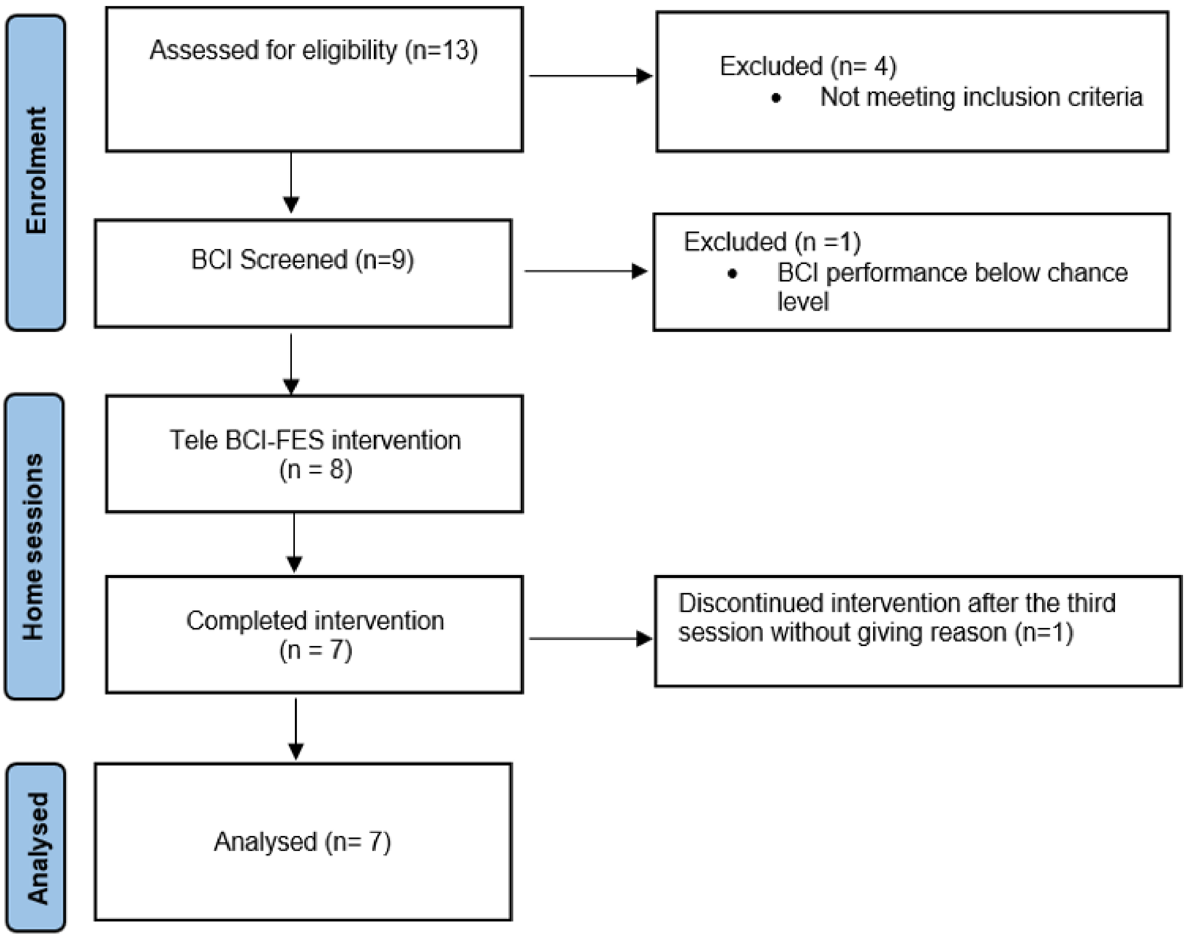


Figure 5.5.: Flow chart of the study from enrollment to analysis.

study, while one participant decided to withdraw from the study after attending three sessions (see figure5.5). The demographic information for each participant who participated in this study is shown in Table 5.1. One participant (P03) had to stop early after seven sessions due to health problems unrelated to the intervention and the final face-to-face session was delayed by three weeks due to illness. Another participant (P05) received botulinum toxin treatment before the start of the study and was therefore not included in the motor functional assessment as the botulinum toxin affect on motor function changes over the time. The average age of the group was 52.43 years, with a range of 29 to 73, and it consisted of four men and three women. The average length of the stroke was 66.14 months, with a range of 10 to 160. Throughout the study, there were no serious adverse events or increases in pain related to the intervention.

Table 5.1.: Participants' demographic information, recorded in the screening session

ID	Gender	Age (years)	Paretic Side	Stroke onset (Months ago)
P01	Female	51	Right	10
P02	Male	33	Left	14
P03	Male	72	Right	144
P04	Female	52	Right	36
P05	Female	57	Left	75
P06	Male	73	Right	160
P07	Male	29	Right	24

5.3.2 Primary Outcomes

Recruitment and retention rates

Fifteen stroke patients were invited to participate in the study, of which thirteen agreed to take part, resulting in a recruitment rate of 86.7%. In total, eight stroke survivors were included in the study, and the retention rate was 87.5%, with seven participants successfully completing at least seven out of nine Tele-BCI FES home sessions. Only one participant withdrew from the study for unknown reasons.

Participation Rate of Patients in Tele BCI-FES Rehabilitation

The results of the study showed that the participation rate of the patients in the proposed Tele BCI-FES rehabilitation was excellent, as assessed by the PRPS. Six out of seven participants attended all nine Tele BCI-FES home sessions, while one participant (P03) attended seven Tele BCI-FES sessions due to illness. The mean PRPS score for the participants was 5.8 out of 6, which indicates a high level of participation [188]. This indicates that the patients were highly engaged in the telerehabilitation program.

Participants' Perception on Adoption of the Technology

Based on the feedback received throughout the experiment, participants generally had a positive experience with the ease of setting up and cleaning the BCI system. In the final qualitative interview, conducted in the final assessment session, one participant mentioned finding the equipment cleaning process tedious, while two others had no issues, and the remaining participants did not comment on it. The main complaint raised by three participants during the final interview was about the electrodes, which they found to be somewhat fiddly to use. While they managed to set up the system, they faced some difficulty inserting and removing the electrodes from the cap. This feedback highlighted a potential issue for improvement going forward. Interestingly, upon examining Figure 5.6.a, it becomes evident that by the final session, participants' responses are centered between "easy" and "very easy" on average. This suggests that despite initial struggles, the majority of participants found the setup process to be moderately easy by the end of the study.

