Universitat Autònoma de Barcelona

BRAIN COMPUTER INTERFACES FOR BRAIN ACQUIRED DAMAGE

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Per a la meva dona, la Núria
i els meus fills, l'Andreu i
l'Agnès, sense vosaltres res
de tot això val la pena.

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Abbreviation list

BCI	Brain Computer Interface
EEG	Electroencephalography
ALS	Amyotrophic Lateral Sclerosis
ECoG	Electrocorticography
MEG	Magnetoencephalography
fNIRS	Functional Near-Infrared Spectroscopy
ERPs	Event-related potentials
EP	Evoked Potential
AEP	Auditory Evoked Potential
VEP	Visual evoked potential
SSVEP	Steady-State Visual Evoked Potential
SCP	Slow Cortical Potentials
SMR	Sensorimotor Rhythms
MI	Motor Imagery
ERS	Event-Related Synchronization
ERD	Event-Related Desynchronization
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
GABA	Gamma-Aminobutyric Acid
ICH	Intracranial Hemorrhage
CSF	Cerebrospinal Fluid
MMP	Matrix Metalloproteinases
M1	Primary Motor Cortex
CT	Computational Tomography
fMRI	Functional Magnetic Resonance Imaging
qEEG	Quantitative EEG
BSI	Brain Symmetry Index
DAR	Delta Alpha Ratio
PRI	Power Ratio Index
FFT	Fast Fourier Transform
FES	Functional Electrical Stimulation

LC	Laterality Coefficient
AP	Absolute Power
RP	Relative Power
ESS	European Stroke Scale
MRC	Medical Research Council
MAS	Modified Ashworth Scale
MNN	Mirror Neuron Network
FMA	Fugl Meyer Assessment Scale
FMAue	Fugl-Meyer Assessment for the upper extremity
FMAle	Fugl-Meyer Assessment for the lower extremity
SNR	Signal Noise Ratio
LDA	Linear Discriminant Analysis
rEEG	Resting EEG
BBT	Box and Block Test
9HPT or NHPT	9-Hole Peg Test
FTRS	Fahn Tremor Rating Scale
MOCA	Montreal Cognitive Assessment
TPDT	Two Point Discrimination Test
SRQ	Self-Rated Questionnaire
BI	Barthel Index
IQR	Inter-Quartile Rate
SD	Standard Deviation
SWT	Shapiro Wilk Test
SUS	System Usability Scale
MWUT	Mann–Whitney U test
MWWT	Wilcoxon Test or Mann–Whitney W test
MD	Mean Difference
SMD	Standard Mean Difference

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Chapter I - Introduction to the Brain Computer Interfaces

Background

Imagine the possibility of being related to the world without having to move, without having to speak or gesticulate, just by thinking. It is also possible to reverse this sentence, imagine the possibility of being able to know someone's cognitive processes without the need to move, speak or gesticulate. Without a doubt it seems an impossible situation or even typical of a science fiction scene. Although these assumptions may generate incredulity or even fear, this is not about reading the mind, but about understanding the brain's signals to give them meaning. The new methods of interpretation of neuronal impulses based on machine learning and big data, or the new techniques of invasive or non-invasive brain stimulation, are good examples of the advances in neuroscience that are expanding knowledge and reaching new horizons.

The term Brain Computer Interface (BCI) emerged in the 70's by Dr. Jacques J Vidal, who by using electroencephalography (EEG) tried to give an alternative output to the brain signals in order to control an external device [1]. The main objective of this feat was to help patients with impaired movement or communication to relate to the environment.

Since then many neuroscientists have used this idea and have tried to implement it using different methods of signal acquisition and processing, new interaction devices, new goals and objectives. All this has facilitated the implementation of this technology in many areas and currently the BCI is used to play video games [2], [3], move wheelchairs, facilitate writing in people without mobility [4]–[6], establish criteria and purchase preferences in the world of marketing and consumption [7], or even served as a lie detector [8]. Figure 1 shows the main parts of BCI system.

However, the sector that presents the most marked progress and development of the BCI is the biomedical sector. In rough outlines we can use BCI with two different purposes within the neurorehabilitation; to substitute a lost function or to induce neural plasticity changes with the aim to restore or compensate a lost function.

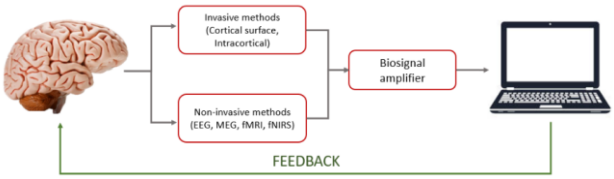

Figure 1. Main components of BCI system.

Normally the BCI systems are based on the attempt of the user to interact with the machine by learning strategies to control the system that gives the expected response. Depending on the complexity of the system and the task, the users should invest more time and effort in order to learn proper mental strategies to interact with the system. There is not a universal calibration that can be used for all people, that is the reason why all BCI devices needs to be calibrated and adapted to each user.

Probably one of the more ambitious uses of BCIs is to **replace lost function** is the control of robotic prosthesis or even an exoskeleton by patients with nerve system injuries. The control of external robotic devices that help the propulsion or articulation of movements is one of the great challenges of this era. However, other types of BCI applications must also be considered, such as the use of this technology to establish communication in people who are in advanced stages of amyotrophic lateral sclerosis (ALS), with locked-in syndrome or another type of paralysis that impede communication through movement. These devices are very helpful, especially because it is not necessary for the patient to train for several sessions in order to achieve the final goal, no lengthy training is required to use this technology. Nevertheless, as it is pointed below, this communication is only feasible if the patient has a minimum of awareness. BCI can also be useful to evaluate the state of consciousness of patients, and in fact this use is a common practice in the field of neurophysiology [9]–[13].

On the other hand, there are BCI systems that aim to **restore a lost function** by inducing neuroplastic changes in the brain. This is undoubtedly a challenging but possible goal through BCI technology. This type of intervention requires that the patient invests time and effort in a therapy based on the practice of motor image and feedback mechanisms in real time.

The goal of this first chapter is to provide a background related to BCI and how this technology can be applied to neurorehabilitation.

Brain signals

The signals that can been obtained from the brain with this type of technology depend essentially on the acquisition technique used, but all of them are based on the detection and comprehension of the electrical and magnetic activity of the brain or on the detection of the hemodynamic responses to the cerebral activation.

Origin of brain signals

To understand the origin of brain signals we must delve into the flow of ions through the plasma membrane. The active cellular processes are accompanied by an exchange of cations and anions between the internal and external medium of the cell, consequently affecting the electronegativity of both sides of the membrane and giving rise to a potential. The voltage gradient between two points is known as the electric field. Most of the generated current comes from the synapse, although other factors such as calcium peaks, action potentials and post-potential peaks must also be considered. Neuron type, shape and number of

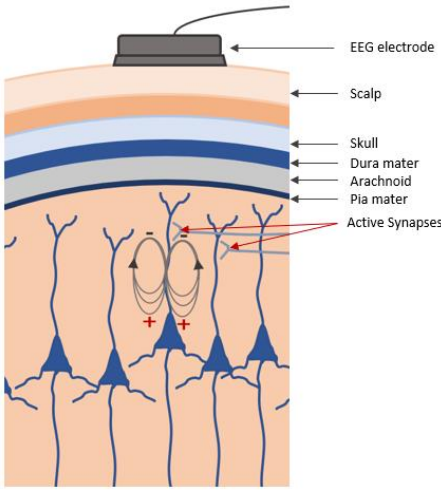

Figure 2. Cortex layers and pyramidal cell distribution.

dendrites influence the creation of the field. Mostly, the registered electrical gradient comes from pyramidal cells, which are between layers I and V of the cortex and have long dendrites that allow the generation of strong dipoles (see Figure 2). Not only the type and location of the cell influence the extracellular field. Both the spatial alignment of the neuron and the temporal synchronization are the most influential factors in the extracellular field.

Voltage changes can be monitored using different types of electrodes, depending on the purpose of the recording.

Acquisition methods

Invasive

Invasive methods refer to those techniques in which recording electrodes are placed inside the cranial cavity. This is the case for electrocorticography (ECoG), in which a small mesh of electrodes is surgically placed on the cortical surface. The location of electrodes on the cortex or even within the brain itself makes it possible to detect voltage changes in very localized areas. These techniques offer a very good spatial and temporal resolution, although they present some important limitations such as the risks inherent in the intervention, the difficulty of changing the position of electrodes or the difficulty of being able to carry out prolonged recordings in time.

Non-invasive

Among the non-invasive techniques, the best known and most widespread one is electroencephalography (EEG). The EEG allows the recording of brain signals through electrodes placed on the scalp. Each electrode registers an area of at least 6 cm^2 of cortical activity [14]–[16]. Due to the hair and scalp, it was necessary to use a conductive gel between the electrode and the skin to reduce impedance and thus noise and signal distortion. This has long been a limitation of the technique, not only because of the discomfort caused by the gel, but also due to the difficulty of reducing ambient noise in different situations. However, technological advances in recent years have facilitated the emergence of dry electrodes, which do not need gel to record good signals. There are also other techniques such as magnetoencephalography (MEG), which record the magnetic fields associated with the neuronal activity [17].

Functional near-infrared spectroscopy (fNIRS) also records brain activity, but from a different principle. Through fNIRS, changes in blood oxygen saturation in different parts of the brain can be measured, facilitating the visualization of the brain regions that consumes more oxygen and therefore are more active. fNIRS technology can be combined with EEG in order to collect different types of information.

Features of neural signals

Different features can be extracted from this signals that are interesting for the study of the brain. In this section two types of signals will be described: the event-related potentials and the oscillatory rhythms.

Event-Related Potentials (ERPs)

Event-related potentials (ERPs) are voltage changes that appear as a response to an event or stimulus. The response to these stimuli is of great importance in many neurophysiological studies because brain waves caused by external stimuli provide vital information about the reaction state of the brain. The brain processing or the cognitive load of the stimulus strongly influences ERP's responses.

We can distinguish different subtypes of ERPs'; here we describe the evoked potentials and the slow cortical potentials.

Evoked potentials (EP)

During the first few milliseconds after applying a stimulus we can detect a brain response as shown in Figure 3. This characteristic wave represents different states that the brain has passed through in the first milliseconds following the application of two stimuli (blue line and green line). For a moment, we will focus only in the blue line. At 100 ms, we can see a negative concavity that corresponds to the detection of sound by the subject, this negative concavity at 100 ms is called 'N100'. Subsequently, the blue wave returns to positive values and is maintained with a certain constancy because the stimulus has had no importance for the subject. This is a good example to explain the action-reaction process of the stimulus-response, where we can reach the conclusion that if the N100 does not appear it may be due to a problem of the stimulus itself (excessively low frequency) or to a problem of the user (impossibility to detect it).

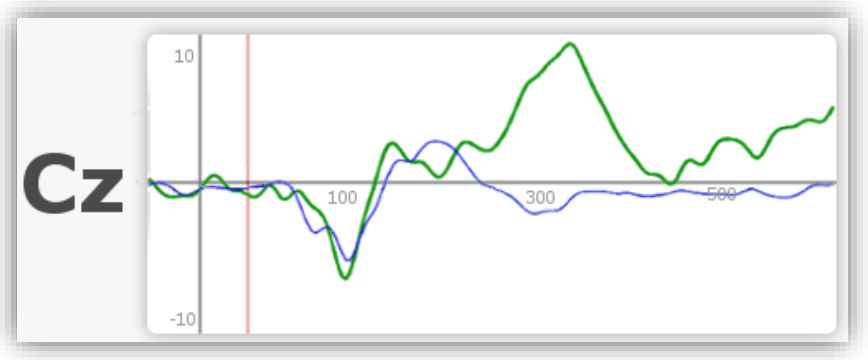

Figure 3. Typical evoked potential in CZ electrode. The red line represents the application of the stimuli. In this case the stimulus is auditory, and the blue curve represents the brain response to a non-target sound. The green curve corresponds to target sounds. Both lines look very similar until the 300 milliseconds, where the green line presents a positive concavity caused by the cognitive workload.

These potentials are very fast, difficult to control voluntarily. Depending on the location of the recording, different potentials can be detected at different times. The types of evoked potentials would

depend on the type of stimuli; auditory, tactile, visual, for example. The most studied EPs are the visual and auditory potentials.

Auditory potentials (P300)

When we talk about the use of auditory potentials at BCI we basically focus on the P300 potential. Despite not being the only potential studied, it is the one with most applications, including the possibility of communicate with ALS patients [10], [12], [18]. The P300 (also called P3) is a component that appears in the central areas of the cortex 300 ms after a stimulus [19]. It is not an exclusively auditory potential and can also be evoked by visual or tactile stimuli. Figure 3 shows an auditory P300. In this plot, two curves can be seen, the green one, which shows a positive potential at 300 ms, and the blue one, which does not show this potential. In order to detect the auditory P300, a paradigm consisting of a sequence of clearly different sounds is used, the so-called 'oddball response' [20], [21]. In this paradigm the user is concentrated on listening to a chain of sounds waiting to hear the 'strange' (or odd) sound (target stimuli), which is presented with less frequency than normal sounds (non-target stimuli). The fact that the subject expects to be surprised by a particular sound, triggers a P300 at the moment it is detected. The target sound has to be less common than the non-target sound, otherwise it can be difficult to differentiate the target response from the non-target ones.

Focusing again on Figure 3, we can see two lines, the blue corresponds to non-target sounds, while the green corresponds to target sounds. In both lines there is a negative potential at 100 ms (N100), indicating that the sound has been heard, but only the green curve shows a peak of positive potential at 300 ms (P300).

Visual potentials

Visual evoked potential (VEP) is a set of characteristics signals which occur in the V1 area during the first milliseconds after a visual stimulus. First, a negative potential is detected at 75 ms followed by a positive potential at 100 ms (P100) and a negative one at 145ms (N145). Repeated visual stimulation is known as steady-state visual evoked potential (SSVEP) [22]. SSVEPs as well as VEPs have been extensively studied and used effectively in BCI systems for medical applications such as orthotic control [23], [24] or speller communication [25]–[27].

Slow cortical potentials (SCP)

This type of wave is due to slow potential changes, detectable in the EEG for periods greater than the evoked potentials. It is often necessary to combine different periods of relaxation and activity in order to detect this characteristic in the signal [28]. These potential changes occur between 0.5-10 seconds. Negative SCPs are associated with high cortical activations while positive SCPs are associated with low cortical activation [19]. These types of potentials have been widely studied for decades, although they present some important limitations in BCI systems that offer real-time user interaction. On the one hand, the long period needed to detect these characteristics in the signal, and on the other hand, the

training time that the user needs to be familiar with the paradigm and be able to control the system. Even so, if the user comes to control the system, potential changes in the SCP can be used for basic word processing and other simple tasks [29], [30].

Oscillatory rhythms

Brain electrical activity in normal conditions may resemble a sea of oscillatory waves or rhythms of different frequency ranges and locations related to different processes. Sensorimotor rhythms (SMR) are the most common used in BCI systems. These rhythms are recorded in the sensorimotor cortex in the frequency bands μ (8-12Hz) and β (13-30Hz). Changes in these frequency bands are related to motion and sensation, as well as to the motor image (MI) [28]. Through some training sessions, the user can voluntarily control μ and β waves [31], [32], a fact that can be very useful to control external devices such as exoskeletons or robotic arms. During the pre-movement and movement phase there is a desynchronization of the activity in the μ band at the cortical level, the so-called 'Event-Related Desynchronization' or ERD. The decrease of the μ power band in the zones responsible for the movement is accompanied by a synchronization in the same band of the areas that are not involved in that movement, process that it is called 'Event-Related Synchronization' or ERS. When the imagery period is finished, the contralateral motor cortex restores the synchronization state (ERS) and increases again the amplitude of the signal [33]–[35]. The ERD/ERS events will be handed in detail in the study "Clinical trial I – EEG biomarkers for stroke diagnosis and prognosis".

Neural basis of Brain Computer Interfaces in Stroke survivors

Stroke has been defined as an acute episode of focal dysfunction of the brain, retina, or spinal cord lasting longer than 24 hours, or of any duration if imaging (CT or MRI) or autopsy show focal infarction or hemorrhage relevant to the symptoms [36]. It is characterized by sudden, non-convulsive loss of neurological function. The definition includes thus encompassing ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage and cerebral venous sinus thrombosis [37].

This condition is one of the major global health problems, second leading cause of death worldwide, and is one of the leading causes of disability [38]. Up to 87% of its global burden is attributed to ischemic stroke, which is a heterogeneous disorder with more than 100 pathologies implicated in its pathogenesis [38], whereas non-traumatic intracerebral hemorrhage accounts for 10–20% of strokes worldwide [39] and it is the most common hemorrhagic stroke subtype. After the acute episode, important disabilities remain, [40] such as persistent cognitive, motor, sensory and visual impairments [41].

Preclinical studies have suggested a large number of therapies that may improve recovery from stroke. These are in various stages of translation, although most of these at an early point of clinical trials [42]. In fact, current therapeutic management of ischemic stroke does not provide fully satisfactory outcomes [43] and neither does management of hemorrhagic ones [44].

Physiology of ischemic stroke

In the ischemic stroke, the affected tissue suffers a gradient of hiperfussion [46]. The regions suffering from the most severe hypoperfusion levels rapidly progress to irreversible damage, representing the "**ischemic core**" [45] The remaining hipoperfused tissue also shows impairments of the normal blood flow and it is known as penumbra [46].

The ischemic core shows very low cerebral blood flow (CBF), cerebral blood volume (CBV) and metabolic rates of oxygen and glucose [46]. Electrical silence and volume of the ischemic core is highly correlated to neurological deficit [46]. Furthermore, it has been suggested that the numbers of oligodendrocytes and oligodendrocyte progenitor cells (which support myelination of axons) are reduced in the ischemic core through processes similar to those involved in neuronal cell death [45]. Ischemic core is beyond therapeutic rescue and it is defined as the tissue that exists below the perfusion threshold of infarction. It can rise over time to reach penumbra threshold [46].Therefore, infarct expansion occurs earlier in tissue suffering from more severe hypoperfusion and inflammation [47]. In ischemic penumbra, oxygen metabolism is preserved relative to cerebral blood flow, oxygen extraction fraction is elevated and cerebral blood volume is normal or elevated [46] thanks to the collateral blow flow pathways (such as the Circle of Willis), which can sustain its viability for a period of time [45], [48]. This affected cerebrovascular tissue will contribute to the clinical deficit, but the alteration is reversible with rapid therapeutic interventions [48], [45]. In fact, penumbra is potentially salvageable, being a key target for therapies, but it decreases over time by gradual recruitment into the core [46], [48]. Reperfusion therapy [48] in the 3 hours window and beyond it, neuroprotection techniques and Oxygen therapy techniques are currently being tested to save as much ischemic penumbra as possible [45], [46]. On the other hand, contralateral blood flow pathways can change over time within the same individual [45]. In addition to this, the course of events can vary from patient to patient, exhibiting substantial volumes of penumbra exceptionally even days after stroke onset [46].