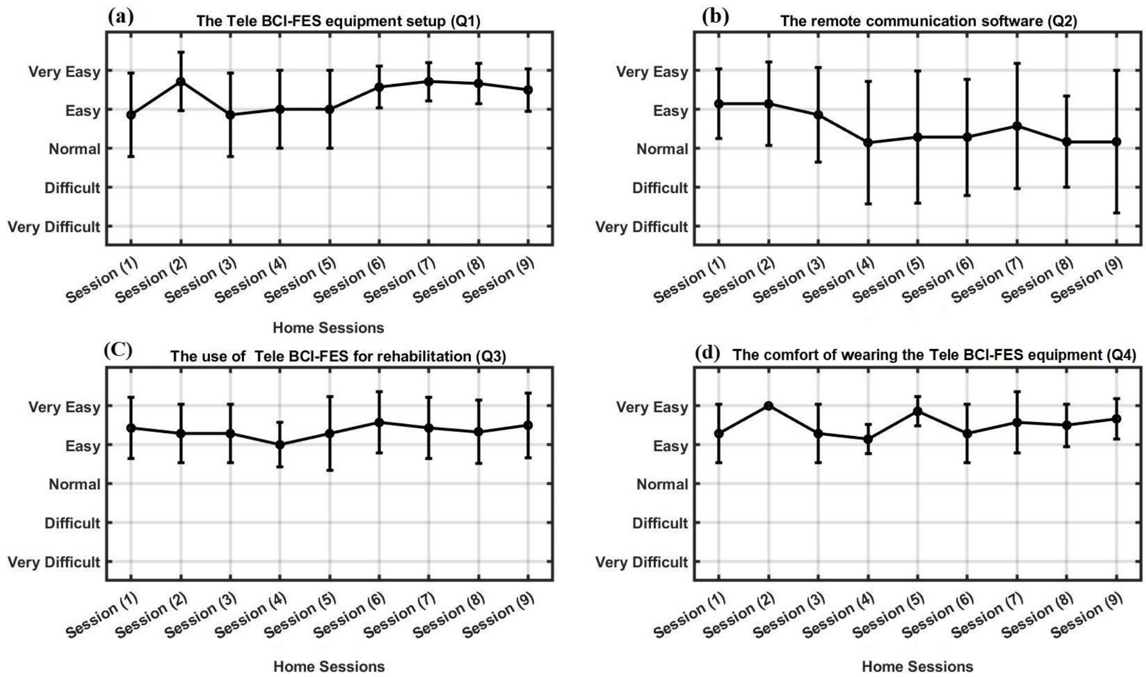


Figure 5.6.: The line plot with error bars, presents the average responses obtained from quantitative interviews conducted with the seven participants during the nine Home-based Tele BCI-FES sessions. Subplots a, b, c and d are displaying the participants' responses to the questions 1, 2, 3 and 4 respectively.

During the trial period, the effectiveness of the remote supervision provided was generally well received by participants. Overall, the majority of participants found the remote supervision to be effective in facilitating the sessions. However, it is worth noting that there were occasional issues with the remote communication software, particularly related to sound problems. These technical issues resulted in disruptions during some sessions, impacting the overall user experience. To mitigate the sound issues, research team resorted to using phones for communication with the participants as an alternative method. This solution proved to be effective, enabling uninterrupted communication during the sessions. Despite this workaround, it was observed that the sessions affected by sound problems received lower scores, as indicated in Figure 5.6.b.

In addition to technical challenges, only two participants provided specific suggestions for improvement. They expressed concerns about the low volume of the beeps used during the sessions. One participant also mentioned that the initial video screen size was too small for their preference.

Based on the data presented in Figure 5.6.c, feedback about the ease of using the system for rehabilitation was generally positive. Participants found the instructions easy to follow and highly effective. One participant recommended adding some form of gamification, as they found the system monotonous over time, while two others appreciated the simplicity of the text, finding the lack of distractions beneficial.

When asked about the ease of wearing and comfort of the system, the primary issue raised by participants was the use of gel in the electrodes. One participant expressed being uncertain about using the system in the long term due to the gel, while two others stated they would be happy to use a few times per week, but a daily usage would be problematic due to the use of EEG gel. Cleaning out the gel took a while, especially for more disabled participants who needed assistance with showering. Some participants arranged their sessions for early morning or evening to allow time for cleaning. The EEG cap was only provided in three sizes, i.e. small, medium and large, as these were the only options available from the manufacturer. As a result, two participants expressed concerns about the limited variation in cap sizes available, with one participant experiencing a slightly tight cap and two others facing a slightly loose cap. However, except for one participant whose cap became tight in later sessions due to their hair growing, most found the equipment comfortable to wear (Figure 5.6.d).

Participants provided valuable feedback regarding potential improvements for the system, including implementing distinct beeps for different commands, incorporating a progress bar, and using dry electrodes. They also expressed a desire for more comprehensive information about brainwaves and BCI, as well as schematic diagrams to simplify the setup process.

Overall, both participants and caregivers showed motivation to continue using the Tele BCI-FES system, considering it worthwhile despite the additional setup requirements. Encouragingly, they also expressed a willingness to recommend it to other stroke patients. However, certain aspects of the system, particularly the gel and the complexity of the setup process, should be addressed to enhance the overall user experience.

5.3.3 Secondary Outcomes (Functional Assessment)

Table 5.2 and figure 5.7 show the FMA_UE and LASIS scores before and after the intervention for 6 out of 7 participants. One participant (P05) was not included in the functional assessment due to having received botulinum toxin treatment prior to the study. On average, there was a significant improvement in FMA_UE scores after intervention (mean = 23.33, $p = 0.032$) compared to pre-intervention (mean = 19.50). Hence, the differences between FMA_UE scores before and after the intervention was 3.83 points.

In terms of individual FMA_UE score, P01, P02 and P03 achieved the highest increase in FMA_UE score (9, 4, 6 points respectively). The FMA_UE scores of the remaining participants increased slightly by 2 points for P04 and by 1 point for both P06 and P07. The high standard deviation of both pre and post measurements ($\pm$ 12.44 and $\pm$ 12.97 respectively) suggests a large variability in the FMA_UE scores among participants. However, the statistical significance of the results (p=0.032) highlights the overall positive effect of the Tele BCI-FES intervention on the FMA_UE score.

For the LASIS score, the mean value measured before the intervention was 27.83, while the mean value measured after the intervention was 27.17, indicating that spasticity as assessed by LASIS improved slightly after the intervention ($p=0.80$). Notably, certain individuals (P01, P03, P04) experienced positive changes in their arm movement, including heightened awareness, enhanced stability, and increased mobility in the shoulder, elbow, and fingers. Moreover, the system enabled easier nail cutting, improved grip and release, and enhanced passive movement (P04).

It is important to emphasize that the primary focus of this study was to assess the acceptability and feasibility of the Tele BCI-FES rehabilitation approach. Given the limited number of sessions (9) provided in this study compared to other BCI rehabilitation studies which typically involved 18 to 20 sessions, significant functional improvements were not anticipated. Furthermore, it should be noted that no follow-up assessments were conducted in the weeks following the conclusion of the intervention.

Table 5.2.: Clinical scores for 6 participants

ID	FMA_UE		LASIS	
	Pre	Post	Pre	Post
P01	12	21	28	25
P02	17	21	35	31
P03	37	43	18	22
P04	8	10	33	25
P06	10	11	30	39
P07	33	34	23	21
Mean	19.50	23.33	27.83	27.17
$\pm$ **Std**	12.44	12.97	6.37	6.76

P05 was administered botulinum toxin treatment prior to the study, which resulted in her exclusion from the functional assessment.

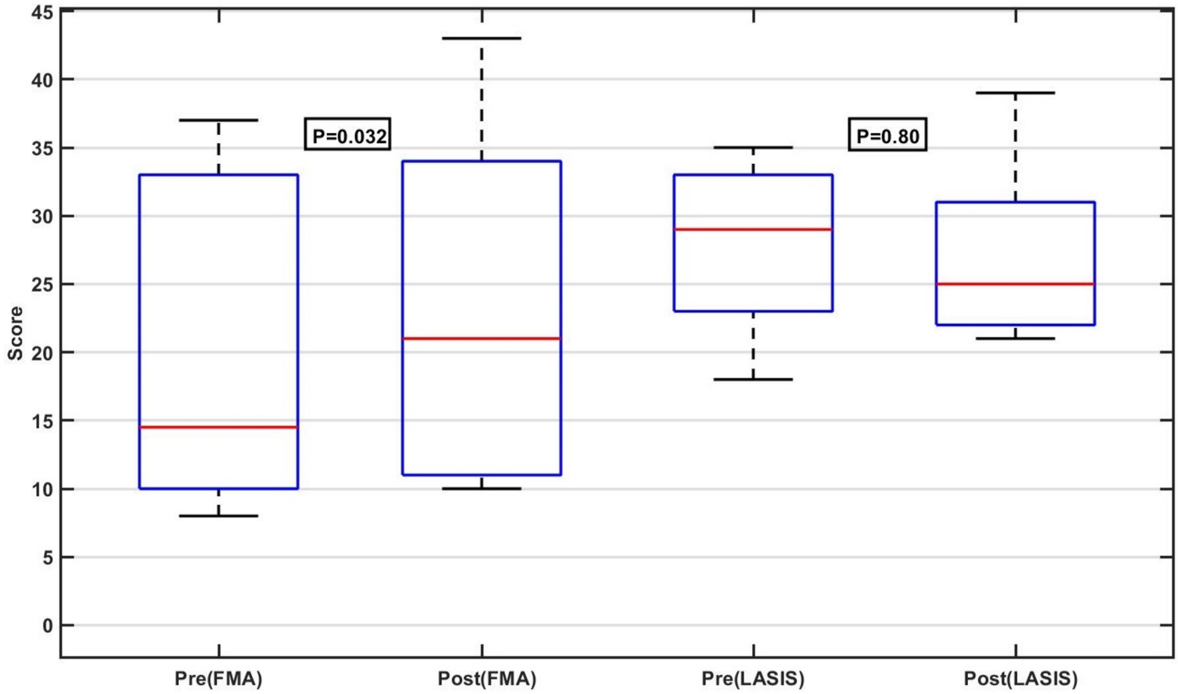


Figure 5.7.: The box-plot shows average (Pre-Post) FMA_UE and LASIS scores of 6 stroke patients

5.4 Discussion

The present study aimed to investigate the feasibility and acceptability of a novel Tele BCI-FES system for upper limb rehabilitation in individuals with stroke. In this study, seven participants with chronic stroke completed a home-based Tele BCI-FES intervention. The results showed that the system is feasible and safe for use in individuals with stroke, with a high recruitment rate of 86.7% and a retention rate of 87.5%. The participants' feedback suggested that the system is generally acceptable. Moreover, the secondary outcome analysis showed that the Tele BCI-FES intervention resulted in a significant improvement in the FMA_UE score compared to the pre-intervention score. The findings of this study suggest that the proposed Tele BCI-FES system may be a promising tool for upper limb rehabilitation in individuals with stroke.

Interestingly, the high recruitment and retention rates suggest a strong interest in the use of the Tele BCI-FES system as a new rehabilitation tool. This is in line with previous studies that have shown a positive attitude towards the use of technology-assisted interventions and home-based training in stroke rehabilitation [189, 190]. The feedback from the participants suggested that the ease of setup for the BCI system was mixed, with some aspects being manageable while others were tedious or complex, particularly in regards to connecting the electrode cables. However, as seen in figure 5.6, participants reported an increased ease of use and efficiency in setting up the system with each subsequent session. Having said that, these findings highlight the importance of user-centered design in the development of such technologies, with a particular focus on ensuring ease of use and minimizing the burden on the user [191].

When considering the utilization of the Tele BCI-FES system for rehabilitation purposes, participants' feedback highlighted concerns regarding the gel used in the electrodes. In order to address this issue, dry electrodes present themselves as a potentially convenient alternative. Unlike wet electrodes, dry electrodes eliminate the need for conductive gel or saline solution, simplifying the application process and minimizing messiness. However, it is worth noting that dry electrodes may yield lower quality signals compared to wet electrodes, potentially impacting the accuracy of collected data [192, 193]. Additionally, certain designs of dry electrodes, characterized by spiky textures, have been associated with reported pain and discomfort when used for extended periods of time [194].