Ischemic stroke phases

Acute phase

The acute phase is measured in hours and varies according to features of injury [42]. It involves neuronal excitotoxicity, cell death within the infarct core and periinfarct region [49], loss of brain structural integrity, angiogenesis and activation of immune mechanisms [48] alongside with sever systemic effects such as hypertension, arrhythmias (including bradycardia) and pulmonary exudates [45] .

Ischemic stroke leads to oxygen reduction in the brain, causing several cellular and molecular consequences that affect neuronal and glial function, vascular alterations and inflammation [45]. Neuronal function relies on the continuous availability of ATP (which requires a constant supply of oxygen and glucose to the brain) [45], [48]. When this supply stops as in stroke, there is an impairment in neural signaling [48], [45] and an iron-induced damage risk [47]. Degeneration of distant nerve fibers

(Wallerian degeneration) in tracts that serve the infarcted brain (such as the corticospinal tract) occurs and predict long-term clinical outcome in humans. Spreading depolarization is often initiated in regions of anoxia (such as the core [46]) but propagates to surrounding brain regions, increasing the metabolic demand of the penumbral tissue and leading this tissue transitioning to infarction [45], [46]. In addition, blood–brain barrier dysfunction and release of signaling molecules (for example, cytokines [45], [47]) from astrocytes, microglia and oligodendrocytes lead to an inflammatory response [45], brain edema formation [50] (cytotoxic and vasogenic [48]), and further neuronal death [47]. Reactive astrogliosis occurs 48-96 hours after ischemia, forming glial scar that inhibits neuronal regeneration. Furthermore, pericytes death after ischemia prompt an irreversible capillary constriction and further inflammation. In neurons, the cumulative effect is cell death, mediated through diverse pathways including necrosis and apoptosis [45].

Some articles also sustain that neuroprotective mechanisms are triggered by the ischemic cascade as a defense against apoptotic and necrotic cell death [48].

Fewer data are available regarding the inflammatory response in humans, but it has been suggested that neutrophil accumulation in the ischemic core, with activation and proliferation of microglia in the penumbra, occurs during the early stages of stroke (within the first 3 days); and afterwards, they adopt an amoeboid phagocytic phenotype and clear cellular debris [45]. Later on, macrophages will manifest with predominantly anti-inflammatory phenotypes [45].

In this phase, therapeutic strategies focuses on reducing the extent of injury and main treatment approaches include reperfusion (although large vessel reperfusion can worsen the clinical status in some patients [45]), neuroprotective techniques [42], [48], and edema resolution [51].

Subacute phase or recovery stage

The acute phase is followed by a subacute phase (days to weeks [49], [42]) of protection [45] and heightened neuroplasticity [51] (after 2 weeks [45]), defined as the capacity of one or more units of the brain to undergo biochemical, structural, or functional changes in response to intrinsic or extrinsic signals [49]. This phase of neural growth begins shortly after the acute injury has stimulated restorative processes, and varies in relation to factors such as gene expression, molecular milieu, environment and experience [42].

During this subacute period, a number of endogenous processes are highly active, including increases in levels of growth factors, axonal sprouting, dendritic remodeling, and changes in cortical excitability and synaptic plasticity [49]. In fact, an experimental stroke alters expression of numerous genes, leading to increased levels of key growth factors, growth of synapses and dendrites, axonal remodeling and angiogenesis, and enhanced brain excitability mediated by alterations in glutamate and gamma-aminobutyric acid (GABA) receptor subtypes [42]. In addition, these events are often concentrated in perilesional tissue but are not confined there; indeed, spontaneous growth-related changes following a

unilateral infarct arise broadly [51], within the contralesional hemispheres, in ipsilesional areas connected to the lesioned area and even downstream in the spinal cord [42]. Moreover, some areas of the brain take over the functions previously performed by the damaged regions [51].

This heightened neuroplasticity involves a "sensitive period" early after stroke, during which there is increased responsiveness to rehabilitative training [49], [41]. For example, in rodents with experimentally induced stroke, exposure to an enriched environment with skilled reach practice leads to significantly greater behavioral improvements when started 5 to 14 days after inury, but not at 30 days [49]. Therefore, in this stage it is important to therapeutically enhance the processes underlying spontaneous recovery, as well as to modify inflammation, lifting diaschisis, or reducing late neuronal death [42]. Main treatment approaches include growth factors, monoclonal antibodies, drugs, cell-based therapies, activity-based therapies and brain stimulation [42].

Chronic phase or chronic state

The acute phase of injury involves cell death and excitotoxicity, which requires a therapeutic strategy focused on neuroprotection (defined as the ability to protect neurons from injury and cell death) and countering excitotoxicity, but once neurons survive this phase and the excitotoxicity has subsided, the environment becomes predominantly inhibitory [49].

The chronic phase starts once spontaneous behavioral recovery has reached a plateau and the recovery stage critical period has ended [42] with a stabilization of post-stroke behavioral deficits [49]. This stage typically occurs by three months post-stroke for the motor system, sometimes later in the cognitive and language domain, and continues for the lifetime of the stroke survivor [42].

Therapeutic priority in this phase should shift from neuroprotection to neural repair, consisting of interventions to induce a state of enhanced plasticity such as the use of pharmacological and cell-based therapies, activity based therapies and brain stimulation [42].

Intracranial Hemorrhage (ICH) pathophysiology

Primary brain damage

ICH is the most critical subtype of stroke and lacks effective treatment [52]. Hematoma expansion in spontaneous ICH occurs within the first 24 hours after ictus in about one third of patients and its volume and expansion are predictors of functional outcome and mortality [53], [54], [55]. Furthermore, ICH is related to poor neurologic outcome, nearly doubling the odds of long-term disability as compared to ischemic stroke [56]. It is not clear which is the relation between blood pressure and hematoma expansion, and whether high blood pressure is the cause or a consequence of ICH [53].

Circulation impairment of the cerebrospinal fluid (CSF) due to the eruption of blood into the ventricular system and the arachnoid villi causes hydrocephalus. In fact, dilatation of the third and the forth ventricle is considered an independent mortality predictor after ICH [53], [54].

Hematoma-induced inflammatory response and edema are contributors to secondary neuronal damage in ICH. There are three stages of edema after ICH; in the first stage, the hemorrhage spreads along the white matter tissue and several hours after edema forms. The second stage is characterized by a strong inflammatory response within the first 2 days, where ongoing thrombin production is activated by the coagulation cascade, complement system, and microglia, therefore attracting polymorphonuclear leukocytes and monocyte/macrophage cells, which creates a disruption of the blood-brain barrier and worsens the edema. After the first two days third stage occurs, when red blood cell lysis leads to hemoglobin-induced neuronal toxicity. This provokes an increased volume of the perihematomal edema by approximately 75% during the first 24 hours after spontaneous ICH [53].

On the other hand, patients with ICH can have elevated intracranial pressure due to hematoma-related mass effect, cerebral edema, and hydrocephalus, which can compress the microvasculature, increasing resistance and therefore causing ischemia in the periphery of the clot [53], [54]. In addition, mechanical forces that occur during hematoma formation and chemical toxicity may cause necrosis in the adjacent brain tissue. Furthermore, apoptosis has been described both in the center of the hemorrhage and also in the periphery which can be related to brain injury after ICH [53].

Secondary brain damage

Several biochemical mediators have been implicated in secondary brain damage after ICH such as thrombin [55], an essential component of the coagulation cascade, which at low concentrations is necessary to achieve homeostasis but, at high concentrations leads to apoptosis, early cytotoxic edema and activation of complement cascade and increased permeability of the blood brain barrier [53], [54].

Delayed brain edema can cause iron degradation [53] and hemoglobin oxidative stress [55], [54]. Hemoglobin is metabolized into iron, carbon monoxide and biliverdin by heme oxygenase [53]. Furthermore, intracerebral infusion of iron can happen, which causes brain edema [47], [54], aggravates thrombin-induced brain edema [53], and plays a key role in the pathophysiology of ICH [53].

On the other hand, several cellular inflammatory mediators such as Leukocytes have been identified [53]. Leukocytes infiltrate the perihematomal area [54], [55] in the first 24 hours, with a peak on day two or three and a decrease to basal values from days three to seven [53]. Infiltrating leukocytes secrete proinflammatory mediators and reactive oxygen species [53]. Active microglia also contribute to leukocyte recruitment and astrocyte activation in the perihematomal area [53]. Although reactive astrocytes can contribute to local inflammation, they can also modulate it and amielorate glutamate excitotoxicity, therefore, playing a neuronal protective role [52], [53].

Several molecular mediators such as transcription factor NF-κB and its downstream inflammatory mediators, including TNFα and IL-1β, are activated in the perihematomal area within hours of ICH, all of them causing further inflammation [55], [53]. TNFα and IL-6 also increases in the peripheral blood in ICH patients 24h after the onset [53].

On the other hand, matrix metalloproteinases (MMP), endopeptidases involved in extracellular matrix remodeling, may play a role in blood brain barrier disruption, leading to further brain edema and an increase of vascular permeability [53].

Lastly, some studies have shown that both sex and age are important factors affecting ICH-induced brain injury, being men and old people the ones with the worse inflammatory effects [55]. Moreover, even though there is a wide difference between ischemic and hemorrhagic stroke pathophysiology, it has been stated that there is a relatively predictable pattern in motor recovery regardless of the stroke type [57], [58]. It is also assumed that in the subacute phase of an ICH (the first 3 months), the CNS experiences some degree of injury-induced plasticity similar to that seen after an ischemic stroke [57], although further research is needed to confirm this fact.

BCI and stroke recovery

Cortical or subcortical lesions can lead to loss of control of peripheral muscles and disruption of sensory-motor connections whereas activation of sensory feedback loops and the primary motor cortex may strengthen dormant cortical connections through Hebbian plasticity mechanisms, supporting functional recovery [59]. Therefore, new rehabilitation strategies focuses on approaches concerning skill learning and enhanced activity of the primary motor cortex to promote plasticity [59].

Brain–computer interfaces (BCIs) are a fundamentally new approach to restore communication and motor control in people with severe motor impairment [60], [61], [59], enabling stroke survivors to modulate their sensorimotor rhythms purposefully [62]. Brain activity is measured translating electric, magnetic or metabolic brain activity [62] into signals which can control external devices [63], [61], [64], [62] or to provide a matched sensory stimulation according to certain feedback procedures [59]. As mentioned above, BCI systems can use either invasive (electrocorticography or microelectrode arrays) or noninvasive signal acquisition [62] (based on SMR [65]). EEG signals are the most particularly relevant noninvasive ones, since they are suitable for clinical environments, have a highly accurate temporal resolution and their real-time feedback can induce cortical plasticity and the restoration of normal motor function [64], [59]. Therefore, most BCI systems are composed by different stages: EEG signal acquisition, signal preprocessing, feature extraction, feature selection, classification, and external device communication [63].

Common types of BCI are focused on SMR modulated by a motor-imagery task (MI-BCI), or on event-related-potentials (ERP) elicited by visual paradigms [64].

Motor imagery has been shown to activate the primary motor cortex (M1) [66] and elicits ERD/ERS, which is related to increased or decreased brain activity, and several studies have described that stroke patients can still elicit ERD/ERS during MI of their paralyzed hand and during passive movement provided by robotic assistive devices [63].

In addition to this, movement-related neural activity was found to be present both in the contralateral and the ipsilateral side depending on movement complexity (unilateral or bilateral) and the proximity of the muscle groups to the sagittal plane of the body (shoulder or hand) [62]. Therefore, the ipsilesional primary motor cortex is also thought to play a major role in motor recovery [62]. Furthermore, the use of BCI systems can lead to long-lasting effects [67] on functional brain oscillatory activity in stroke patients and even to a structural reorganization of the brain [62].

Therefore, BCI systems could be used to promote stroke patients' neuroplasticity processes by making the user pay close attention to a task requiring the activation or deactivation of specific brain areas [59] and evaluating changes in brain rhythms, which have been related to brain plasticity [63].

In addition to this, recent data support BCI use in subacute-ischemic-stroke patients [63], [60], [66], and chronic stroke patients [66], [68]. A systematic review from 2017 focused on the BCI systems for functional rehabilitation in patients with stroke and also concluded that BCI interventions were potentially beneficial improving motor outcome measures [63], whereas a meta-analysis from 2018 concluded that brain-computer interfaces for post-stroke motor rehabilitation in sub-acute and chronic patients induced an improvement of motor function, superior to other conventional therapies [62].

BCI systems can be combined with different types of external devices to assist the execution and learning of movement [69]–[73]. The external complements integrated into the system vary depending on the purpose of the system and the physiological mechanism to be stimulated or replaced. However, there is one very important aspect that all these systems must present, whatever the purpose and method used; there must be a fluid interaction between man and machine. Of course, this interaction must be through the biological signals of the individual and the system must respond to them, making present an adaptive relationship between both parties.

The selection of the mechanisms used as feedback are undoubtedly one of the most complex decisions that must be made by researchers when using the system, especially if there is a therapeutic purpose. Within neurorehabilitation there are commonly two types of BCI systems oriented to motor rehabilitation; BCI combined with robotic device, or BCI combined with feedback devices such as electrical stimulators or virtual environments. As discussed above, the applications that can be given to these devices can be either for the substitution of a lost function (e.g., a robotic arm activated through EEG signals), or they can also be oriented to the stimulation of motor learning (e.g., externally induce movements in the affected limb using electromyographic signals in the healthy limb).

Stroke epidemiology shows the importance of post-occurrence rehabilitation. Physical therapy is the preferred treatment to minimize the impact of disability on the activities of daily living. The protocols applied in post-stroke rehabilitation are mostly individualized, and the therapeutic objectives adapted to the subject. However, current techniques have great limitations when patients do not present any type of residual movement in the affected limb. In these cases, physical therapy focuses, among others, on

passive mobility techniques to maintain joint balance and soft tissue flexibility, mirror therapy or non-invasive brain stimulation. The advance of technology and its implantation in the healthcare world enables us to reduce the limitations of conventional physical therapy and achieve better results.

Furthermore, articles with high methodological quality have exposed an increased clinical performance in stroke patients using EEG biofeedback (neurofeedback) to generate wrist extensors movement when this movement has been partly or fully impaired.

EEG biomarkers for stroke diagnosis and prognosis

Diagnostic imaging tools like Computational Tomography (CT) or Functional magnetic resonance imaging (fMRI) are normally used to evaluate brain damage in the acute and sub-acute phases, offering valuable information about the diagnostic and functional prognosis for each case. Recent studies explored new methods to process and analyze brain signals acquired by conventional techniques like electroencephalography (EEG) [74]–[78] or magnetoencephalography (MEG) [79]–[81].

Quantitative EEG (qEEG) is a useful tool to extract features from the EEG signals and thereby help clinicians understanding each patient's clinical state. qEEG parameters have shown multiple correlations with different pathologies, making qEEG an essential tool for different clinical fields. One qEEG parameter is the Brain Symmetry Index (BSI), described by van Putten et al. in 2004 to assess the stroke risk during carotid endarterectomy surgery in real time [82]–[84]. Subsequently, Agius et al. measured the BSI in stroke patients and found correlations between this parameter and functional scales [85]. Other interesting parameters are the Delta Alpha Ratio (DAR) described by Claessen et al. [86] or the Power Ratio Index (PRI) described by Nagata et al. [87]. Classen et al. in 2004, studied 12 different qEEG parameters, and using the Fast Fourier Transform (FFT) to calculate the absolute and relative power of three different frequency bands. The results of this study suggested that the DAR parameter could be useful to detect delayed cerebral ischemia. Nagata et al. in 1985 described for the first time the PRI parameter by developing topographic maps based on the power dysfunction. These maps were correlated with the location of brain tumors. Some years later, other researchers tried to use DAR and PRI to correlate and predict the motor functionality based on the EEG recordings [74], [88], [89].

Electroencephalography can measure brain signals with a high temporal resolution, allowing clinicians to monitor brain activity in real time [90], [91]. Brain signals can be read with a software program to provide to the user an external pathway for these brain outputs [61]. This approach has been employed in numerous Brain Computer Interface (BCI) systems providing real-time communication and control. BCIs have been used to control devices such as a wheelchair, prosthesis or functional electrical stimulator (FES), sometimes in combination with immersive feedback relating to rehabilitation. Over the last several years, many publications have combined BCI, FES and other methods to increase cortical plasticity in stroke survivors, helping them regain movement control [91].

In this approach to movement restoration, stroke survivors perform Motor Imagery (MI) exercises during EEG recording [62]. The detected brain oscillations can be used to move a virtual reality avatar or trigger a FES device to reproduce the imagined movement with the paretic limb (e.g. [92], [93]). These types of rewarding feedback only occur if the patient imagines the desired movement, providing a closed-loop feedback system for patients and an objective means to monitor patient compliance for therapists and scientists.

During the MI tasks, the patient should concentrate on imagining a specific movement instructed by a therapist, such as wrist dorsiflexion. During MI, the contralateral motor cortex will exhibit event-related desynchronization (ERD), which is a decrease of EEG bandpower in the μ (8-13 Hz) and β (16-30 Hz) range. After the patient finishes performing MI, the contralateral motor cortex exhibits an increase in μ and lower β rhythm activity, called event-related synchronization (ERS). An ERS can also occur during MI in the ipsilateral hemisphere in the μ range, and it is related to an idling state of those areas [33], [34], [94], [95]. Many people with stroke exhibit atypical ERD/ERS activation patterns; for example, the affected cortex may be less excitable, and the changes in EEG activity may be more prominent over nearby cortical areas [33], [34].

Hence, stroke patients often have abnormal changes in ERD/ERS and other EEG patterns resulting from MI. Kaiser et al. [34] investigated how these abnormal patterns relate to the patient's functional state and spasticity, using a new parameter, the Laterality Coefficient (LC). For functional assessment, they used the European Stroke Scale (ESS), the Medical Research Council (MRC) and the Modified Ashworth Scale (MAS). The LC presented significant correlations with the MRC scale and MAS. The findings of Kaiser and colleagues showed that strong ERD patterns on the contralesional hemisphere are related to a high degree of impairment.

Improving BCI performance for neurorehabilitation

Feedback is an essential feature of EEG-BCI rehabilitation. EEG-BCI signal analysis can be used to trigger functional electrical simulation (FES) [98] and to control robotic orthoses in order to assist the realization of the motor activity [65]. In this way, the disrupted sensorimotor loop is closed. This closed-loop has been proven to be a key factor to induce neural plasticity changes towards improving functional behavior. Visual feedback is necessary to learn how to create mental images. In addition, during the routine use of BCI, it provides users with self-awareness and assessment of how they are performing. The suitability of different forms of feedback has been discussed [99], [100]. On one hand, symbolic widgets such as progress bars and arrows are simple and fast to implement, but they have been found to be difficult to understand and may even distract users [101], [102]. On the other hand, embodied avatar representations of the patient's limb promote Action Observation mechanisms and activate the Mirror Neuron Network (MNN) inducing thus cortical plasticity [103], [104]. Moreover, the sense of embodiment that a realistic avatar provides impacts positively on BCI control [105], [106].

BCI sessions are based on repetition of exercises, they are cognitively demanding and can lead to a reduced patient engagement in rehabilitation. Gamification is defined as the introduction of game-design elements and principles such as narratives, scores and awards in non-game contexts to increase persons satisfaction and interest in realizing activities by bringing intrinsically motivational playful experiences [107]. Gamification has become a popular research topic with applications in a variety of domains from corporate business transformation to education and health [108]. However, several studies in domains such as education [109], have shown that it is not always effective and can even yield to a reduction in the efficacy of the activity it aims at making more motivating. The effects of gamification are greatly dependent on the context and on the users. In particular, rewards, badges and leaderboards should be used with precaution as they may backfire [110].

Gamification has been largely used in conventional upper-arm rehabilitation in order to alleviate the repetitiveness of sessions, increase motivation, and engagement [111], [112]. Commercial computer games have been adapted and new games have been designed on purpose to enhance the rehabilitation experience [113]. These games use the movement of the patients measured through various tracking systems [114] as the input system of the game, substituting thus conventional devices such as mouse and joysticks.

The introduction of gamification in BCI rehabilitation is quite challenging because using brain signal as the only user input reduces the scope of possible game narratives. Moreover, in order to keep the benefits of embodiment [115], games should somewhat integrate the patient's upper limb avatar. This is why existing studies typically involve driving or navigation tasks: for instance, destroying asteroids using left/right hand [116] or rowing boats while trying to collect flags [117]. Existing gamified BCI solutions have been basically tested with volunteer participants without stroke, thus there is a lack of data on actual patients. In particular, little is known about the impact of introducing external stimuli such as game elements aside from the avatar's limb on the efficacy the training activity.

Objectives of the thesis

The main objective of the thesis is to evaluate the effects of rehabilitation based on BCI Systems in stroke patients, to explore electroencephalographic parameters obtained during the sessions to better quantify these effects and to optimize BCI Systems.

1. To evaluate the clinical effects of rehabilitation based on BCI system in stroke patients;
    a. Meta-analysis of published studies that use BCI in stroke patients
    b. Evaluation of the effects of BCI system on stroke patients
2. To explore alternative parameters to quantify effects of BCI in stroke patients
    a. Evaluation of different EEG biomarkers for stroke diagnosis and prognosis
3. To optimize the BCI system
    a. Gamification to increase concentration of stroke patients when using BCI systems

Experimental design

To carry out the objectives previously described, the following experimental design have been planned. The experimental design consists of three main experiments; Systematic review of the effectiveness of BCI treatment in stroke patients, Clinical study I for the analysis of EEG biomarkers, and Clinical study II for a new design of BCI system to improve the concentration.

1. Effectiveness of BCI treatment for stroke recovery
    a. Systematic review and meta-analysis: Methods in section “Literature search protocol for the meta-analysis“ page 29, and Results, in section “Effectiveness of BCI treatment for stroke recovery – systematic review with meta-analysis”, page 44.
    b. Effects of BCI in stroke patients: Methods in section “Clinical trial I – EEG biomarkers for stroke diagnosis and prognosis”, page 34, and Results in section “Functional assessment of stroke patients before and after BCI treatment”, page 48.
2. EEG biomarkers for stroke diagnosis and prognosis: Methods in section “Clinical trial I – EEG biomarkers for stroke diagnosis and prognosis”, page 34, and Results in section “EEG biomarkers for stroke diagnosis and prognosis”, page 47.
3. Gamification to increase concentration in stroke patients using BCI: Methods in section “Clinical trial II - Improving BCI performance with gamification”, page 40, and Results in section “Improving BCI performance with gamification”, page 65.

Chapter II - Methods

Literature search protocol for the meta-analysis

Identification and selection of trials

The literature search was done using the PubMed/Medline database (ncbi.nlm.nih.gov/PubMed) in March of 2019. Figure 4 shows the literature search procedure. The terms used in this search can be found in the Appendix A. After the first search, a first screening based on abstract was made. At that point the articles could become excluded for these reasons; unrelated title, BCI not used in the experimental group, not oriented to stroke patients, duplicate studies, studies that did not have the full text available, non-English, not in humans, not randomized clinical trials or meta-analysis, functional scales not available before and after the intervention, incomparable control group. Afterwards, a second screening was carried out based on the full text applying the same criteria previously mentioned. Studies that were not aimed at rehabilitation of the upper limb, or that did not use the Fugl-Meyer Asssessment functional scale for functional assessment, were also rejected. The PEDro quality scale was also used to evaluate the quality of clinical trials and to reject all those with a score of less than 5 points out of 10.

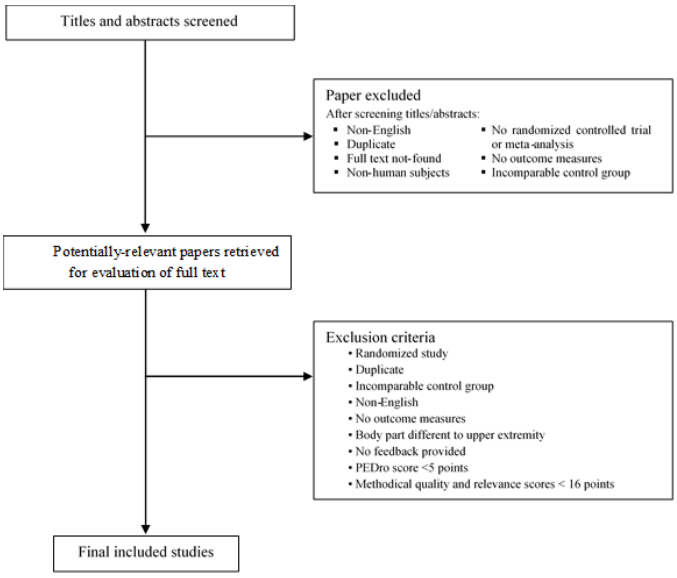

Figure 4. Literature search procedure

Assessment of characteristics of trials

Quality

The quality of randomized clinical trials has been assessed using the criteria above mentioned, Table 1, the PEDro quality scale (see Table 2). Table 1 consists of 4 items; number of patients, statistical analysis of the main variables, outcome measure, body part, biofeedback principle and feedback type.

The scores of methodological quality and relevance were summed up for individual literature (minimum score: 4 points and maximum score: 18 points). When the total score was less than 12 points which is 2/3 of maximum score, it was excluded.

The PEDro scale ranges from 0 to 10 points. All clinical studies with a score of less than 5 points in the PEDro quality scale were excluded.

Table 1. Criteria of quality

Criteria for methodical quality	Description	Assessment
Patient number	Which was the number of available patients?	3…>=50 2…>10-<50 1…<=10
Statistical Analysis	Is a statistical analysis of the outcome measures available?	3…yes 1…no
Outcome measure	Was the Fugl-Meyer score used as outcome measure?	3…Fugl-Meyer upper extremities 1…Other 0…No measure (exclusion)
Body part	Is wrist dorsiflexion covered by the study?	3…extensors of the wrist 2…upper limb 0…not addressed or different (exclusion)
Biofeedback principle	Is the biofeedback principle involving the brain signals?	3…EEG BCI 2…biofeedback based on motor imagery 1…other BCI 0…no feedback (exclusion)
Feedback type	Is the feedback type?	3…FES and visual 2…FES or visual 1…different (e.g. robot)

Table 2. Quality based on PEDro scale.

Criteria	Description	Score
Random Allocation	Subjects were randomly allocated to groups	1…Yes 0…No
Concealed Allocation	Allocation was concealed. Concealed allocation means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to	1…Yes 0…No
Groups Similar at Baseline	The groups were similar at baseline regarding the most important prognostic indicators	1…Yes 0…No
Participants Blinding	There was blinding of all subjects	1…Yes 0…No
Therapist Blinding	There was blinding of all therapists who administered the therapy	1…Yes 0…No
Assessor Blinding	There was blinding of all assessors who measured at least one key outcome	1…Yes 0…No

<15% Dropouts	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	1…Yes 0…No
Intention-to-Treat Analysis	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	1…Yes 0…No
Between-Group Difference	The results of between-group statistical comparisons are reported for at least one key outcome	1…Yes 0…No
Point Estimate and Variability	The study provides both point measures and measures of variability for at least one key outcome	1…Yes 0…No
Total (0-10)	Sum of previous items.	> 4 points… inclusion < = 4 points… exclusion

Participants

Participants' demographics such as number, sex, and age were collected to assess similarity of studies.

Intervention

The studies selected for final analysis had to have some type of neurofeedback treatment in the intervention group. The treatment provided to the participants in the control group differed only from the experimental treatment in the use of neurofeedback.

Outcome measures

This study is aimed at understanding the effect of BCI technologies on motor rehabilitation. Therefore, all included studies should present functional values before and after therapy. All of them must have used a valid functional scale as the Fugl Meyer Assessment Scale (FMA), used for the motor evaluation of the upper limb. If researchers present more than one motor upper extremity scale, the FMA for this analysis will be chosen whenever possible. The FMA functionality scale is widely used for motor assessment of patients with physical limitations after stroke. The use of FMA in our analysis allows a better comparison between clinical studies.

Data analysis

The data were entered into Review Manager 5.3 software for statistical analysis [118].

BCI system used for the clinical trials

The BCI system used in this study is recoveriX (g.tec medical engineering GmbH, Austria) [119], Figure 5 depicts different system components and the physical layout during a BCI session. This system managed all EEG data recording and real-time interactions with the patient and therapist, including visual feedback using a virtual reality avatar and proprioceptive feedback using FES. Participants wore EEG caps with 16 active electrodes. at positions FC5, FC1, FCz, FC2, FC6, C5 C3, C1, Cz, C2, C4, C6, Cp5, Cp1, Cp2 and Cp6, according to the international 10/10 system (extended 10/20 system). A reference electrode was placed on the right earlobe and a ground electrode at FPz.

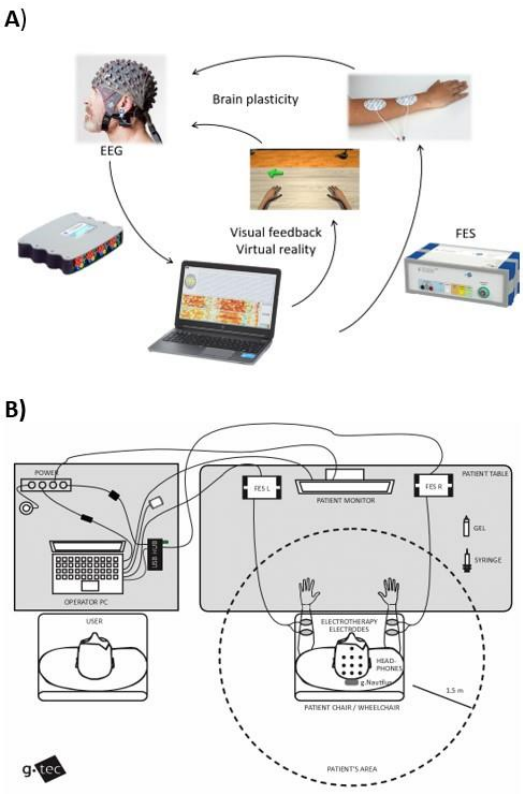

Figure 5. BCI system components description. A) shows the motor learning loop. B) System setup.

Two FES electrodes were placed on the skin over the wrist extensors of the left and right forearms. The frequency was set to 50 Hz, the pulse-width to 300µs. Then, the stimulation parameters were adjusted for each patient and session individually until either (1) the optimal passive movement without pain for patients with mild or moderate muscle spasm, or (2) muscle contraction was observed in the target muscle of the paretic side for patients with severe muscle spasm.

Instructions of a BCI therapy session

At the beginning of each therapy session, the therapist talked with each patient to confirm that the patient understood the MI task and the upcoming procedure and addressed any questions or concerns. Next, the EEG cap and FES pads were placed on the patient, and FES parameters were adjusted, as detailed below. After this preparation, the patient was seated in a comfortable chair in front of a table. A monitor was placed on that table showing to the patient a virtual reality display with two hands (see Figure 5.B). The patient was asked to place both hands on the table and perform MI while following cues and feedback presented on the monitor. Each session contained up to three runs of 80 trials each, depending of the patient's fatigue. At the end of each session, the cap and FES pads were removed, and the skin was cleaned with a moist cloth. Each session required about 60 minutes total, including preparation and cleaning.

MI exercise

Figure 6 depicts the timing of each trial. Each movement starts with a beep, to help the participant focus on the upcoming task. Two seconds later, the system presents an arrow pointing to the left or right on the patient's monitor and the word "left" or "right" in the participant's mother tongue via headphones. These simultaneous visual and auditory cues both direct the patient to imagine dorsiflexion of the left or right wrist (in pseudorandom order). The participant is instructed to start the MI immediately after receiving the command and to continue the MI until the relax command is presented auditorily. The feedback phase starts 1.5 seconds after the command presentation. The feedback devices can only be activated during this phase.

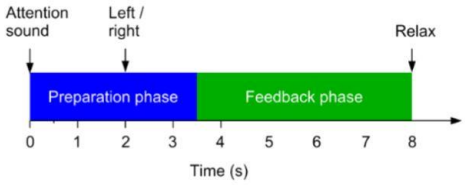

Figure 6. Trial description.

Motor Imagery Accuracy

The EEG data were bandpass filtered (0.5-30 Hz) to increase the signal to noise ratio (SNR) and to remove unnecessary components. We also applied a 50 Hz notch filter to reduce line noise. We then created 8 second epochs of EEG data for every trial in the paradigm and divided them into two classes: left or right.

Each epoch was band pass filtered (8-30 Hz) and an artifact rejection is applied (same as in the lateralization coefficient). Using the current frames, a CSP filter is created and then it is used to get 4 spatially filtered channels from the 16 EEG channels. For every frame we defined 14 timepoints, separated 0.5 seconds between each other, from second 1.5 to the second 8 of the frames. For each timepoint we calculated a set of 4 features.

For each timepoint, we calculated the variance of each spatially filtered signal using a window of 1.5 seconds. The resulting 4 features for each timepoint are normalized, and we then derive their logarithmic values. Using all the features from all the timepoints and the entire frame collection, we calculate a linear discriminant analysis (LDA) classifier.

Using the CSP filter and the LDA classifier, the classifier accuracy is assessed with a 10-fold cross validation process. During this process, a classifier is created for every fold using 90% of the frames (training set), which is then assessed with the other frames (testing set). This is done 10 times, and ultimately yields a mean accuracy for each class (left and right hand) and every timepoint. Finally, for each class, the MI accuracy is calculated as the maximum, among all timepoints, of the means between the accuracy.

Clinical trial I – EEG biomarkers for stroke diagnosis and prognosis

Thirty-two healthy subjects and thirty-six stroke patients with upper extremity hemiparesis were recruited for this study. All healthy participants were volunteers recruited through the Universitat de Vic, Spain. The stroke patients were recruited in the rehabilitation center RecoveriX Gym in Schiedlberg, Austria. Two patients dropped out from the study because personal reasons.

The inclusion criteria for stroke patients were: i) residual hemiparesis, ii) the stroke occurred at least four days before the first assessment, iii) functional restriction in the upper extremities. Additionally, for all participants, the following criteria were applied: iv) able to understand written and spoken instructions, v) stable neurological status, vi) willing to participate in the study and to understand and sign the informed consent, vii) able to attend meetings. Ethics approval was obtained from the Ethikkommission des Landes Oberösterreich in Austria for the patients, and the ethics committee of Comitè d'Ètica de la Recerca-CER of Universitat de Vic (Spain) for the healthy controls.

Protocol

Healthy controls

The healthy controls sat in a comfortable chair for 8 minutes while resting EEG (rEEG) was collected. During this resting state assessment, participants were asked to avoid unnecessary movements and keep their eyes open, aside from normal blinking.

Stroke patients

Each stroke patient participated in four assessment sessions and 25 therapy sessions.

Figure 7. Therapy timeline.

Four Assessment Sessions: A clinician assessed each patient twice before the therapy began and twice after the last therapy session. Each of these four assessment sessions had two components: (1) the clinician recorded 8 minutes of rEEG with the same settings as described above for healthy controls and (2) the clinician tested the patient's motor function. Figure 7 shows the timeline. The Pre1 assessment was performed 1 month before starting the therapy, and the Pre2 assessment was performed just before the therapy started. The Post1 assessment was performed just after the last session, and the Post2 assessment occurred one month after the last session. 136 assessment sessions were performed in total (4 per patient).

25 Therapy Sessions: Patients should complete 25 sessions of BCI therapy, with two sessions per week. All patients and therapist were instructed to use the BCI system as it is explained in the section "Instructions of a BCI therapy session".

Assessment tests

We used ten tests to assess each patient's functional capabilities during each of the four assessment sessions. All of these tests are well-established in the scientific literature and clinical practice. Each of these ten tests measure different aspects of motor function, other motor impairments (tremor and spasticity), cognitive function, sensory discrimination, and self-reported impact.

Fugl-Meyer Assessment (FMA): The primary measure of this study is the Fugl-Meyer Assessment for the upper extremity (FMAue). This scale contains values between 0 to 66 points, where a score of 0 reflects no motor function in the upper extremities and 66 points indicates normal function.

We also used the Fugl-Meyer Assessment for the lower extremity (FMAle) to assess the motor function of the lower limb. The FMAle scale ranges from 0 points (no lower-limb functionality) to 34 points (normal function).

Box and Block Test (BBT): In the BBT, the patient must move 100 small blocks from one container to another, while avoiding an obstacle between them. The outcome is measured in the number of boxes moved within a specific time (one minute).

9 Hole-Peg Test (9HPT): Like the BBT, this test measures how patients can grasp and move small objects from one area to another. In the 9HPT, each patient must pick up nine small pegs from a box and place them in 9 holes and then remove them, while only holding at most one peg at any time. The outcome is measured in completion time; a shorter completion time indicates higher motor function. Like the BBT, some patients with more severe disabilities may be unable to perform this task at all.

Fahn Tremor Rating Scale (FTRS): This test is designed to measure each patient's tremor. The patient performs the test with both hands, resulting in a score between 0 points (no tremor) to 12 points (maximum tremor) for each hand.