In terms of functional assessment, one participant (P05) was excluded due to receiving botulinum toxin a few weeks prior to the study. Botulinum toxin treatment can reduce spasticity, which may help improve motor function for a few weeks [195]. Therefore, this improvement in motor function could have affected the results of the assessment. This demonstrates the importance of careful participant selection and consideration of confounding factors when conducting research.

The functional assessment analysis of 6 participants showed a significant improvement in the FMA_UE scores after the Tele BCI-FES intervention, with an average increase of 3.83 points. In addition, the present study demonstrated that the Tele BCI-FES system has the potential to improve motor function in chronic and severe stroke patients, even several years after the stroke (see Table 5.1 and Table 5.2). Importantly, some participants reported some improvements in their arm movement, with increased movement in the shoulder, elbow, and fingers. However, the large variability in FMA_UE scores among participants highlights the need for individualized treatment and the importance of identifying potential factors that may influence treatment response. Future studies should investigate the optimal parameters for Tele BCI-FES interventions, including the intensity, frequency, and duration of the intervention [196].

It is worth noting that the Tele BCI-FES intervention in this study had a relatively short duration, consisting of only nine sessions, which is shorter compared to other lab-based BCI studies such as the study by Sebastian et al. [43] and Miao et al. [42]. Specifically, in the study by Sebastian et al., stroke patients received 25 sessions of BCI-FES intervention in a laboratory setting. Despite the remote and brief intervention period in the study, promising results were obtained, suggesting that even a limited amount of Tele BCI-FES intervention can have a positive impact on upper limb stroke rehabilitation in a home setting. However, further research is needed to determine the optimal duration and frequency of Tele BCI-FES intervention for stroke patients in a home setting. This information could help to guide the development of more effective and efficient rehabilitation protocols, and enhancing patient outcomes.

Overall, these findings add to the body of evidence supporting the growing trend towards home-based medical care by demonstrating the feasibility and acceptability of Tele BCI-FES for upper limb stroke rehabilitation in a home setting [197–199]. These results suggest that home-based care options have the potential to improve outcomes for stroke patients and highlight the need for continued research in this area. By providing access to effective rehabilitation interventions in a familiar and comfortable environment, home-based care may offer a promising alternative to traditional clinic-based rehabilitation, particularly for patients with geographical or mobility constraints.

5.5 Limitations and Improvements

The study's findings are limited by the small sample size, which restricts their generalizability. Further research with larger sample sizes and longer intervention periods is essential to establish the robustness of Tele BCI-FES in enhancing upper extremity recovery. Addressing this limitation was constrained by practical considerations such as fund availability and study feasibility within the allocated time-frame. Additionally, participant selection criteria, including demographics, diversity, and educational levels, could impact accessibility, motivation, and the extent of caregiver support, all of which should be carefully considered in future researcher to better understand the broader applicability of the intervention. The set-up process for the Tele BCI-FES system could also be improved to be more user-friendly for less technically-minded participants. Additional labels or instructions could be provided to help participants navigate the system more easily. Furthermore, an initial in-person session at the participant's house to help set up the equipment and show how it works could be a useful improvement to ensure a smooth and comfortable experience for the participants during the study. The use of none-gel EEG electrodes can be considered in future studies to ensure participants' convenience. However, it's also important to ensure that the electrodes are effective and comfortable for the user to wear.

During the study, it was found that the audio quality using third-party video conferencing software between the research team and participants was not always effective. As a result, the research team sometimes had to resort to using phone calls to communicate with participants. Additionally, a few participants encountered challenges when trying to open the webcam and audio during home sessions due to the small size of the icon. Therefore, it is recommended that alternative video conferencing software and methods be explored in future studies.

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5.6 Conclusion

In summary, the present chapter offers evidence supporting the feasibility and acceptability of the proposed Tele BCI-FES system for upper limb rehabilitation in individuals with chronic stroke. The high recruitment rate suggests patients' interest in the proposed Tele BCI-FES system; however, this observation requires confirmation through studies with larger sample sizes and long-term interventions. Despite suggestions for future improvements, the overall retention rates, ease of use, and positive feedback from participants indicate a strong acceptance of this device. The noteworthy improvement in FMA_UE scores underscores the potential of the Tele BCI-FES system to enhance motor function in chronic and severe stroke patients, even years after the stroke occurred. Nevertheless, further research is required to fine-tune intervention parameters and assess the effectiveness of this technology in larger sample sizes and longer intervention periods.

In conclusion, the findings offer promising evidence for the role of Tele BCI-FES as a valuable tool in stroke rehabilitation.

6

Conclusions

6.1 Key Achievements

This thesis detailed scientific achievements that have added important new knowledge to the discipline of BCI for upper extremity stroke rehabilitation.

1. The thesis successfully conducted a systematic review and meta-analysis and showed that BCI has significant immediate and long-term effects in improving upper-limb motor functions after stroke, compared to conventional therapies. The results supported using intention of movement of the impaired hand as the BCI mental practice, the band power features as the BCI classification features, and the functional electrical stimulation as the BCI feedback in future BCI-based stroke rehabilitation studies.

2. This thesis successfully analyzed EEG datasets of 136 stroke patents with upper limb weakness and showed that contralesional hemisphere can be used to control BCI effectively. Particularly, the thesis showed that this ap-

proach may be used for controlling BCI by those who have a high motor impairment and cannot achieve a meaningful control using their ipsilesional hemisphere.

3. This thesis successfully developed a novel Tele BCI-FES system for stroke rehabilitation that is portable and can be used at the patient's home with only remote supervision. The feasibility and acceptability of the proposed BCI system was confirmed by conducting clinical trial.

The following sections describe these contributions in more details.

6.2 Efficacy of BCI and the Impact of Its Design Characteristics on Post stroke Upper-limb Rehabilitation

The first objective of this research project was to investigate the BCI and its design characteristics' impact on post-stroke upper-limb rehabilitation. Through a comprehensive meta-analysis of 12 clinical trials involving 298 patients, the study successfully demonstrated that BCI has significant and lasting effects on improving upper-limb motor functions compared to conventional therapies.
The results revealed substantial effect sizes, with 0.73 for short-term and 0.33 for long-term improvements, confirming the superiority of BCI interventions. Subgroup analyses provided valuable insights into the role of different BCI designs in treatment outcomes. Notably, employing the "intention of movement" as the BCI mental practice resulted in a significantly higher effect size (Hedge's g = 1.21) compared to "motor imagery" (Hedge's g = 0.55). Moreover, interventions utilizing "band power features" exhibited notably higher effect sizes (Hedge's g = 1.25) than those using "filter bank common spatial patterns features" (Hedge's

g = -0.23). Additionally, using "functional electrical stimulation" as the BCI feedback led to the most substantial effect size (Hedge's g = 1.2) among all other devices studied.

This project has therefore successfully provided robust evidence supporting the effectiveness of BCI for post-stroke upper-limb rehabilitation. The study emphasizes the significance of "band power features," "intention of movement," and "functional electrical stimulation" as pivotal considerations in designing successful BCI interventions for stroke survivors. These findings could serve as valuable guidelines for future BCI designs in upper-limb stroke rehabilitation.

6.2.1 Exploring the ability of stroke survivors in using the contralesional hemisphere to control a BCI

The second objective of this research aimed to investigate the effectiveness of BCI in detecting motor imagery of the affected hand from the contralesional hemisphere in stroke patients. A comprehensive analysis was conducted on a substantial EEG dataset from 136 stroke patients, who performed motor imagery of their impaired hand.

BCI features were extracted from channels covering the ipsilesional, contralesional, or bilateral hemisphere, and the offline BCI accuracy was computed using 10x10-fold cross-validations. The results revealed that most stroke patients could successfully operate the BCI using either their contralesional or ipsilesional hemisphere.

Furthermore, interesting correlations were observed between BCI accuracy and motor impairments. Stroke patients with ipsilesional BCI accuracy below 60% exhibited significantly higher motor impairments compared to those with ipsilesional BCI accuracy above 80%. Interestingly, individuals with ipsilesional BCI accuracy below 60% demonstrated significantly higher contralesional BCI accuracy, while those with ipsilesional BCI accuracy above 80% had notably poorer contralesional BCI accuracy

These findings suggest that contralesional BCI might prove to be a valuable approach for stroke patients with high motor impairments, who may struggle to accurately generate signals from the ipsilesional hemisphere for effective BCI operation.

6.2.2 A clinical trial evaluating the feasibility and acceptability of BCI as telerehabilitation for chronic stroke survivors

The third objective of this research project focused on the development of a novel telerehabilitation system called 'Tele BCI-FES, integrating BCI and FES technologies for poststroke upper limb rehabilitation. This system allows stroke survivors to receive therapy remotely from the comfort of their homes while ensuring supervised therapy and real-time adjustments.

The study involved seven chronic stroke patients and their caregivers, who completed nine home-based Tele BCI-FES sessions (three sessions per week), while receiving remote support from the research team. The primary outcomes were recruitment and retention rates, as well as participants' perceptions of technology adoption. The secondary outcomes assessed upper extremity function improvements using the Fugl-Meyer Assessment for Upper Extremity (FMA_UE) and the Leeds Arm Spasticity Impact Scale (LASIS).

Results indicated high retention (87.5%) and recruitment rates (86.7%), with participants providing mixed feedback on setup ease. However, they gradually found the system easier to use, and the setup process became more efficient with continued sessions. Participants also offered suggestions for enhancing user experience. Following the intervention, there was a significant increase in FMA_UE scores, with an average improvement of 3.83 points ($p = 0.032$).

This project has therefore successfully demonstrated the feasibility and acceptability of the proposed Tele BCI-FES system for upper extremity rehabilitation in stroke survivors.

6.3 Summary

In summary, this thesis makes significant advancements in the understanding and application of BCI in stroke rehabilitation. The findings offer valuable insights for designing effective BCI interventions and tele-rehabilitation approaches. Notably, the novel Tele BCI-FES system holds promise in revolutionizing stroke rehabilitation, expanding stroke patient access to therapy, and ultimately enhancing their quality of life.

6.4 Future works

In future works, a priority will be given to designing a more user-friendly Tele BCI-FES system, considering the valuable feedback from participants in Chapter 5. Additionally, future works may also include:

1. Conducting a clinical trial with a larger and more diverse sample size to validate the effectiveness of the Tele BCI-FES system for upper limb rehabilitation in stroke patients. This would help establish the generalizability of the findings and provide more robust evidence of its clinical efficacy.

2. Extend the intervention period to evaluate the long-term effects of using the Tele BCI-FES system. Assess the sustainability of motor function improvements and the potential for continued progress beyond the initial intervention period.

3. Investigate the use of none-gel EEG electrodes to enhance participant convenience and comfort during the setup and usage of the Tele BCI-FES system. Validate the effectiveness and reliability of these alternative electrodes in acquiring accurate brain signals.

4. Conducting a randomized clinical trials to compare the effectiveness of the Tele BCI-FES system with other innovative rehabilitation technologies, such as virtual reality-based interventions or robot-assisted therapies, to identify the most effective and efficient approach for stroke rehabilitation.

5. Expanding the use of Tele BCI-FES to include lower limb rehabilitation and other acquired brain injuries, such as multiple sclerosis, spinal cord injury, and motor neuron diseases,.

6. Finally, Conducting a randomized clinical trials to compare the effects of contralesional and ipsilesional BCI interventions on improving motor function after stroke.