Modified Ashworth Scale (MAS): The MAS is used to assess each patient's spasticity. The minimum score is 0 points (no spasticity) and maximum score is 4 points (passive range of motion is totally restricted for the spasticity).

Montreal Cognitive Assessment (MOCA): The MOCA was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visual construction skills, conceptual thinking, calculations, and orientation. The maximum possible score is 30 points, and a score of 26 or above is considered normal.

Two Point Discrimination Test (TPDT): The TPDT was employed to assess finger sensitivity. This test evaluates the minimum distance between two points that patients can discriminate. The clinician touches the patient's fingertips with two very sharp tips (like needles) and asks if the patient can feel

both points. If so, the clinician reduces the distance between the two tips and repeats the test until the patient reports feeling only one point. Patients who can feel two distinct tips that are closer together have greater finger sensitivity.

Self-Rated Questionnaire (SRQ): The SRQ is a questionnaire with five parts: Pain (0-70 points); Function (0-70 points); Memory and thinking (0-70 points); Ability to be mobile at home and in the community (0-90 points); Stroke recovery (0-10 points). Each of these parts has descriptions of different tasks. The patient estimates the difficulty in performing the task on a scale from 0-10, where 0 means 'unable to do', and 10 means 'no difficulty'. The scale is different for the Pain part, where 0 means 'none' and 10 means 'extreme'.

Barthel Index (BI): This scale is widely used to evaluate how well patients can perform activities of daily living (ADL). Like the SRQ, it is a questionnaire that measures the impact of stroke from the patient's personal, subjective perspective. The minimum score is 0 points, which indicates that the patient cannot perform any ADLs. The maximum score is 100, in which the patient can perform all ADLs well.

Statistical analysis

The statistical analyses were performed using MATLAB R2017a. The normal distribution of the data was tested using Shapiro-Wilk test. The statistical test was chosen according to the normality of the sample, the homogeneous of variance (Levene's or Brown-Forsythe test of equal variance) and sample size. Descriptive statistics will be showed as mean and the standard deviation (SD), or the median with the inter-quartile rate (IQR) of 0.25 and 0.75.

Quantitative EEG Biomarkers

Resting state paradigm

Brain Symmetry Index

The BSI is a parameter that compares the spectral power of the two hemispheres of the brain using bandpass filtered EEG signals. The BSI value ranges from 0 to 1 and is a measure of the symmetry between both hemispheres. A BSI value of 0 reflects total symmetry and 1 total asymmetry. The BSI value should be closer to 0 in healthy people and higher in stroke patients.

Method

The BSI of a segment of EEG is calculated using a revised BSI formula [82], which is based on the squared value of the Fourier coefficients:

$$BSI(t) = \frac{1}{K}\sum_{n=1}^{K}\left|\frac{R_n^*(t) - L_n^*(t)}{R_n^*(t) + L_n^*(t)}\right|$$

with

$$R_n^*(t) = \frac{1}{M}\sum_{ch=1}^{M} a_n^2(ch,t)$$

where $a_n(ch,t)$ is the Fourier coefficient with index n of channel ch at time t. For the right hemisphere $R_n^*(t)$, the same formula is applied for the left hemisphere electrodes.

We collected data from 16 channels. For the BSI calculation, we discarded the central sites and split the rest in two sets: right and left. For the right hemisphere the electrodes were: FC3, C5, C3, C1, CP3 and CP1. For the left hemisphere, the electrodes were: FC4, C2, C4, C6, CP2 and CP4.

For each participant, we processed 8 minutes of resting state EEG (in each group, healthy and stroke group). We bandpass filtered (1-25 Hz) the whole EEG, and then we cut it in frames of 4 seconds, with a 2-second overlap. We used a Hamming window to prevent spectral distortion. We used an artifact detection method based on the overflow of the EEG variance within a moving window of 1.5 seconds. Any frame with more than 1.5 times of the total variance for each channel was rejected from the BSI calculation. Finally, the Fourier coefficient was calculated from the power density estimation using the Welch method.

Band power

Absolute Power

The classical frequency bands were defined as delta (1 to 4 Hz), theta (4.25 to 8 Hz), alpha (8.25 to 12 Hz) and beta (12.25 to 30 Hz). For each band and each electrode, a single power value was calculated using the Welch's method among all EEG epochs and averaging all the frequency points. A Hamming window was used to get the epochs. Then, the absolute power of each band was defined as the mean value among all the electrodes.

Relative Power

The relative power of one specific band is defined as the ratio between its absolute power and the sum of the absolute power of all the bands.

Delta – Alpha Ratio

The Delta – Alpha Ratio (DAR) is the ratio between the absolute power of the delta band and the absolute power of the alpha band.

Power Ratio Index

The Power Ratio Index is defined as the sum of the absolute power of the delta and theta band divided by the sum of the absolute power of the alpha and beta band.

Motor Imagery paradigm

Event-Related Synchronization and Desynchronization

Figure 8 presents ERD/S patterns that typically occur during MI. During MI, the contralateral motor cortex produces a desynchronization (event-related desynchronization or ERD) of cortical motor neurons, showing a decrease in the bandpower of the waves with a frequency of 8-13 Hz (mu frequency rhythm). The ipsilateral motor cortex shows very strong ERS patterns to suppress corresponding motor areas during MI of the opposite hand side [33], [34], [94], [95]. To create such maps, the change of EEG bandpower of several bandpass filtered frequency bands is calculated and plotted visually. The frequency bands chosen here range from 8Hz to 30Hz in steps of 2 Hz. In each band, the power is calculated stepwise in windows of 16 samples (0.0625s). Then, the bandpower of each window is compared to the bandpower of the reference period (grey area in Figure 8), during which the participant is supposed to be in a resting state. The comparison used the following formula, in which A is the bandpower of one single window and R the bandpower within the reference period:

$$ERD = \frac{A - R}{R} * 100\%$$

Finally, a bootstrapping significance test ($\alpha = 0.05$) is done for all windows. Values that are not significant are set to 0 and are plotted in white in Figure 8. High ERD values (decreased bandpower) are plotted in in red, whereas high ERS values (increased bandpower) are plotted in blue.

Laterality Coefficient

The raw EEG data recorded during the MI sessions was used to calculate the LC parameter. The LC coefficient is calculated for each session twice: first for trials of MI of the paretic (p) hand and again for trials of the healthy (h) hand. We employed the following formula, where C and I refer to the contralateral and ipsilateral values of the ERD/ERS patterns during the MI.

$$LC_{p/h} = (C-I) / (C+I)$$

We followed six steps to calculate C and I:

1) Band filtering (8-13 Hz or 13-30Hz) of the EEG signal;

2) Frame artifact rejection if a sample overflows a threshold based on the median variance among the samples of all the frames;

3) Laplacian derivation using the surrounding electrodes.

4) ERD/ERS patterns calculation according to [95];

5) Summation of all ERD/ERS values from second 2 until the end of the ERD map (second 8); and

6) Apply the formula to obtain the LC coefficients.

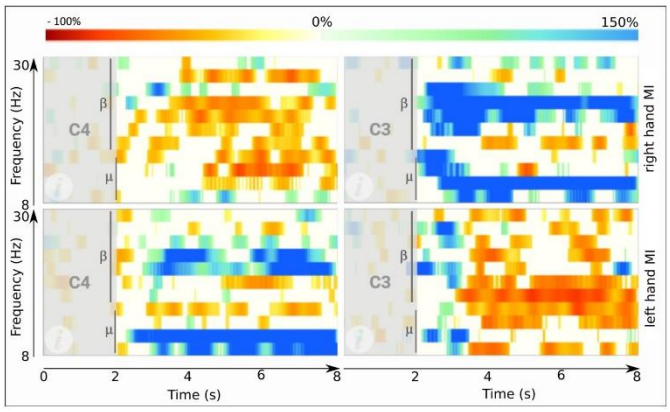

Figure 8. ERD/ERS maps. Top right: ERD map during MI of the right hand on the position C3. Top left: right hand MI on C4. Bottom right: left hand MI on C3. Bottom left: left hand MI on C4. Each plot shows the time from 0 to 8 seconds (x-axis) and frequencies between 8Hz and 30Hz (y-axis). Red areas indicate high ERD. Blue areas mark the opposite: an ERS. Vertical bars indicate the cue onset at 2 seconds.

The following table (see Table 3) shows a summary of the studied qEEG parameters on this work.

Table 3. Summary of the studied qEEG parameters.

Name	**Acronym**	**Paradigm**	**Subjects**
Brain Symmetry Index	BSI	Resting state	Healthy / Stroke
Absolute Power Delta	APΔ	Resting state	Healthy / Stroke
Absolute Power Theta	APθ	Resting state	Healthy / Stroke
Absolute Power Alpha	APα	Resting state	Healthy / Stroke
Absolute Power Beta	APβ	Resting state	Healthy / Stroke
Relative Power Delta	RPΔ	Resting state	Healthy / Stroke
Relative Power Theta	RPθ	Resting state	Healthy / Stroke
Relative Power Alpha	RPα	Resting state	Healthy / Stroke
Relative Power Beta	RPβ	Resting state	Healthy / Stroke
Delta Alpha Ratio	DAR	Resting state	Healthy / Stroke
Power Ratio Index	PRI	Resting state	Healthy / Stroke
Laterality Coefficient in Alpha band	LCα	Motor Imagery	Stroke
Laterality Coefficient in Beta band	LCβ	Motor Imagery	Stroke

Clinical trial II - Improving BCI performance with gamification

Game design

The game was developed on top of this system with the main requirements of not altering the pace of the rehabilitation and not modifying the gesture of the avatar in order to avoid altering the sense of identification of the user with the virtual forehand. With these limitations, the narrative was restricted to a game in which the unique action of the avatar was raising and lowering the wrist. Moreover, to make the virtual situation as similar as possible to the real one, we avoided driving-like actions that imply a virtual navigation of the avatar. We also wanted to have feedback of the current exercise and of the total training stage so far. Hence, the goal of the game is to compete with a mouse in order to preserve food. Figure 9 shows the 'standard' avatar and the new game appearance. At the beginning of the session 80 pieces of cheese (one for each exercise) are set between the two virtual arms. At each exercise, a mouse appears from the right or left corner of the room (the side of the wrist that must move) and stands nearby the pile of cheese during the cue sub-stage. In the feedback sub-stage, the game receives a cue of boolean events that indicate if the mental image is being correct or not. The avatar's hand moves accordingly stopping when a cue is incorrect and proceeding otherwise. In the relax sub-stage, if 5 consecutive events are considered correct, when the virtual arm lowers, the mouse runs away empty-handed. Otherwise, it takes a piece of cheese. The size of the pile is thus an indicator of the overall progress of the training stage. In addition, a scoring panel was added to reinforce the awareness of the user. This panel could be deactivated, shown intermittently or constantly displayed. The game was implemented with Unity and connected to the recoveriX® replacing the non-gamified version.

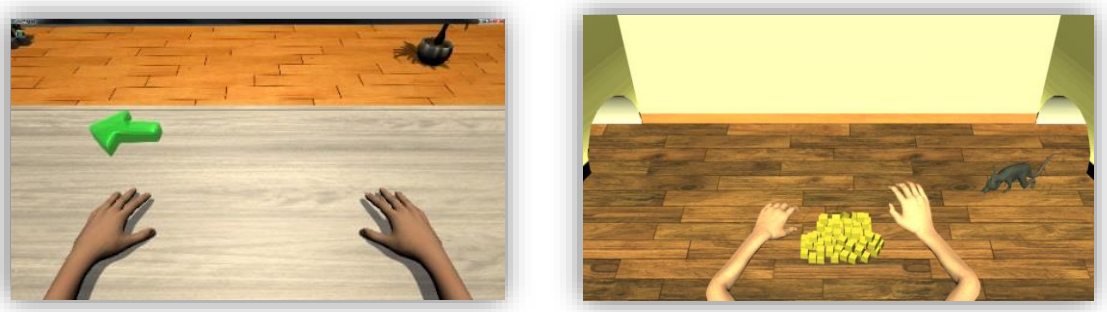

Figure 9. Standard avatar and new game appearance. In the left side, is the avatar used in recoveriX system, the green arrow indicates in which hand the movement should be performed. In the right side is the new animated game, both arms are in the same position than the standard avatar. In front of the virtual subject there are 80 pieces of cheese that the user should try to keep. The rat indicates which hand should move.

Participants

Ten stroke patients with hemiparesis in the upper limb and six healthy subjects were recruited for this study. The stroke subjects were patients from Institut Guttmann. All participants were volunteers. The inclusion criteria for stroke patients were: i) residual hemiparesis, ii) the stroke occurred at least four

days before the first assessment, iii) functional restriction in the upper extremities. Additionally, for all participants, the following criteria were applied: iv) able to understand written and spoken instructions, v) stable neurological status, vi) willing to participate in the study and to understand and sign the informed consent, vii) able to attend meetings. Ethics approval was obtained from the Ethic committee of Institut Guttmann, Barcelona, Spain. Finally, all participants were informed about the goals of the project, and they provided their written informed consent before participating in the study.

Experimental design

All participants took part in the same procedure: control users in the research lab and patients in the rehabilitation institution. All participants performed two training sessions separated in time by a minimum of 1 day and a maximum of 2 weeks. Each session was composed of three runs or stages: Calibration (C-S1, C-S2), Training 1 (T1-S1, T1-S2) and Training 2 (T2-S1 and T2-S2). All patients and therapist were instructed to use the BCI system as it is explained in the section "Instructions of a BCI therapy session".

As for clinical trial 1, each run was composed of 80 trials (80 movements) and lasted 12 minutes. There was a resting time of about 5 minutes between stages. The calibration run was used to train the LDA classifier, thus, during this run the online feedback provided to users is always positive. After the calibration run, all participants were moved to the 'Training' mode, where the feedback is triggered by the MI in real time. During Training 1 feedback was based on the classifier built after Calibration, and during Training 2 it was based on an enhanced version of the classifier using data of the previous two stages. Each session started from scratch; thus Session 2 did not use the classifier of Session 1.

In the first session, calibration (C-S1) and Training 1 (T1-S1) were without game, only with the regular avatar, while Training 2 (T2-S1) used the game without any feedback of time and scoring (no feedback). In the second session, all stages used the game: C-S2 no feedback, T1-S2 showing score and time every ten exercises (intermittent feedback) and T2-S2 showing time and score constantly (constant feedback).

Assessment test

For this study two variables were analyzed; BCI performance and users' experience. The BCI performance was studied using the MI accuracy of each run computed as exposed above. In addition, the users' experience was assessed using a questionnaire.

Questionnaire

The opinions of users about the game were gathered through a customized version of the System Usability Scale (SUS) composed by 8-items to be answered in a scale of 1 to 5 (being 1 the worst case and 5 the better). See Table 4. The full questionnaire is available in Appendix B.

Table 4. Users' experience questionnaire

#	Question	Score
Q1	Evaluate the level of fun in the game.	[1] no fun; [2] little fun; [3] indifferent ; [4] fun ; [5] very fun
Q2	Evaluates the visual aspect of the game.	[1] very bad; [2] bad; [3] indifferent; [4] good; [5] very good
Q3	Evaluate the easeiness of use of the game.	[1] very hard ; [2] hard ; [3] normal ; [4] easy; [5] very easy
Q4	Evaluate the clarity of rules of the game.	[1] very confusing; [2] confusing; [3] indifferent; [4] clear; [5] very clear
Q5	With regard to the narrative plot (the fight against the mouse to protect the cheese), you thought so.	[1] very inadequate; [2] inadequate; [3] indifferent; [4] adequate ; [5] very adequate
Q6	With regard to the level of concentration required to perform the exercise, in your opinion, adding the game to the rehabilitation session has contributed to: .	[1] has distracted me a lot; [2] has distracted me; [3] has not influenced me; [4] has helped me to concentrate; [5] has helped me to concentrate a lot
Q7	With regard to possible boredom while exercising, in your opinion, adding the game to the rehabilitation session has contributed to: .	[1] It's t increased a lot more boredom; [2] It's bored me more; [3] It has not influenced me; [4] It alleviated boredom more; [5] It alleviated boredom a lot more
Q8	In general, the idea of introducing a game (not necessarily this one) into rehabilitation therapy, seems: .	[1] very bad; [2] bad; [3] indifferent; [4] good; [5] very good

Statistical analysis

The software used for the statistical analysis was MATLAB R2017a and a python script using scipy stats, numpy and pandas. The first step of the statistical analysis was the comparison of the baselines of each group of participants; age, gender and precision. Before any comparative calculation was made, a normality test of the variables to be analyzed was performed using the Shapiro-Wilk Test (SWT). For the comparison between groups ('Healthy' and 'Stroke'), t-test for independent samples (in case of assumption of normality) or Mann–Whitney U test (in case of non-normality) was used.

For the analysis of the impact of the serious game combined with BCI on the user's concentration, the MI accuracies of each subject obtained in each game mode were compared. For this no independence could be assumed. The selected test for the analysis was repeated measures ANOVA (32–35), which allows the results' comparison of the same group of participants at different time points. For that, two assumptions are needed: normality distribution (Shapiro-Wilk test >0.05) and assumption of sphericity (Mauchly's sphericity test > 0.05). If these assumptions are not respected, Friedman's test will be used.

Finally, a quantitative analysis of the answers in the questionnaire of each participant was carried out.

Chapter III - Results

Effectiveness of BCI treatment for stroke recovery – systematic review with meta-analysis

The aim of this section is to establish the usefulness of BCI devices for stroke rehabilitation based on randomized clinical trials. The analysis will focus on motor rehabilitation of the upper limb. We will carry out a meta-analysis to study the last evidence of the BCI-based treatment for the motor rehabilitation of the upper extremity in stroke survivors. Clinical studies will be searched to see whether neurofeedback provide additional positive effects when it is combined with other therapies.

In the literature search, 10 out of 466 articles were identified by the search strategy after excluding articles according to inclusion/exclusion criteria. Full text of the remaining 17 articles were reviewed, and 7 of them were excluded because of the following reasons: incomparable control group (1 study), no outcome measures (1 study), non-English (1 study), no randomization in group assignment (1 study), duplicate (2 studies), and low quality (1 study: PEDro score $\leq$ 4). The remaining 10 articles are summarized on the Appendix A. 7 out of 10 articles combined BCI neurofeedback with standard physiotherapy in the experimental group, and the other 3 articles only did BCI therapy. In all cases the treatment provided to the participants in the control group differed only from the experimental treatment in the use of neurofeedback.

Outcome measures

FMA-UE was a primary outcome measure or one of secondary outcome measures in all included 10 trials. A meta-analysis method was implemented to investigate the therapeutic effect particularly on FMA-UE of neurofeedback group over control group. On these publications where the study design had more than two groups (three arms for example), such as Ang 2014 (Ang et al. (a)), the BCI-haptic knob (HK) and HK intervention was analyzed because these two arms are more appropriate to review the neurofeedback effect than the third intervention, standard arm therapy intervention.

The effect of neurofeedback on upper-limb sensorimotor outcomes was examined by pooling data after intervention from 10 trials of 234 participants. Neurofeedback group improved by 3.00 points more in FMA-UE than control group, (Mean Difference (MD), 3.00; 95% CI, 1.74-4.25; I^2=38%, Z = 4.68, *P* <0.00001; Figure 10). For the effect size, the Standard Mean Difference (SMD) between the neurofeedback group and control group was 0.73, which is a moderate effect size. See Figure 11.

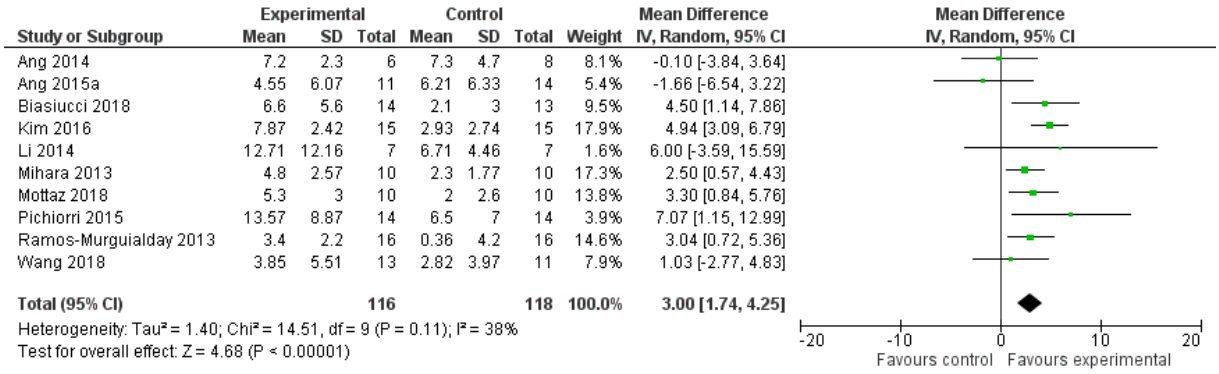

Figure 10. MD (95% CI) of the effect of neurofeedback compared with a control group on FMA-UE by pooling data from 10 comparisons (n=234). Abbreviations: IV, inverse variance; SD., standard.

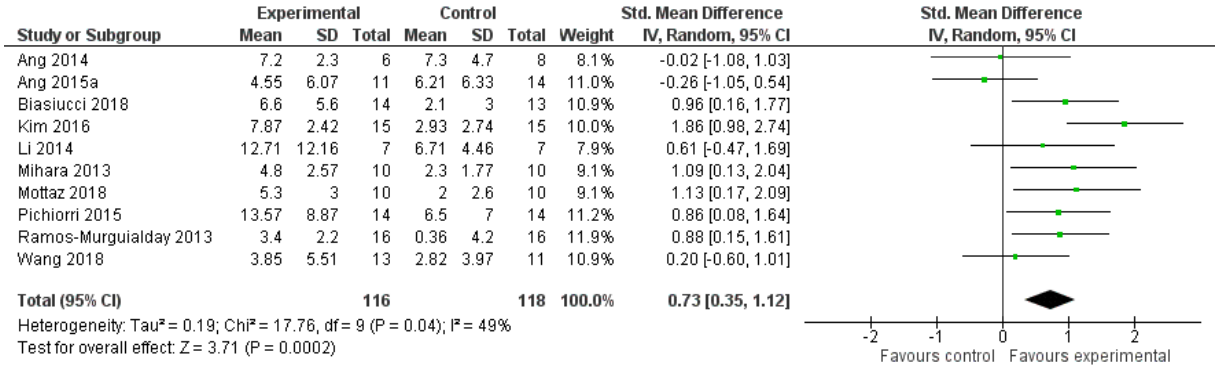

Figure 11. SMD (95% CI) of the effect of neurofeedback compared with a control group on FMA-UE by pooling data from 10 comparisons (n=234). Abbreviations: IV, inverse variance; SD, standard.

Therapy dosage and outcome measures

The weighted mean improvement in FMA-UE of all the 10 publications is 6.81 (SD = 4.89) points in experimental groups (n=116) and 3.68 (SD = 4.16) points in control groups (n=118). The neurofeedback dosage was estimated from all 10 publications, who received the neurofeedback intervention 60 minutes, 3 sessions per week over 4 weeks (Table 5). 7 out of 10 interventions included additional physiotherapy with 40 minutes, 3 sessions per week over 4 weeks.

Patients who underwent the neurofeedback therapy alone improved by 4.78 (SD = 5.07) in FMA-UE and those who received it combined with physiotherapy improved by 7.51 (SD = 4.83) in the same assessment.

Table 5. Neurofeedback Therapy in all 10 publications

	Duration per session [mins]	**# of sessions per week**	**# of weeks**	**Total therapy time [mins]**
Neurofeedback therapy (10 publications)	60 [30 60]	3 [3 4]	4 [4 6]	780 [510 1170]
Neurofeedback + stantard therapy (7 publications)	40 [30 60]	3 [3 4]	4 [4 5]	600 [420 780]
Neurofeedback alone (3 publications)	90 [75 90]	3 [3 3]	6 [5 6]	1440 [1260 1530]

Rest period and preparation time are included in the neurofeedback time. Table 6 shows the total feedback time based on the trial duration and repetitions number. The period of possible neurofeedback was found in all the publication except Kim et al., and the total feedback time was 1.75 hours in the end of the treatment.

Table 6: Feedback time in neurofeedback therapy from 9 publications

Duration per trial [secs]	**Repetition in one session**	**# of sessions per week**	**# of weeks**	**Total feedback time [in minutes] ***
5 [4 8.3]	80 [50 90]	3 [2.8 3.3]	4 [4 6]	6300 [4320 to 11520]

EEG biomarkers for stroke diagnosis and prognosis

On this section, we investigate thirteen different qEEG parameters and their relationship with the diagnosis and functional prognosis of stroke patients. One group of healthy participants and one group of stroke patients participated in the study. Stroke patients performed functional assessment sessions, and BCI rehabilitation therapy for the upper extremity. EEG was recorded in two different situations: 8 minutes of resting state with open eyes (rEEG), and MI using a BCI system for motor rehabilitation. BSI, DAR, PRI, absolute power bands and relative power bands parameters are analyzed in rEEG, whereas LC has been calculated during the MI period. To assess each patient's functionality before and after the therapy, we primarily used the Fugl-Meyer assessment (FMA) [96], [97]. We also evaluated nine other standardized tests used in rehabilitation to assess motor function, spasticity, cognitive function, and other parameters, including the Fahn Tremor Rating Scale, MAS, Barthel Index, Box and Block Test, 9 Hole Peg test, 2 Point Discrimination Test and Montreal Cognitive Assessment. This is the first work to employ such a broad range of tests along with analyses of BSI and other EEG-based parameters across several therapy sessions. To do not lose the thread of the previous section, firstly the functional improvements after BCI therapy will be presented, and secondly the analysis of the qEEG parameters.

Participants' baselines

Thirty-two healthy subjects were enrolled in the study, 13 males and 19 females. The mean age in the healthy group was 42.3 years (SD = 15.4). Thirty-four stroke patients participated (excluding two who dropped out). The stroke patients' mean age was 65.3 years (SD = 14.4); this evident difference in age will be addressed at a later stage of this analysis. 22 of the patients were male (64.7%), and the other 12 stroke participants were female (35.3%). Table 7 shows the participants' baselines. The stroke participants were classified in four groups based on their stroke diagnosis: Cortical, Subcortical, Cortical + Subcortical, Healthy. The most common type of stroke was Subcortical with 17 patients (50.0%), followed by Cortical+Subcortical with 12 patients (35.3%) and Cortical with 5 patients (14.7%). Twenty-seven of these patients were in chronic phase (79.4%), and only 7 in subacute phase (20.6%). 23 patients had a stroke in the right hemisphere (67.7%), whereas the stroke was in the left hemisphere in 11 patients (32.4%).

Table 7. Participants' baselines.

Group	n	Age (y)	SD	Male	Female
Healthy	32	42.3	15.4	13	19
Patient	34	65.3	14.4	22	12
Cortical	5	57.6	27.3	4	1
Subcortical	17	66.4	12.7	9	8
Cortical + Subcortical	12	67.0	09.4	9	3

Functional assessment of stroke patients before and after BCI treatment

The results in this section summarize differences from the Pre2 to Post1 assessments across different tests (see Figure 12). We used the Wilcoxon signed rank test for statistical analysis, since the data did not present a normal distribution (see Table 8). The improvement of each scale is presented using the IQR, and the mean and SD are also provided if differences are significant.

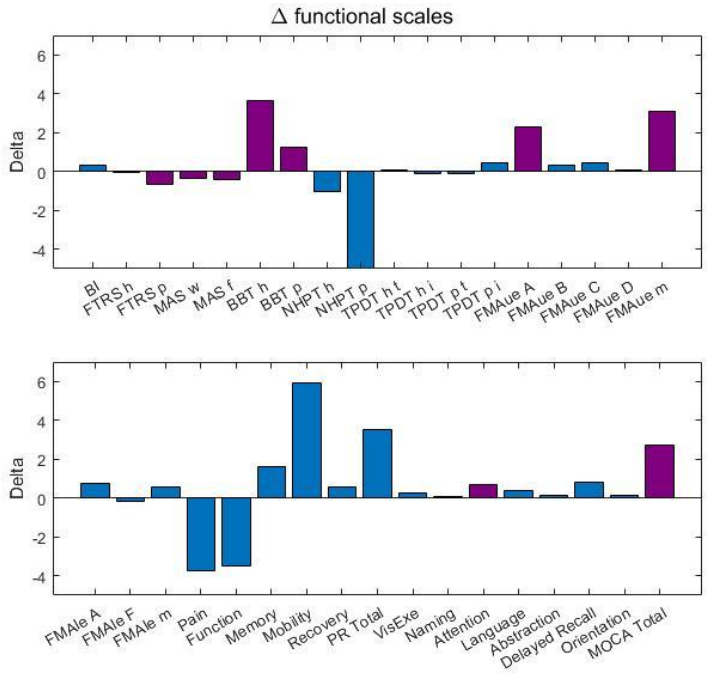

Figure 12. Changes in functional scales after BCI therapy. The significant changes are represented with violet bars.

FMA: The FMAue test has a score range of 0 to 66. One of the 34 patients had only slight hemiparesis and attained the maximum FMAue score in the pre-assessment. The Wilcoxon signed rank test shows that there is a significant improvement in FMAue after the therapy (ΔFMAue = 1 [0-8], $P = 0.002$). The mean improvement is 3.12 (SD = 5.1). 21 patients (61.8%) improved at least 1 point in the FMA score. Among patients who improved, the mean improvement was 5.76 points (SD = 4.61). 6 patients (17.68%) decreased at least 1 point in FMA score, and the mean decrease in this group was -2.5 points (SD = 1.76). The remaining 6 patients (17.68%) had an improvement equal to 0.

BI: The BI did not show significant improvements after the therapy (ΔBI = 0 [0-5], $P = 0.480$). The BI score decreased in 7 patients (20.59%), 11 patients (32.35%) reported positive changes in the BI after the therapy, and 16 patients (47.06%) did not show changes in this parameter.

FTRS: The FTRS for the healthy hand (FTRS_h) did not show a significant difference before versus after the BCI therapy (ΔFTRS_h = 0 [0-0], $P= 0.984$). The FTRS in the paretic hand (FTRS_p) did show a significant improvement (ΔFTRS_p = 0 [-1-0], $P = 0.018$). The mean improvement of FTRS_p is -0.65 (SD = 1.5). 32 of the 34 patients (94.12%) reported some degree of tremor in the paretic hand

(FTRS_p) before the therapy. After the therapy, 10 of these 32 patients (31.25%) exhibited a decreased tremor in the paretic hand. 1 of these 32 patients (3.13%) showed an increase of tremor after the therapy. The other patients did not report any changes.

MAS: The MAS scale showed a statistical reduction of the spasticity in the wrist (ΔMAS_w = 0 [-1-0], *P*= 0.003, mean improvement -0.37 (SD = 0.69)), and in the fingers (ΔMAS_f = 0 [-1-0], *P* = 0.001, mean improvement -0.41 (SD= 0.63)). 23 of the 34 patients (67.65%) reported some spasticity in the wrist (MAS > 0), and 25 patients (73.53%) reported some spasticity in the fingers. 12 of the 23 patients (52.17%) who reported wrist spasticity prior to therapy reported a decrease after therapy. 14 of the 25 patients (56.00%) who reported finger spasticity prior to therapy reported a decrease after therapy.

BBT: We found a statistical improvement of BBT in the healthy hand (ΔBBT_h = 2 [1-8] and *P* = 0.005, mean improvement 3.64 (SD = 7.4)). The changes in the paretic hand are also significant (ΔBBT_p = 0 [0-1] and *P* = 0.034, mean improvement 1.22 (SD = 3.5)). 10 patients (29.41%) improved the BBT score with the paretic hand, 2 patients (5.88%) decreased the BBT score with the paretic hand, and 22 patients (64,71%) did not change from the initial BBT score. In 3 cases (8.82%), it was impossible to perform the BBT before the therapy due to the severity of the motor impairment, but after the therapy, these patients could move at least 1 block in the BBT.

9HPT: The 9HPT in the paretic hand is one of the most commonly used tests of grasp function. Only 5 patients (14.71%) could perform the test before the therapy, and 6 patients (20.59%) could perform this test after the treatment. No significant improvements have been observed after the therapy in the healthy hand (Δ9HPT_h = -1 [-2-2], *P* = 0.325), or in the paretic hand (Δ9HPT_p = -24.5 [-70-2], *P* = 0.375). The results show that the time in the healthy hand has slightly decreased, and in the affected hand the decrease in time was great. For this calculation, we used only the patients able to perform the test before the therapy.

TPDT: This test did not show significant changes before vs. after the therapy in the thumb or index of the healthy hand (ΔTPDT_h_t = 0 [-0.75-1], *P* = 0.720; ΔTPDT_h_i = 0 [-1-0.5], *P* = 0.667). The paretic hand did not show a significant improvement either (ΔTPDT_p_t = 0 [-1.25-1], *P* = 0.888; ΔTPDT_p_i = 1 [-0.25-1], *P* = 0.324). 8 patients (23.53%) improved the discrimination between two points in the healthy thumb by at least 1 mm, and 9 patients (26.47%) improved in the healthy index finger. 6 patients (17.65%) improved in the TPDT at least by 1 mm in the paretic thumb, and 3 patients (8.82%) reported at least 1 mm of improvement in the paretic index.

SRQ: 16 patients (47.06%) reported at least 1 point of pain reduction, and 11 patients (32.35%) reported at least 1 point of pain increase. 13 patients (38.24%) reported an improvement in the ability to perform ADLs, and 6 patients (17.65%) reported a decrease in ADL performance. 11 patients (32.35%) reported an improvement in the memory part, and 11 patients (32.35%) reported a decrease in memory. 16 patients (47.06%) reported an improvement in the mobility part of the questionnaire, while 11 patients

(32.35%) reported a decrease in mobility. Finally, 12 patients (35.29%) reported a better general recovery after BCI therapy, and 10 patients (29.41%) reported a worse recovery after BCI therapy. There are no significant changes in any part of SRQ (ΔPain = -2 [-7.5-6], *P* = 0.285; ΔFunction = 0 [0-4], *P* = 0.444; ΔMemory = 0 [-3-6.5], *P* = 0.614; ΔMobility = 5 [-3-10.5], *P* = 0.056; ΔRecovery = 0 [-2-3], *P* = 0.311).

MOCA: The comparison between before and after the therapy showed a significant improvement in cognitive function, ΔMOCA = 2.5 [0-6], *P* = 0.012, with a mean improvement of 2.71 (SD = 3.29). 10 patients (29.41%) improved by at least one point after therapy, and the MOCA score decreased in two patients (5.88%). The remaining patients reported no change.

Table 8. Changes in the functional scales. The first column shows the results of the Shapiro-Wilk Test (SWT), to assess the normality of the dependent variable. The last column (*P*) presents the probability results of the Wilcoxon signed test, with statistically significant differences colored red.

Scale	SWT		Pre	Post	Δ		*P*
	H	*P*	Median [IQR]	Median [IQR]	Median [IQR]	Mean (SD)	
BI	1	0.001	85 [70-95]	85 [65-100]	0 [0-5]	0.29 (6.15)	0.480
FTRS_h	1	> 0.001	0 [0-0]	0 [0-0]	0 [0-0]	-0.03 (0.83)	0.984
FTRS_p	1	> 0.001	12 [7-12]	12 [4-12]	0 [-1-0]	-0.65 (1.52)	0.018
MAS_w	1	> 0.001	1.25 [0-3]	1 [0-2]	0 [-1-0]	-0.37 (0.69)	0.003
MAS_f	1	0.001	2 [0-3]	1 [0-2]	0 [-1-0]	-0.41 (0.63)	0.001
BBT_h	0	0.346	54 [44-68.75]	54.5 [47-73]	2 [1-8]	3.64 (7.4)	0.005
BBT_p	1	> 0.001	0 [0-3.5]	0 [0-4.25]	0 [0-1]	1.22 (3.5)	0.034
9HPT_h	1	> 0.001	23 [18.75-27.25]	23 [20-26]	-1 [-2-2]	-1.06 (4.6)	0.325
9HPT_p	1	0.046	164 [76-346.25]	135.5 [93-324]	-24.5 [-70-2]	-34 (45.35)	0.375
TPDT_h_t	1	> 0.001	3 [2-4]	3 [2-4]	0 [-0.75-1]	0.06 (1.34)	0.720
TPDT_h_i	1	0.001	3 [3-4]	3 [3-4]	0 [-1-0.5]	-0.09 (1)	0.667
TPDT_p_t	0	0.127	4 [3-5]	4 [3-5]	0 [-1.25-1]	-0.08 (1.75)	0.888
TPDT_p_i	1	0.001	3 [3-4.5]	4 [3-4.75]	1 [-0.25-1]	0.46 (1.66)	0.324
FMAue_m	1	0.003	19 [10-37]	23 [12-41]	1 [0-8]	3.12 (5.06)	0.002
FMAle_m	0	0.443	17 [9.75-24.25]	19 [9-25]	-0.5 [-2-2.5]	0.56 (4.1)	0.856
Pain	0	0.275	25 [16-37]	21 [15.5-36.5]	-2 [-7.5-6]	-3.75 (11.93)	0.285
Function	1	> 0.001	3 [0-12]	6 [0-12]	0 [0-4]	-3.46 (16.71)	0.444
Memory	1	0.003	55 [39.75-70]	59 [43.5-68]	0 [-3-6.5]	1.63 (12.89)	0.614
Mobility	1	0.023	67 [35-79]	70.5 [43.5-81.5]	5 [-3-10.5]	5.93 (17.54)	0.056
Recovery	0	0.174	5 [4-8]	6 [5-7]	0 [-2-3]	0.6 (2.91)	0.311
MOCA_Total	1	0.043	24.5 [17-27]	26 [21-27.75]	2.5 [0-6]	2.71 (3.29)	0.012

Brain Symmetry Index (BSI)

BSI differences between age groups: To date, there is no evidence to demonstrate the variability of BSI with age. We performed a statistical analysis using the rEEG data from the healthy subjects. The data follows a normal distribution according to the Shapiro-Wilk test (*P* =0.117). We explored the relationship between BSI and age using Pearson's method and One-way ANOVA. Figure 13. A show

that the Pearson's correlation did not show significant correlation between BSI and age (rho = -0.110, *P* = 0.548). Subsequently, we compared BSI across age groups (under 30 years, between 30 and 50 years and over 50 years). The variance of each group, using Levene's test, did not show significant results (*P* = 0.278, fstat = 1.338, df = 29.00). The analysis of variance shows that there is no significant difference in the BSI parameter based on the three age groups (F = 0.3843, *P* = 0.684). See Figure 13.B and Table 9.