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A

Appendix: Supplemental Material for Chapter 3

A.1 Equations

We analyzed the data using the comprehensive meta-analysis software CMA https://meta-analysis.com/. The effect size of the intervention, g, for each individual RCT study was calculated using Hedge equation with correction for small studies as follows [121]:

$$g = \left(\frac{\mathrm{M_e} - \mathrm{M_c}}{\mathrm{SD_{pool}}} \right) J, \tag{A.1}$$

where $\mathrm{M_e}$ and $\mathrm{M_c}$ are the mean of changes in FMA-UE scores from pre to post intervention for the experimental group and control group respectively. J is the correction factor, and $\mathrm{SD_{pool}}$ is the pooled standard deviation of changes in

FMA-UE scores of the patients from both groups. J was calculated as [200]

$$J = 1 - \left(\frac{3}{4(\mathrm{n_e} + \mathrm{n_c}) - 9} \right), \tag{A.2}$$

where $\mathrm{n_e}$ and $\mathrm{n_c}$ are number of patients in the experimental and control group respectively. $\mathrm{SD_{pool}}$ was calculated using the following equation:

$$\mathrm{SD_{pool}} = \sqrt{\frac{(\mathrm{n_e} - 1)\mathrm{SD_e^2} + (\mathrm{n_c} - 1)\mathrm{SD_c^2}}{(\mathrm{n_e} + \mathrm{n_c} - 2)}}, \tag{A.3}$$

where $\mathrm{SD_e}$ and $\mathrm{SD_c}$ are the standard deviation of changes in FMA-UE scores for the experimental and control group respectively. Subsequently, the 95% confidence interval (95% CI) for the intervention effect size of each RCT, g, was calculated as [120]:

$$\text{95\% CI} = g \pm 1.96\,\mathrm{SE_g}, \tag{A.4}$$

where $\mathrm{SE_g}$ is the standard error of g, calculated using the following equation:

$$\mathrm{SE_g} = \left(\sqrt{\frac{1}{\mathrm{n_e}} + \frac{1}{\mathrm{n_c}} + \frac{g^2}{2(\mathrm{n_e} + \mathrm{n_c})J^2}} \right) J. \tag{A.5}$$

Considering all the RCTs, the overall effect size of the intervention, $\overline{g}$, was calculated as

$$\overline{g} = \frac{\sum_{i=1}^{k} w_i g_i}{\sum_{i=1}^{k} w_i}, \tag{A.6}$$

where g_i is the effect size of the i^{th} study, $i \in \{1, 2, 3, ..., k\}$. Similarly, w_i is the weight assigned to the i^{th} study, calculated as

$$w_i = \frac{1}{\mathrm{SE_{g_i}^2}}. \tag{A.7}$$

In order to study the heterogeneity between the included RCT studies, the Higgins' I^2 statistic percentage was used [122]. A high I^2 statistic means there are high deviations in the intervention effect sizes across the RCTs. Higgins' I^2 statistic was calculated as:

$$I^2 = \left(\frac{Q - \mathrm{df}}{Q}\right) \times 100, \tag{A.8}$$

where df is the degree of freedom, calculated as $\mathrm{df} = k - 1$ where k is the number of included studies. Q is the Cochran's statistical test for heterogeneity, calculated as follows [120]:

$$Q = \sum_{i=1}^{k} w_i (g_i - \overline{g})^2. \tag{A.9}$$

Followed by calculating $\overline{g}$, to predict the possible effect size for the future RCT studies, we calculated 95% predictive interval (95% PI) using the following equation:

$$95\%\mathrm{PI} = \overline{g} \pm t\, \mathrm{SD_{PI}}, \tag{A.10}$$

where t is two tailed critical value. $\mathrm{SD_{PI}}$ is the standard deviation of 95% PI calculated as [201]:

$$\mathrm{SD_{PI}} = \sqrt{\overline{\mathrm{SE_g}}^2 + \tau^2}, \tag{A.11}$$

where $\overline{\mathrm{SE_g}}$ is the standard error of $\overline{g}$, and τ^2 is the variance between the effect size of the studies. τ^2 was computed using the following equations [202]:

$$\tau^2 = \begin{cases} \frac{Q - \mathrm{df}}{C}, & \text{if } Q > \mathrm{df} \\ 0, & \text{if } Q \leq \mathrm{df} \end{cases}$$

and

$$C = \sum w_i - \frac{\sum {w_i}^2}{\sum w_i}. \tag{A.12}$$

Appendix Table A.1. Search strategy used in the considered databases

#1 Search: stroke rehabilitation

#2 Search: (Brain-computer Interface) OR (Brain-machine Interface)

#3 Search: (BCI) OR (BMI)

#4 Search: ((((Randomized controlled trial) OR (randomized controlled trials)) OR (controlled clinical trial)) OR (random allocation)) OR (double-blind method)

#5 Search: ((#1) AND ((#2) OR (#3) AND (#4))

Supplemental Table S3.2. PEDro scale for assessing the methodological quality of the included studies.

Items	Ang et al.	Ang et al.	Ang et al.	Biasiucci et al.	Cheng et al.	Frolov et al.	Kim et al.	Li et al.	Mihara et al.	Pichiorri et al.	Ramos et al.	Wu et al.
1. Eligibility Criteria Specified	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.Randomly allocated	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3.Allocation was concealed	No	No	No	No	No	No	Yes	No	Yes	Yes	Yes	No
4.Baseline comparability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5.Blinding of subjects	No	No	No	Yes	NO	No	No	No	No	No	Yes	No
6.Blinding of therapists	No	No	No	Yes	No	No	No	No	Yes	No	Yes	No
7.Blinding of assessors	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
8.Adequate follow up	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
9. Intention of treat analysis	No	No	No	No	No	No	No	No	No	No	No	No
10.Between group comparisons	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11.Points Estimates and variability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total score	6/10	6/10	6/10	7/10	6/10	5/10	7/10	6/10	8/10	7/10	8/10	6/10