Table 9. Results of BSI-based age analysis.

One-way ANOVA

	SS	Df	MS	F	*P*
Groups	0.000983	2	0.000492	0.3843	0.6844
Error	0.0371	29	0.0013		
Total	0.0381	31			

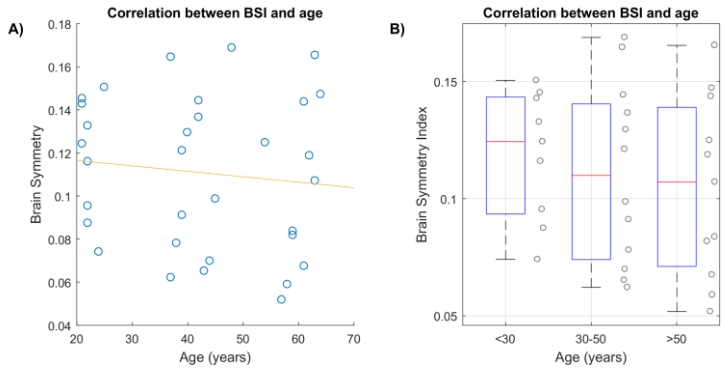

Figure 13. BSI analysis based on age. Figure 5A shows the result of the correlation between age and BSI using Pearson's method. Figure 5B shows the BSI results based on three clusters.

BSI based on gender: Figure 14 presents the results of this subgroup analysis. Both groups have similar variance (Levene´s test results: *P* = 0.198, fstat = 1.733, df = 30.00). The result of this analysis shows that there is a statistical difference in BSI based on gender, according unpaired t-test (t-value = |2.333|, *P* = 0.027).

BSI between groups: Since the results obtained in the BSI based on age did not show significant differences in the healthy group, we compared the BSI between groups (stroke and healthy) despite the age difference. We first

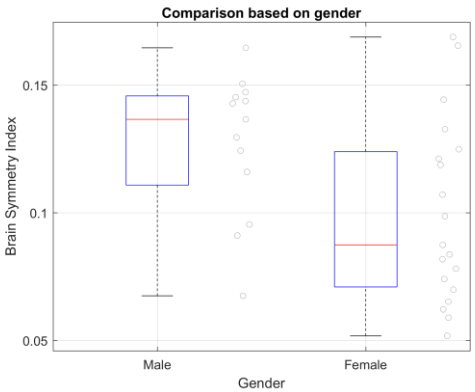

Figure 14. BSI subgroup analysis based on gender in the healthy group. Mean and SD of each group; Male = 0.1272 (SD = 0.0278); Female = 0.0997 (SD = 0.0357). Significant difference between groups using unpaired t-test; t-value = |2.333| *P* = 0.027.

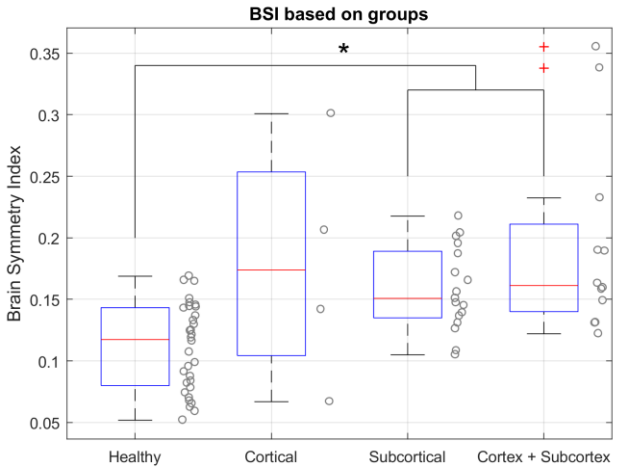

Figure 15. BSI values in resting state with open eyes for each group. (*) indicates the significant differences based on Games-Howell test. BSI of healthy group is significantly different to the subcortical group and cortex + subcortex group. Healthy group median = 0.1173, IQR = 0.0799 – 0.1432. Cortical group = 0.1739, IQR = 0.1043-0.2534. Subcortical group = 0.1507, IQR = 0.1349-0.1890. Cortex + Subcortex group = 0.1612, IQR = 0.1400-0.2110.

analyzed the resting state data collected during the assessments, consisting of 136 assessment sessions from 34 stroke patients, and 32 EEG recordings from 32 healthy subjects. We calculated the BSI of each assessment (Pre1, Pre2, Post1, Post2) from each patient's rEEG data. For this analysis, we used the median of Pre2 and Post1. The first step was the normality testing of each group. The first three datasets presented no significance level using the Shapiro-Wilk Test; hence a normal distribution can be assumed. Group 4 (cortex + subcortex) is the only one not normally distributed. The equality of the variances cannot be assumed (Levene's Test results: P = 0.001, fstat = 5.798, df = 61.00). We used Welch's ANOVA test to compare the BSI parameter across the four groups, because this method is reasonably robust to deviations of normality, when the variances are substantially different and even if the sample sizes are unequal [120], [121]. Table 10 summarizes results from each group. Welch's ANOVA F test has an associated probability of P = 0.003 and F = 8.929, so the assumption that sample means are equal was not met. As the Welch's test shows significant results, the Games-Howell test is used to complete the analysis. Single-step Games-Howell test (see Table 11) shows significant differences between group 1 (healthy group) and both group 3 (subcortex group) and group 4 (cortex + subcortex group). Figure 15 shows the BSI values for each group.

Table 10. Summary statistics from the samples.

Sample	Size	Mean	Variance
1	32	0.1109	0.0012
2	4	0.1789	0.0098
3	17	0.1580	0.0011
4	12	0.1931	0.0061

Table 11. Single-step Games-Howell test. Result of group comparison using Games-Howell test. The first column shows the group code; 1 – Healthy group, 2 – Cortical group, 3 – Subcortical group, 4 – Cortex + Subcortex group. The column 'H' shows the significant (H = 1) and non-significant (H = 0) differences at alpha level, as well as the column 'P' shows the significance level of these comparisons.

Comparison		Delta	SE	Df	Q_star	R	*P*	H	lb	ub
1	2	-0.068	0.045	4.157	0.045	3.975	0.505	0	-0.246	0.110
1	3	-0.047	0.010	33.870	0.010	2.732	0.001	1	-0.075	-0.019
1	4	-0.082	0.023	12.708	0.023	2.964	0.019	1	-0.151	-0.013
2	3	0.021	0.045	4.275	0.045	3.924	0.965	0	-0.156	0.198
2	4	-0.014	0.050	6.171	0.050	3.432	0.992	0	-0.185	0.156
3	4	-0.035	0.024	13.937	0.024	2.929	0.481	0	-0.105	0.035

Correlations between BSI and functional tests: Figure 16 shows a significant correlation between BSI and patients' outcomes on the FMAue scale. The correlation coefficient of this relationship is -0.430 and $P = 0.046$. Lower BSI values are related to better functionality.

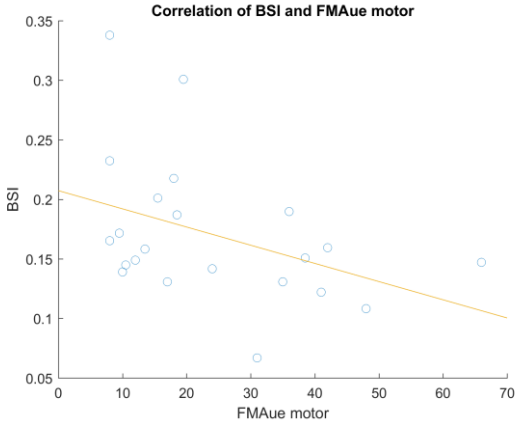

Figure 16. Correlation between BSI and FMA upper extremity. rho = -0.430, $P = 0.046$.

Band power analysis

DAR and PRI based on age: For the comparison between the healthy and the stroke group, it is mandatory to study the differences in these qEEG parameters between the three age groups (<30, 30-50, >50 years old). The analysis is very similar to the BSI based on age. The data follows a normal distribution according to the Shapiro-Wilk test. To test the homoscedasticity assumption have been used Levene's test, who did not show significant results (DAR; $P = 0.060$, fstat = 3.109, df = 29.00. PRI; $P = 0.055$, fstat = 3.204, df = 29.00.). As the normality and homoscedasticity assumption have been respected, we explored the differences between groups using One-Way ANOVA. The analysis of variance shows that there is no significant difference in the DAR parameter based on the three age groups (F = 0.5894, $P = 0.561$). See Table 12 and Figure 17.A. Also, the comparison of PRI between the three age groups is no significant (F = 0.3606, $P = 0.7003$). See Table 13 and Figure 17.B.

Table 12. Results of DAR-based age analysis.

One-way ANOVA					
	SS	**Df**	**MS**	**F**	***P***
Groups	14.75	2	7.3727	0.5894	0.5612
Error	362.76	29	12.5091		
Total	377.51	31			

Table 13. Results of PRI-based age analysis.

One-way ANOVA

	SS	Df	MS	F	*P*
Groups	1.45038	2	0.7252	0.3606	0.7003
Error	58.32	29	2.0109		
Total	59.77	31			

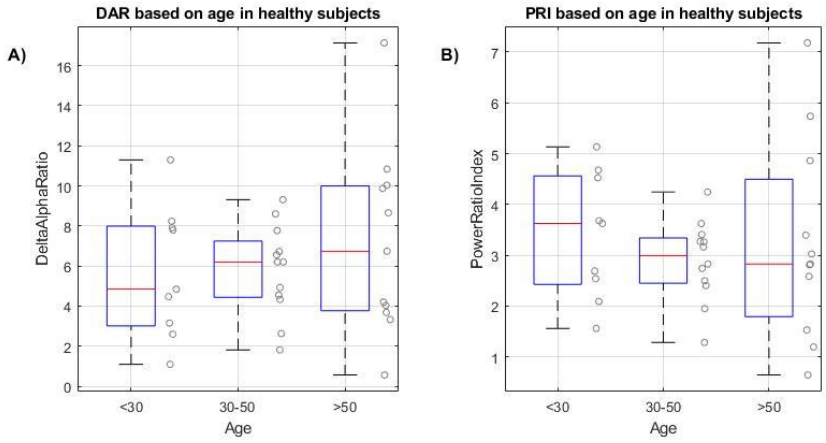

Figure 17. DAR and PRI based on age in healthy subjects. A) DAR based on age: <30 group = 5.71, SD = 3.29; 30-50 group = 5.80, SD = 2.26; >50 group = 7.19, SD = 4.69. B) PRI based on age:<30 group = 3.39, SD = 1.24; 30-50 group = 2.89, SD = 0.79; >50 group = 3.25, SD = 1.98.

DAR and PRI based on gender: Figure 18, shows the comparison of DAR and PRI based on gender. There are no statistical differences in DAR or PRI based on gender. Both groups are normally distributed using Shapiro-Wilk test, and similar variances using Levene's test (DAR; P = 0.878, fstat = 0.024, df = 30, PRI; P = 0.877, fstat = 0.024, df = 30). The unpaired t-test showed no significance differences in both cases (DAR unpaired t-test (30) = -0.938, P = 0.356. PRI unpaired t-test (30) = 0.024, *P* = 0.981).

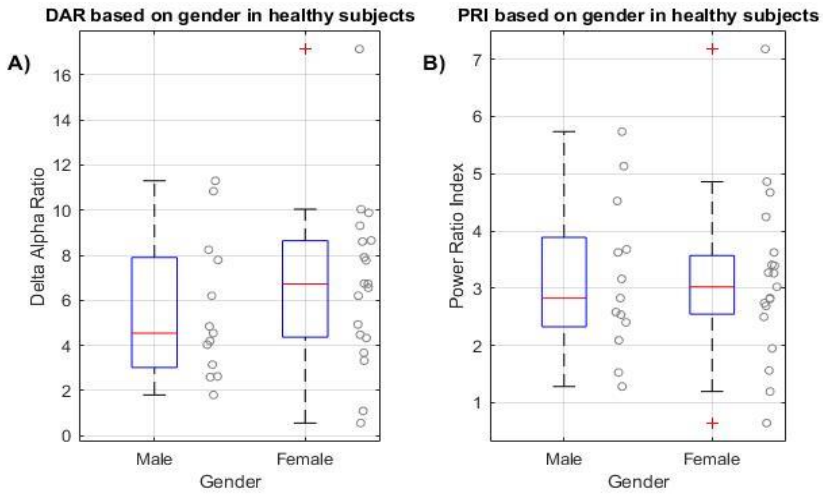

Figure 18. DAR and PRI based on gender in healthy subjects. A) DAR based on gender: Male group = 5.55, SD = 3.11; Female group = 6.73, SD = 3.73. B) PRI based on gender: Male group = 3.16, SD = 1.34; Female group = 3.15, SD = 1.46.

DAR and PRI between groups: Since the results obtained in the DAR/PRI based on age did not show significant differences in the healthy group, we compared the DAR/PRI parameters between groups (healthy and stroke) despite the age difference. For the comparison analysis we used the data of the healthy subjects and the median of Pre2 and Post1 of the stroke subjects. The first step was the normality testing of each group. Shapiro-Wilk test was significant in more than one group, then the normality

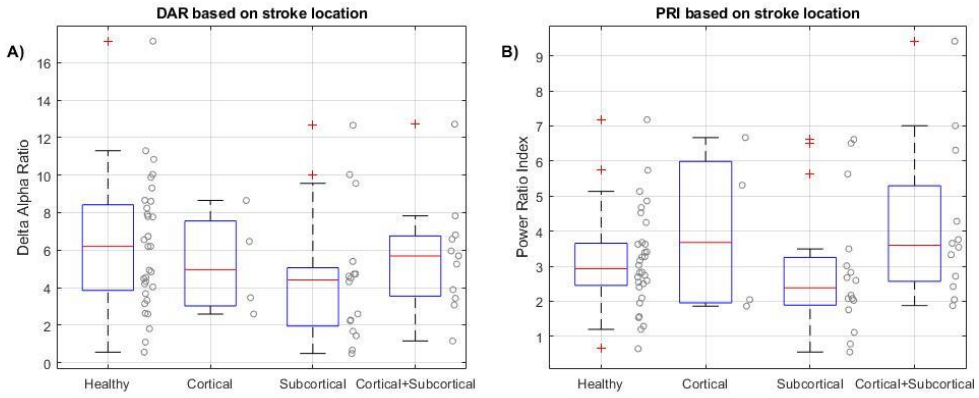

Figure 19. DAR and PRI comparison between groups. A) DAR based on stroke location: Healthy = 6.20, IQR = 3.86 - 8.42; Cortical = 4.96, IQR = 3.03 - 7.56; Subcortical = 4.41, IQR = 1.95 - 5.07, Cortical+Subcortical = 5.69, IQR = 3.55 - 6.76. B) PRI based on stroke location: Healthy = 2.93, IQR = 2.45 - 3.65; Cortical = 3.68, IQR = 1.95 - 5.99; Subcortical = 2.38, IQR = 1.89 - 3.25; Cortical+Subcortical = 3.60, IQR = 2.57 - 5.29.

cannot be assumed. The equality of the variances can be assumed, using Brown Forsythe test (DAR; $P = 0.853$, fstat = 0.262, df = 59. PRI; $P = 0.344$, fstat = 1.131, df = 60). According to the non-assumption of normality, we used Kruskal Wallis test for the comparison. The group comparison was not significant in DAR (H (3) = 3.58, $P = 0.310$), and in PRI (H (3) = 4.23, $P = 0.238$). Figure 19.A shows the comparison of DAR, and Figure 19.B shows the comparison of PRI.

Correlation between Band Power in frequency bands and functional scales: The correlations between each scale with each band power qEEG parameter have been calculated (APΔ, APθ, APα, APβ, RPΔ, RPθ, RPα, RPβ, DAR and PRI). The normality of the variables has been checked before the correlation test, the outcome of each correlation is summarized in Table 14, Table 15 and Table 16. The significant correlations are plotted, but only the most important are explained on this section.

Absolute Power in delta band (APΔ)

The significant correlations of the APΔ are plotted in Figure 20. Looking the results, the high functionality is related with low values of APΔ. Some of the most important correlations between APΔ and functionals scales are with: FMAue (rho = -0.512, $P = 0.003$), BI (rho = -0.692, $P < 0.001$), FTRS of paretic hand (rho = 0.462, $P = 0.008$), MAS of wrist (rho = -0.368, $P = 0.039$), BBT of healthy hand (rho = -0.390, $P = 0.027$) and Mobility (rho = -0.535, $P = 0.002$). The correlation with the BBT of paretic hand seems to be caused by an outlier.

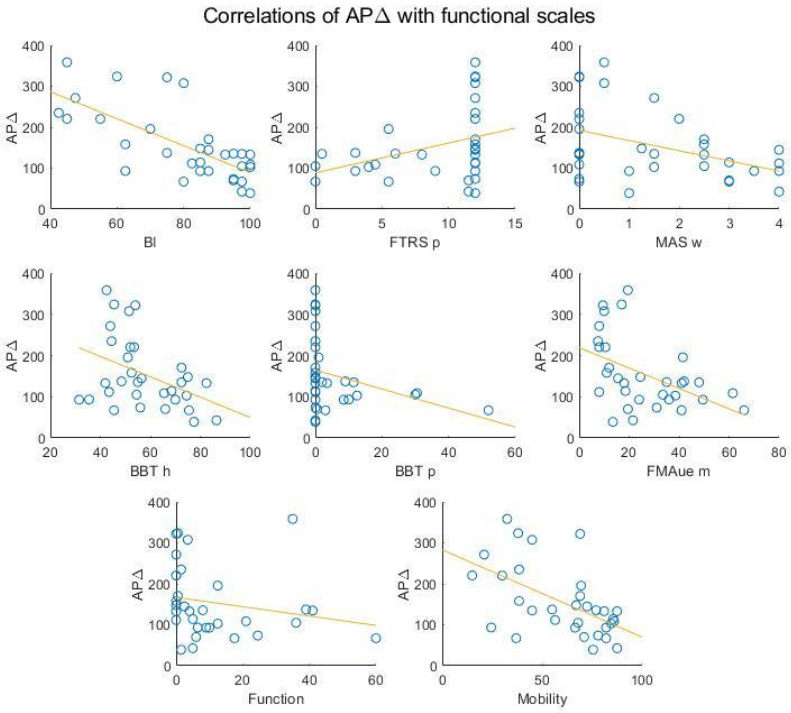

Figure 20. Significant correlations of APΔ with functional scales.

Absolute Power in theta band (APθ)

The significant correlations of APθ and the functional scales are plotted in Figure 21, where we can easily see that the best scores in the functional scales are related with lower values of APθ. The most important correlations are with: BI (rho = -0.583, *P* = 0.001), BBT of the healthy hand (rho = -0.479, *P*

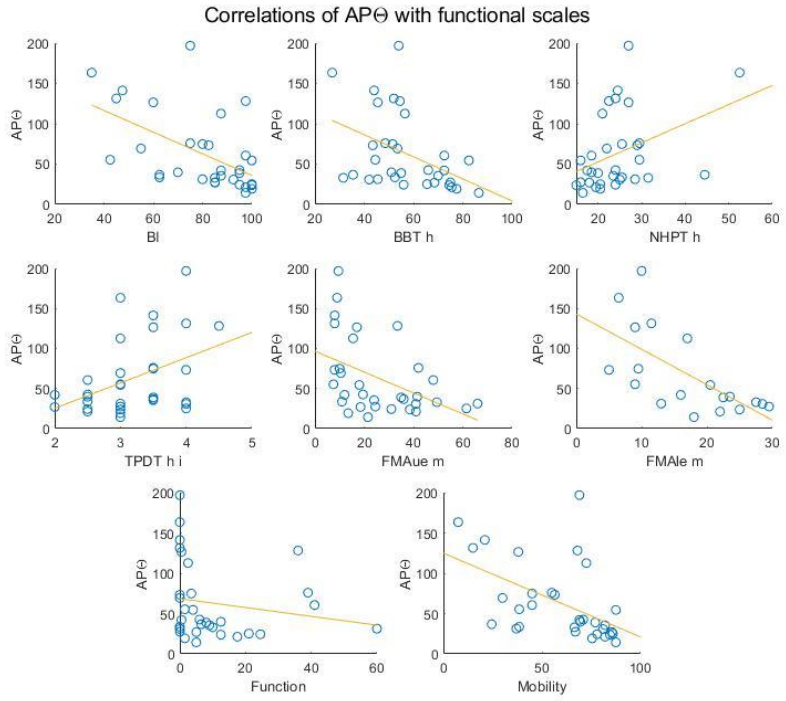

Figure 21. Significant correlations between APθ and functional scales.

= 0.001), TPDT of the index in the healthy hand (rho = 0.360, *P* = 0.043), FMAue (rho = -0.518, *P* = 0.002), FMAle (rho = -0.725, *P* < 0.001) and Mobility (rho = -0.624, *P* < 0.001).

Absolute Power in alpha band (APα)

The significant correlations of APα are plotted in Figure 22. Most of the correlations are similar to the previous ones, where the high degree of functionality is related with low values of APα. The most important correlations currently are between APα and MOCA scale (rho = -0.423, *P* = 0.045).

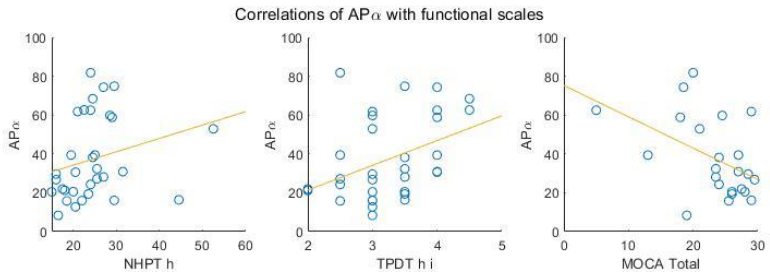

Figure 22. Significant correlations between APα and functional scales.

Absolute Power in beta band (APβ)

There are no significant correlations between this parameter and the functional scales.

Relative Power in delta band (RPΔ)

There is a significant correlation between RPΔ and Pain questionnaire (rho = 0.417, *P* = 0.016). The high values of RPΔ are related with strong pain.

Relative Power in theta band (RPθ)

The significant correlations of RPθ are plotted in Figure 23. The most important correlations are between RPθ and: TPDT of the index in the healthy hand (rho = 0.530, *P* = 0.002), TPDT of the thumb

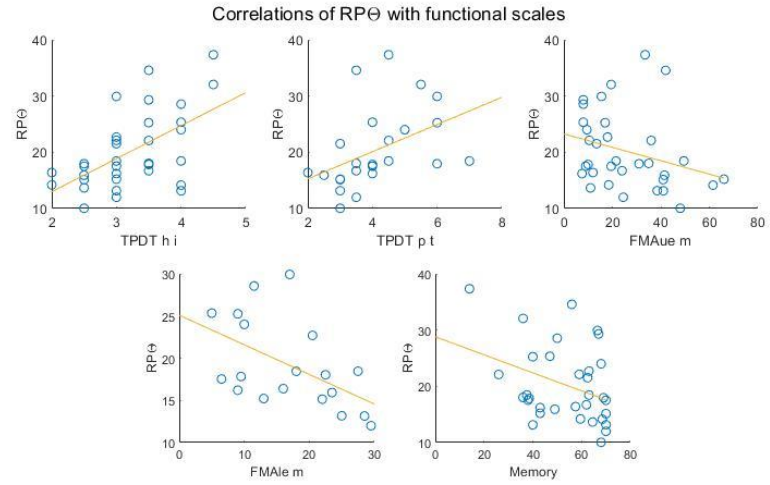

Figure 23. Significant correlations between RPθ and functional scales.

in the paretic hand (rho = 0.651, $P < 0.001$), FMAue (rho = -0.362, $P = 0.038$), and FMAle (rho = -0.520, $P = 0.022$). Again, the lowest values of RPθ are related with better functionality.

Relative Power in alpha band (RPα)

The significant correlations of RPα and functional scales are plotted in Figure 24. The best scores are related with high values of RPα. This parameter is correlated with BI (rho = 0.515, $P = 0.003$), FTRS of paretic hand (rho = -0.386, $P = 0.029$), TPDT of the thumb in the healthy hand (rho = 0.351, $P = 0.049$), and FMAue (rho = 0.445, $P = 0.011$).

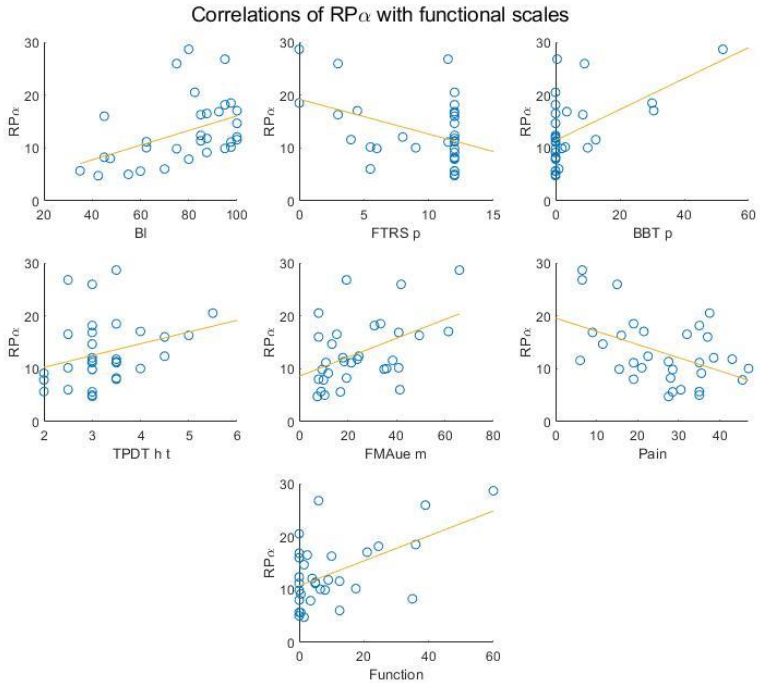

Figure 24. Significant correlations between RPα and functional scales.

Relative Power in beta band (RPβ)

The significant correlations of RPβ and functional scales are plotted in Figure 25. The most interesting correlations are between RPβ and: BI (rho = 0.484, $P = 0.004$), MAS of the wrist (rho = 0.395, $P = 0.023$), and BBT of the healthy hand (rho = -0.378, $P = 0.030$).

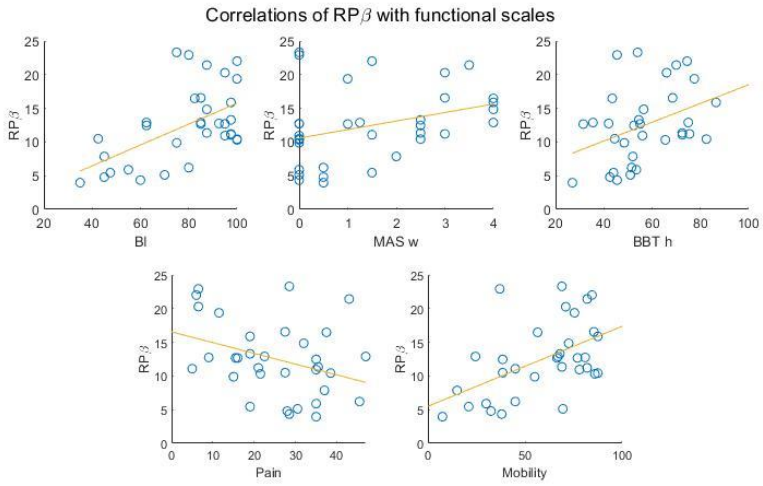

Figure 25. Significant correlations between RPβ and functional scales.

Delta Alpha Ratio (DAR)

The significant correlations of DAR with functional scales are plotted in Figure 26. The high degrees of functionality are related with low values of DAR. The daily living activities assessed by BI are moderately correlated with DAR (rho = -0.422, P = 0.018). The tremor degree, measured by FTRS of paretic hand, is also correlated, but with opposite sign (rho = 0.387, P = 0.032), where higher tremor is related with higher values of DAR. The grasp ability of the paretic hand, assessed by BBT, is also moderately related with DAR (rho = -0.474, P = 0.008). The global function of the upper extremity is directly related with DAR, FMAue (rho = -0.462, P = 0.009). Finally, high DAR values are related with strong pain (rho = 0.433, P = 0.015) and low degrees of functionality (rho = -0.408, P = 0.023).

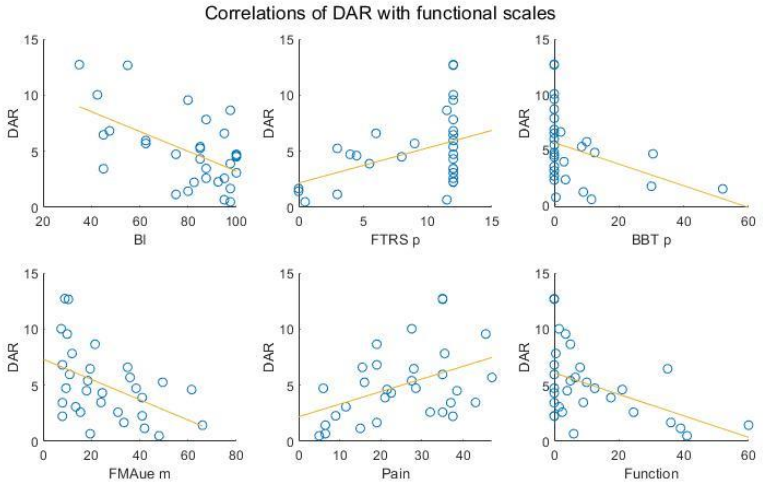

Figure 26. Significant correlations between DAR and functional scales.

Power Ratio Index (PRI)

Finally, the significant correlations between PRI and functional scales are plotted in Figure 27. Low PRI values are related with better performance in the daily living activities (BI, rho = -0.529, P = 0.002), better grasp ability in the paretic hand (BBT, rho = -0.420, P = 0.017) and better functionality of the

upper extremity (FMAue, rho = -0.452, *P* = 0.009). PRI is also directly related with pain degree (rho = 0.495, *P* = 0.004), and low PRI values are related with better memory (rho = -0.373, *P* = 0.036).

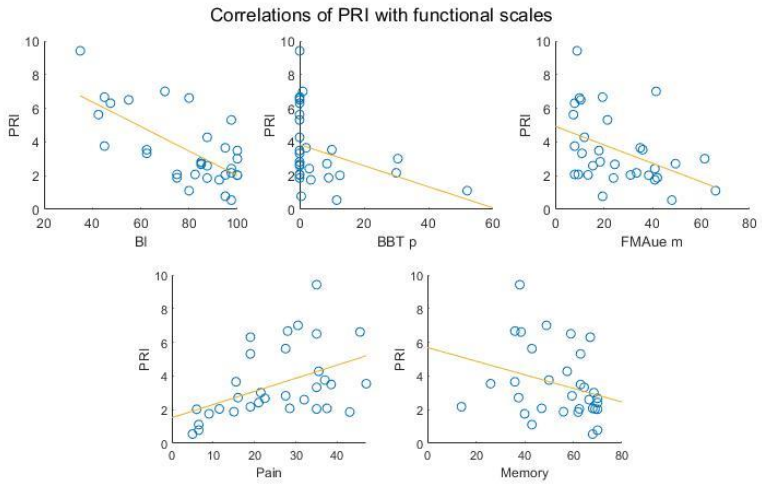

Figure 27. Significant correlations between PRI and functional scales.

Summary of the correlation between the functional scales and qEEG from Band Powers.

Table 14. Correlation table of Absolute Power.

Scale		Absolute Power							
		Δ		**θ**		**α**		**β**	
Name	**Side**	*rho*	*P*	*rho*	*P*	*rho*	*P*	*rho*	*P*
BI	-	-0.692	0.000	-0.583	0.000	-0.147	0.423	-0.099	0.588
FTRS	Healthy	-0.226	0.213	-0.024	0.897	0.286	0.113	0.239	0.188
	Paretic	0.462	0.008	0.202	0.267	-0.097	0.596	-0.090	0.625
MAS	Wrist	-0.368	0.038	-0.098	0.592	-0.006	0.972	0.218	0.232
	Fingers	-0.179	0.326	0.062	0.738	-0.082	0.657	0.161	0.379
BBT	Healthy	-0.390	0.027	-0.479	0.006	-0.307	0.087	-0.150	0.414
	Paretic	-0.400	0.026	-0.202	0.275	0.197	0.288	0.178	0.339
9HPT	Healthy	0.183	0.317	0.444	0.011	0.389	0.028	0.198	0.276
	Paretic	0.357	0.444	-0.286	0.556	-0.543	0.297	-0.214	0.662
2PDT	Thumb H	-0.168	0.357	-0.180	0.324	0.001	0.994	-0.062	0.735
	Index H	0.221	0.225	0.359	0.043	0.407	0.021	0.105	0.566
	Thumb P	0.164	0.443	0.326	0.120	0.291	0.168	-0.027	0.899
	Index P	0.065	0.762	-0.144	0.501	-0.084	0.697	-0.254	0.230
FMAue	-	-0.512	0.003	-0.517	0.002	-0.025	0.891	-0.047	0.797
FMAle	-	-0.440	0.068	-0.725	0.000	-0.352	0.140	-0.313	0.205
SRQ	Pain	0.345	0.053	0.297	0.099	-0.134	0.463	-0.229	0.207
	Function	-0.435	0.013	-0.352	0.049	0.070	0.702	0.114	0.534
	Memory	-0.230	0.205	-0.327	0.068	-0.043	0.817	-0.055	0.765
	Mobility	-0.535	0.002	-0.624	0.000	-0.272	0.132	-0.219	0.227
	Recovery	-0.240	0.185	-0.244	0.179	-0.123	0.502	0.039	0.833
MOCA	-	-0.056	0.805	-0.286	0.185	-0.422	0.045	0.034	0.881

Table 15. Correlation table of Relative Power.

Scale		Relative Power							
		Δ		**θ**		**α**		**β**	
Name	**Side**	*rho*	*P*	*rho*	*P*	*rho*	*P*	*rho*	*P*
BI	-	-0.322	0.068	-0.287	0.105	0.515	0.003	0.484	0.004
FTRS	Healthy	-0.181	0.313	0.062	0.730	0.179	0.327	0.017	0.925
	Paretic	0.319	0.070	0.119	0.510	-0.386	0.029	-0.142	0.431
MAS	Wrist	-0.260	0.145	0.081	0.652	0.199	0.274	0.395	0.023
	Fingers	-0.176	0.328	0.155	0.389	0.030	0.870	0.206	0.251
BBT	Healthy	-0.088	0.627	-0.291	0.101	0.166	0.363	0.377	0.030
	Paretic	-0.304	0.091	-0.244	0.178	0.452	0.011	0.162	0.375
9HPT	Healthy	-0.093	0.607	0.337	0.055	-0.013	0.943	-0.177	0.325
	Paretic	0.393	0.396	-0.571	0.200	-0.771	0.103	-0.250	0.595
2PDT	Thumb H	-0.271	0.127	0.219	0.221	0.351	0.049	0.225	0.208
	Index H	-0.237	0.184	0.530	0.002	0.143	0.436	-0.086	0.633
	Thumb P	-0.082	0.698	0.651	0.000	0.004	0.987	-0.163	0.437
	Index P	0.117	0.577	0.122	0.560	0.016	0.942	-0.125	0.551
FMAue	-	-0.201	0.262	-0.362	0.038	0.445	0.011	0.175	0.330
FMAle	-	0.135	0.581	-0.520	0.022	0.338	0.157	0.131	0.593
SRQ	Pain	0.417	0.016	0.265	0.136	-0.350	0.049	-0.345	0.049
	Function	-0.331	0.059	-0.076	0.674	0.356	0.046	0.086	0.634
	Memory	-0.127	0.480	-0.372	0.033	0.207	0.255	0.270	0.128
	Mobility	-0.092	0.609	-0.315	0.075	0.314	0.080	0.459	0.007
	Recovery	-0.137	0.446	-0.161	0.372	0.136	0.458	0.200	0.263
MOCA	-	0.249	0.251	-0.298	0.167	-0.141	0.521	0.012	0.955

Table 16. Correlation table of DAR and PRI.