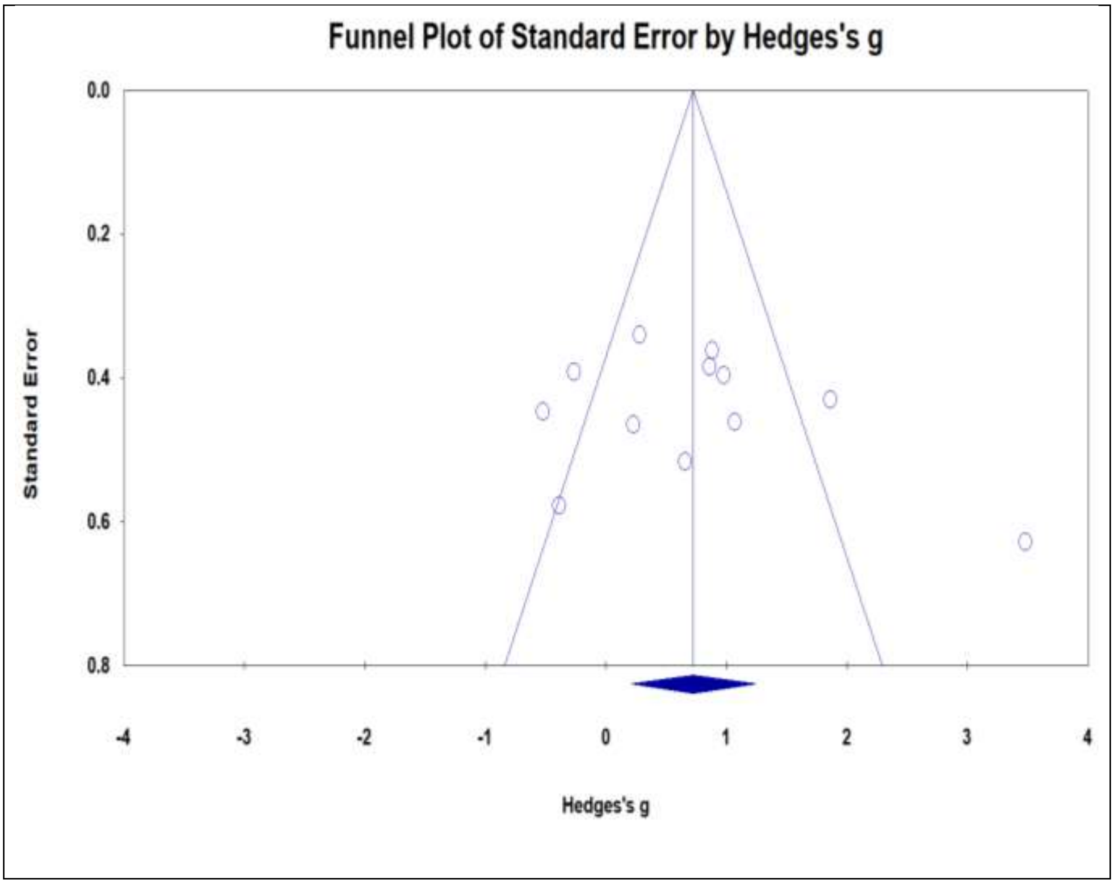
Appendix Table A.3: The mean and standard deviation (SD) of the changes in Fugl-Meyer Assessment scores between the pre- to the post-intervention for the selected randomized controlled trials. N refers to the number of participants.

Study	Experimental (i.e. BCI)			Control		
	N	Mean	SD	N	Mean	SD
Ang et al.	6	7.2	2.3	15	6.18	4.78
Ang et al.	11	4.5	5.19	14	6.3	7.6
Ang et at.	10	0.9	3	9	2.8	4
Biasiucci et al.	14	6.7	5.6	13	2.1	3
Cheng et al.	5	3.8	5.36	5	5.6	2.61
Frolov et al.	36	5.29	4.5	11	4.09	2.91
Kim et al.	15	7.87	2.42	15	2.93	2.74
Li et al.	7	12.7	11.3	7	6.7	4.1
Mihara et al.	10	4.8	2.6	10	2.3	1.8
Pichiorri et al.	14	13.6	8.9	14	6.5	7
Ramos et al.	16	3.4	2.2	16	0.36	4.2
Wu et al.	14	16.93	2.56	11	8.36	2.21

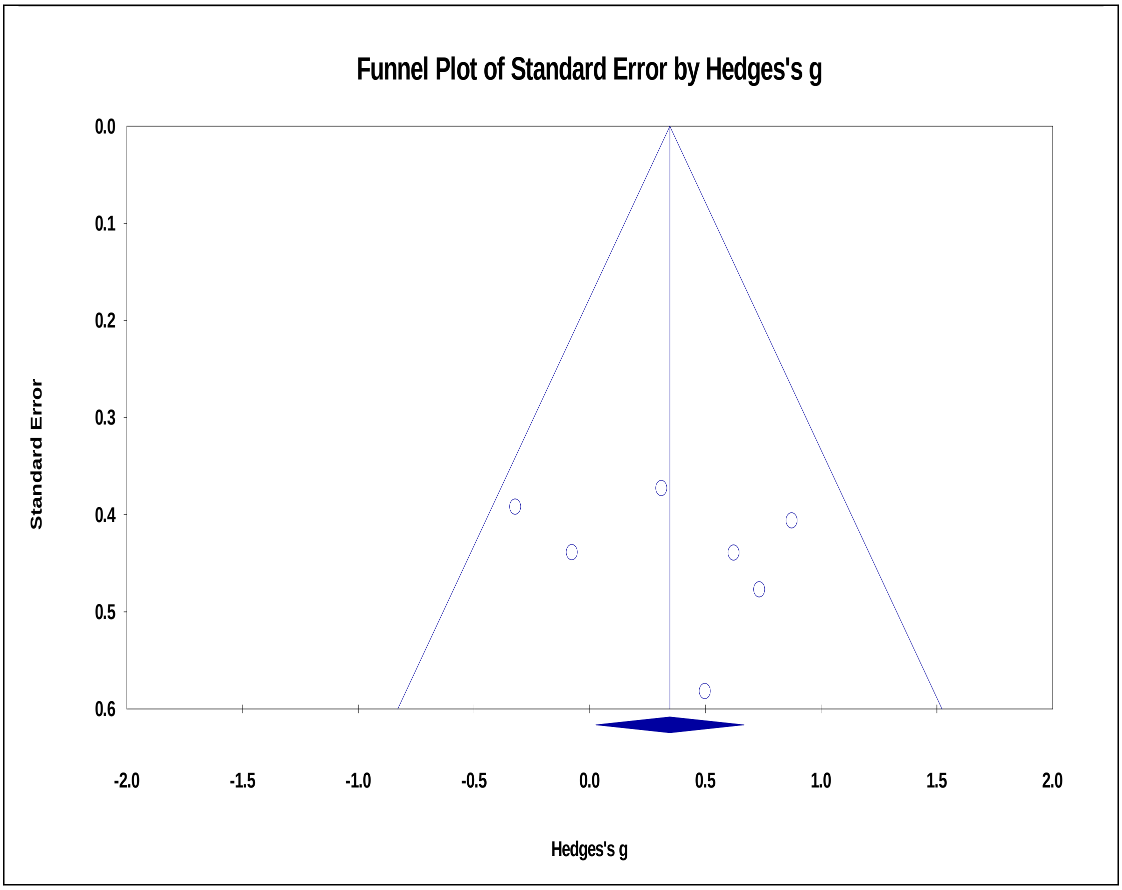
Appendix Table A.4: The mean and standard deviation (SD) of the changes in Fugl-Meyer Assessment scores from the first to the follow up session which was a number of weeks after finishing the intervention. The studies without a follow up session were excluded from this table. N refers to the number of participants.

Study	Experimental (i.e. BCI)			Control		
	N	Mean	SD	N	Mean	SD
Ang et al.	6	9.7	2.6	15	6.1	5.26
Ang et al.	11	5.2	5.12	14	7.4	7.6
Ang et at.	10	5	4.4	9	5.4	5.7
Biasiucci et al.	13	6.9	4.1	12	2.8	4.97
Cheng et al.	5	4.6	4.77	5	2	4.64
Mihara et al.	10	6.6	4.4	10	4.2	2.8
Ramos et al.	16	2.28	2.59	16	1.46	2.52

Appendix Figure A.1. Funnel plot as a visual aid for investigating publication bias in our meta-analysis, assessing the immediate effect of BCI intervention.



Appendix Figure A.2. Funnel plot of the meta-analysis for investigating publication bias in the long-term effects of BCI on upper-limb motor function rehabilitation after stroke.



B

Appendix: Supplemental Material for Chapter 4

The figure below presents examples of the inter-subject variability in brain activation during motor imagery for 6 stroke patients, obtained using the relevant CSP filter. As can be seen, participant P01 exhibited significant contralesional sensorimotor brain activation, whereas P06 exhibited ipsilesional sensorimotor activation. Interestingly, P05 presented activation in both ipsilesional and contralesional motor cortex. Results for participants P02, P03, P04, and P06 showed changes in frontal, sensorimotor, and parietal brain activation in the ipsilesional hemisphere. This observation may imply that brain activation is present not only in sensorimotor regions (C3, C4, CP1, CP2, and CP6), but also in parietal regions (P3, P4) and frontal regions (FC6) during the motor imagery of the stroke-affected hand. The BCI based stroke rehabilitation could be able to identify and use this activity to trigger the feedback.

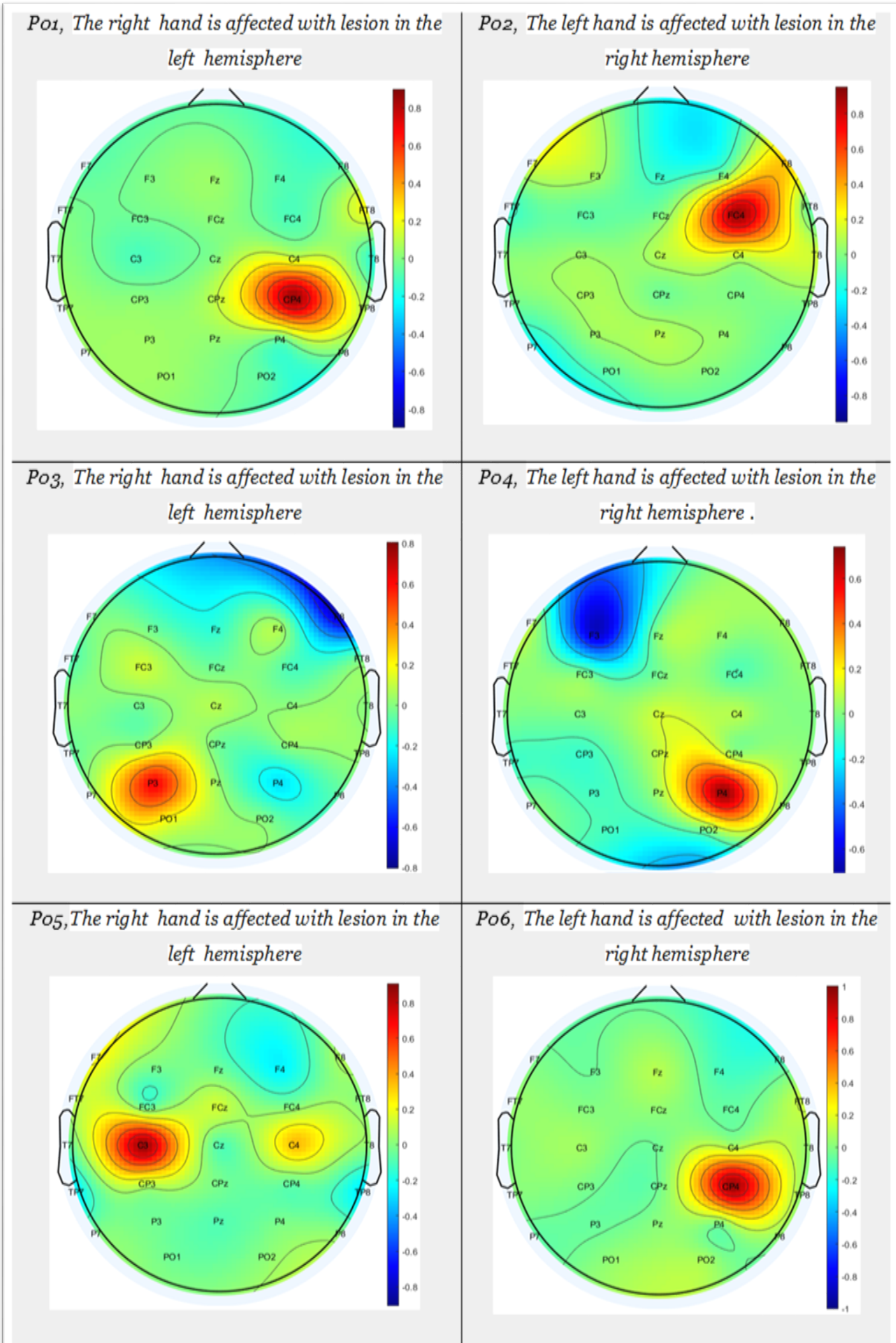


Fig. *1*. Scalp maps of six participants showing weights of spatial patterns during motor imagery, obtained using the CSP approach.