Scales		**DAR**		**PRI**	
Name	**Side**	*rho*	*P*	*rho*	*P*
BI	-	-0.422	0.018	-0.529	0.002
FTRS	Healthy	-0.150	0.420	-0.129	0.482
	Paretic	0.387	0.032	0.319	0.075
MAS	Wrist	-0.114	0.542	-0.101	0.584
	Fingers	0.017	0.928	0.107	0.560
BBT	Healthy	-0.211	0.255	-0.274	0.130
	Paretic	-0.474	0.008	-0.420	0.019
9HPT	Healthy	0.054	0.772	0.035	0.851
	Paretic	0.086	0.919	-0.036	0.963
2PDT	Thumb H	-0.082	0.661	-0.045	0.805
	Index H	-0.097	0.604	0.044	0.813
	Thumb P	0.024	0.915	0.183	0.392
	Index P	0.023	0.916	0.026	0.903
FMAue	-	-0.462	0.009	-0.452	0.009
FMAle	-	-0.375	0.138	-0.291	0.242
SRQ	Pain	0.433	0.015	0.495	0.004

	Function	-0.408	0.023	-0.339	0.058
	Memory	-0.248	0.178	-0.373	0.036
	Mobility	-0.210	0.257	-0.342	0.055
	Recovery	0.078	0.678	-0.059	0.749
MOCA	-	0.213	0.355	0.084	0.709

Laterality Coefficient

The LC was calculated separately for the MI tasks of the healthy (LCh) and paretic (LCp) hand. We calculated the LC for the alpha (LChα and LCpα) and beta (LChβ and LCpβ) bands. We explored the LC (α and β) between groups (Cortical, Subcortical and Cortical + Subcortical), and found no significant differences of LC between groups.

In this part of the analysis, we correlated the LC average of the 25 BCI therapy sessions against the results from motor tests collected in the assessment visits (Pre1, Pre2 and Post1). The Shapiro Wilk Test shows that the data is non-normally distributed at alpha level. The Spearman test has been used for the correlation analysis. Table 17 shows the correlation's results of LC against the functional scales.

Alpha band: The LC calculated during the MI task with the healthy hand (LChα) is the parameter that shows the highest correlation with functional scales. In general terms, the results show that LC values near 0 are related to better functionality and less tremor in the paretic upper extremity (see Figure 28).

Tremor of the paretic hand assessed by FTRS shows a significant correlation with the LChα. The correlation coefficient is positive (rho = 0.450 and P = 0.008). Thus, low degrees of tremor are related to LChα values near to 0.

In the BBT of the paretic hand, there is a stable correlation with all the LC parameters and bands. Here, the LChα shows a correlation but with a negative sign. The correlation is strong (rho = -0.616 and P < 0.001). This correlation shows that good scores in the grasp ability, as assessed by BBT, are related to low values of LChα.

Moreover, the LChα parameter showed significant correlations with the FMA upper and lower extremity. The FMAue correlation has a stronger correlation coefficient (rho = -0.706 and P < 0.001) than the FMAle (rho = -0.601 and P = 0.006). The correlation coefficient is negative in both cases, and these results are consistent with the other relationships explained above - better motor function in the lower and upper extremity, as assessed by FMA, is related to LChα values near to 0.

Finally, the LChα is also correlated with the function score of the SRQ (rho = -0.427 and P = 0.0212). The function score of SRQ is based on the subjective opinion of the patient doing different motor tasks. The negative correlation shows that good scores in the function score of SRQ are related to low values of LChα.

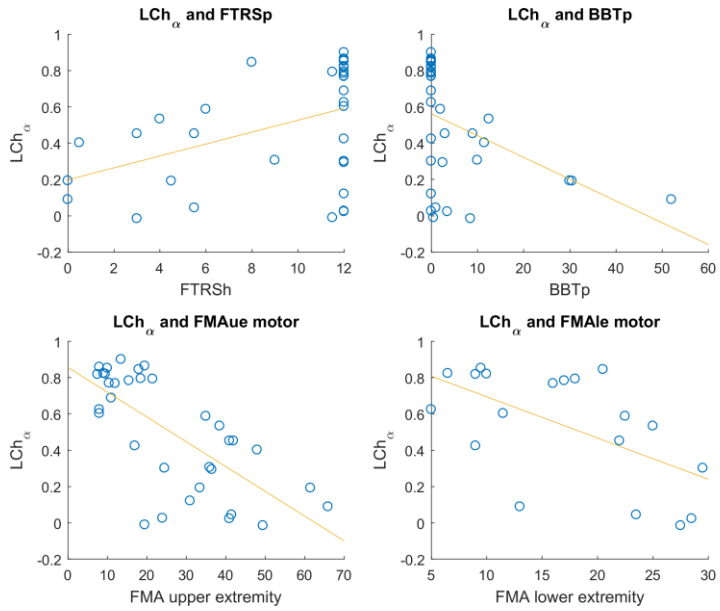

Figure 28. Significant correlations between LC of the healthy hand in alpha band and functional scales. A) Correlation between LChα and BBT of the paretic hand with rho = -0.641 and $P < 0.001$. B) Correlation between LChα and FTRS of the paretic hand with rho = 0.486 and $P = 0.004$. C) Correlation between LChα and FMAue of the motor part with rho = -0.623 and $P < 0.001$. D) Correlation between LChα and FMAle of the motor part with rho = -0.509 and $P = 0.026$.

Other similar correlations with opposite signs have been found for the LCpα. In this case, LCp values near to 0 are related to better performance in the FMAue score (rho = 0.400 $P = 0.019$) and also in the BBT of the paretic hand (rho = 0.354 and $P = 0.043$).

Beta band: LChβ and LCpβ also presented some interesting correlations with the functional scales. In general, the correlations found on this frequency band are weaker than the correlations found in the alpha band. The low tremor degree in the paretic hand assessed by FTRS (higher scores in this scale) is correlated with values near to 0 in LCpβ (rho = -0.490 and $P = 0.003$). The good grasp ability in the paretic hand, assessed by BBT (BBT_p) is also correlated with low values of LChβ (rho = -0.418 and $P = 0.016$) and values near to 0 in LCpβ (rho = 0.569 and $P = 0.001$). The general motor function of the upper extremity, assessed by FMA, is also correlated with LChβ (rho = -0.440 and $P = 0.009$), and with LCpβ (rho = 0.384 and $P = 0.025$).

Finally, there is a correlation between the function scale part of SRQ and LChβ (rho = -0.488 and $P = 0.003$) and LCpβ (rho = 0.447 and $P = 0.008$). Again, the best functionality is related to values near to 0 of both LC parameters. All correlation results regarding the LC and functional scales can be seen in Table 17.

Table 17. Significant correlations between LC and functional scales using Spearman Correlation are colored red.

Scale		Laterality Coefficient							
		α				**β**			
		LC_h		LC_p		LC_h		LC_p	
Name	**Side**	*rho*	*P*	*rho*	*P*	*rho*	*P*	*rho*	*P*
BI	-	-0.260	0.138	0.058	0.743	-0.154	0.383	0.184	0.296
FTRS	Healthy	-0.038	0.829	0.105	0.555	-0.093	0.600	0.060	0.734
	Paretic	0.450	0.008	-0.245	0.162	0.336	0.052	-0.490	0.003
MAS	Wrist	0.076	0.670	-0.216	0.220	-0.116	0.514	0.034	0.848
	Fingers	0.237	0.176	-0.262	0.134	0.109	0.539	-0.099	0.579
BBT	Healthy	0.102	0.566	-0.154	0.386	0.059	0.741	-0.141	0.425
	Paretic	-0.616	0.000	0.354	0.043	-0.418	0.016	0.569	0.001
9HPT	Healthy	-0.042	0.813	0.036	0.839	-0.167	0.345	0.186	0.291
	Paretic	0.536	0.236	-0.357	0.444	0.714	0.088	-0.607	0.167
2PDT	Thumb H	-0.169	0.340	0.031	0.862	0.038	0.830	-0.005	0.979
	Index H	-0.010	0.956	0.041	0.820	-0.053	0.765	0.157	0.374
	Thumb P	0.000	0.999	-0.067	0.746	-0.139	0.499	0.152	0.459
	Index P	0.065	0.751	-0.079	0.701	-0.082	0.689	-0.125	0.543
FMAue	-	-0.706	0.000	0.400	0.019	-0.440	0.009	0.384	0.025
FMAle	-	-0.601	0.006	0.271	0.261	-0.252	0.298	-0.057	0.817
SRQ	Pain	0.287	0.100	-0.157	0.374	0.095	0.591	-0.115	0.518
	Function	-0.427	0.012	0.316	0.069	-0.488	0.003	0.447	0.008
	Memory	-0.068	0.704	-0.130	0.465	-0.226	0.198	-0.033	0.855
	Mobility	-0.216	0.219	-0.034	0.849	-0.150	0.396	0.033	0.855
	Recovery	0.065	0.717	-0.205	0.245	0.083	0.642	0.061	0.732
MOCA	-	0.005	0.982	-0.032	0.884	-0.232	0.288	0.043	0.847

Improving BCI performance with gamification

On this last section, we present an experimental study on gamified BCI post-stroke functional rehabilitation of the upper limb. The goal of the study is to analyze how gamification impacts on the efficacy of the treatment and on patients' experience.

Participants baseline

Six healthy subjects and ten stroke patients were enrolled in the study, 7 of them were females and 9 males. The mean age of the healthy group was 35.3 years old (SD = 16.0), with a range from 58 to 23 years old. The mean age of the stroke group was 55.8 years old and the range was from 79 to 26 years old. In the Stroke group, 4 patients had the right side affected, whereas 6 had the left side. The mean time since stroke was 33.0 months (SD = 22.8), 7 were in subacute phase, 3 in chronic phase, and no one in acute phase. Neither patients nor control users had previous experience in BCIs, except two patients that had used the recoveriX® system years ago. Control users were right-handed with neither previous known neurological disorder nor experience in BCIs.

For the comparison based on the MI accuracy, the accuracy obtained after the first Training run in the first session (T1-S1) is taken as baseline reference for each subject. As mentioned above, in run T1-S1, the participant used the standard visual feedback with a personalized classifier generated in the calibration run of the session 1(T1-C1). Thus, the accuracy obtained on T2-S1, T1-S2 and T2-S2 is compared as a response of T1-S1. The equality of the baselines cannot be assumed because there is a statistical difference in the age between groups. The age variable of the healthy group is not normally distributed (SWT: $P = 0.022$) and Mann-Whitney U test shows a significant difference between both age groups, $P = 0.031$. In order to see how much the age differences can influence the BCI performance, the correlation between the age and the maximum classification accuracy (maximum accuracy of the second run in the first session T1-S2) has been studied. The age variable with all participants, and MI accuracy data follow a normal distribution, (SWT age, $P = 0.075$, SWT accuracy, $P = 0.096$). The Pearson correlation test shows that there is no significant correlation between age and accuracy (rho = -0.195, $P = 0.505$). Thus, the comparison of the MI accuracy between groups is allowed.

The comparison of the accuracy obtained in the first training run T1-S1 (after system calibration), shows that there is no statistical difference in the BCI performance between healthy and stroke group using unpaired t-test, t-value = |1.475| and $P = 0.166$ (SWT >0.05).

Impact of the game in the BCI performance

In order to detect differences in the accuracy using different visual feedback modalities, the MI accuracy of each run has been analyzed using repeated measures ANOVA. All the datasets can be considered normally distributed. Shapiro-Wilk test did not show significant results at alpha level. Mauchly's Test

of Sphericity indicated that the assumption of sphericity has not been violated, $\chi 2(2) = 9.595$, $P = 0.088$. Table 18 shows the results of the accuracy comparison using repeated measures ANOVA. The multiple comparison did not show statistical differences in the accuracy based on the gamification with different visual feedback modalities (see Table 18 and Table 19). The same comparison has been done using only the data from the healthy or stroke group, and no significant differences have been detected.

Table 18. Multiple comparison of MI accuracy using repeated measures ANOVA.

Maximum accuracy

	SumSq	df	MeanSq	F	pValue	pValueGG	pValueHF	pValueLB
intercept	72.272	2	36.136	1.4213	0.265	0.266	0.266	0.261
run2_ses1	49.236	2	24.618	0.96826	0.397	0.374	0.382	0.348
Error	508.50	20	25.425					

Mean accuracy

	SumSq	df	MeanSq	F	pValue	pValueGG	pValueHF	pValueLB
intercept	72.508	2	36.254	1.3514	0.284	0.280	0.281	0.275
run2_ses1	48.422	2	24.211	0.90249	0.423	0.385	0.392	0.367
Error	482.88	18	26.827					

Table 19. Summary of MI accuracy of each group.

Max. Accuracy	**C-S1**	**T2_S1**	**T3_S1**	**T2_S2**	**T3_S2**
All(mean)	80.09(10.76)	78.86(11.47)	78.49(13.32)	82.03(12.48)	82.08(11.61)
Healthy (mean)	84.78(12.9)	85.70(14.25)	83.68(16.9)	86.42(15.39)	88.42(11.41)
Stroke(mean)	78.21(9.91)	76.12(9.65)	75.02(9.9)	79.11(10.02)	77.86(10.22)

Mean. Accuracy	**C-S1**	**T2_S1**	**T3_S1**	**T2_S2**	**T3_S2**
All(mean)	71.53(12.82)	74.29(11.47)	73.07(14.15)	76.09(12.33)	76.45(11.63)
Healthy (mean)	80.40(17.77)	81.86(14.26)	77.84(18.17)	81.93(14.37)	83.77(11.83)
Stroke(mean)	68.87(10.71)	71.27(9.31)	69.88(10.75)	72.20(9.73)	71.57(9.07)

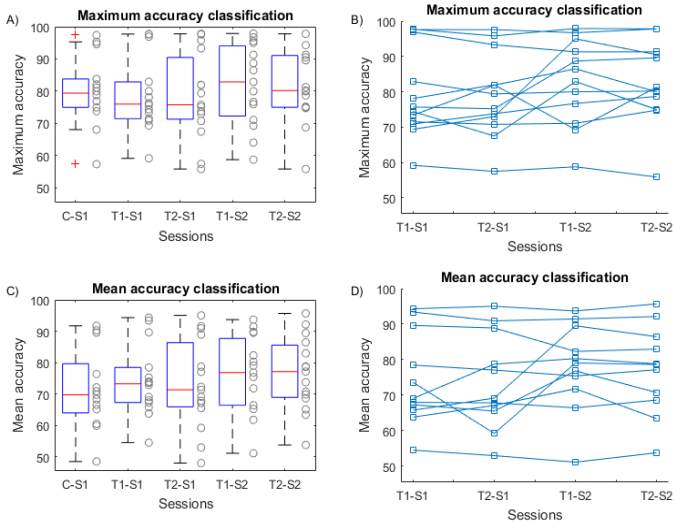

Figure 29. BCI performance using different visual feedback.

Users' satisfaction with the serious game

The users' satisfaction was assessed after the last session using a questionnaire with 8 questions rated from 1 to 5. For the quantification of the results the average of the individual score and the average of each question in the questionnaire has been computed.

Table 20 shows the results in the questionnaire based on groups and gaming experience. The first column shows the group name, the second column the group size, the third column is the averaged total questionnaire score based on the average of score in each question, and the next eight columns show the average result for each group of each question. Figure 30 shows the questionnaire results of each group.

All participants gave high scores in all questions: users' satisfaction is 4.20 points (SD = 0.45) up to 5, the stroke group gave higher score in the questionnaire with 4.23 points (SD = 0.35), while the healthy group was 4.15 points (SD = 0.63). In general, the best aspect of the game was the clarity of the rules (Q4), and the healthy group also highlighted the easiness of use (Q3). The worst aspect was the fun level of the game (Q1). In the informal debriefing after the sessions, users declared being gratified with the game, but suggested some enhancements such as introducing variations in the animation of the rat, which is always the same, and adding new auditory stimuli.

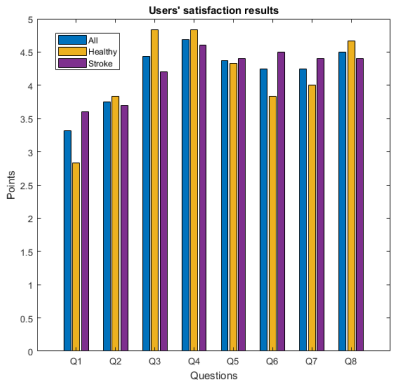

Figure 30. Questionnaire results.

Table 20. Summary of questionnaire results based on group and gaming experience.

	n	Mean (SD)	P1	P2	P3	P4	P5	P6	P7	P8
All	**16**	**4.20 (0.45)**	**3,31**	**3,75**	**4,44**	**4,69**	**4,38**	**4,25**	**4,25**	**4,50**
Healthy	**6**	**4.15 (0.68)**	**2,83**	**3,83**	**4,83**	**4,83**	**4,33**	**3,83**	**4,00**	**4,67**
Often	3	4.54 (0.56)	3,33	4,33	5,00	5,00	4,67	4,33	4,67	5,00
Sometimes	2	3.81 (0.80)	2,50	3,50	4,50	4,50	4,50	3,50	3,00	4,50
Never	1	3.63 (1.06)	2,00	3,00	5,00	5,00	3,00	3,00	4,00	4,00
Stroke	**10**	**4.23 (0.37)**	**3,60**	**3,70**	**4,20**	**4,60**	**4,40**	**4,50**	**4,40**	**4,40**
Often	1	3.75 (1.04)	3,00	2,00	4,00	4,00	3,00	5,00	4,00	5,00
Sometimes	3	4.13 (0.56)	3,00	3,67	4,00	4,33	4,67	4,67	4,33	4,33
AlmostNever	1	3.13 (0.83)	3,00	2,00	2,00	4,00	4,00	3,00	4,00	3,00
Never	5	4.6 (0.24)	4,20	4,40	4,80	5,00	4,60	4,60	4,60	4,60

Finally, no significant correlation was found between the questionnaire score and accuracy.

Chapter IV - Discussion

Effectiveness of BCI treatment for stroke recovery

Effects of BCI treatment on stroke patients by using a meta-analysis of published literature

To evaluate the effectiveness of BCI treatment for stroke patients, we performed a meta-analysis to systematically review to systematically review the state of the art about the effect of the BCI treatment for motor recovery of the upper extremity after stroke. 17 out of 446 articles passed the first screening based on the title and the abstract, and finally 7 of them were rejected according to the exclusion criteria of the section "Assessment of characteristics of trials". Finally, 10 articles remained after the second pass, and the total number of patients included in the meta-analysis was 234. The BCI treatment (116 patients) was compared with the standard treatment (118 patients). 7 out of 10 publications combined BCI therapy with the standard treatment in the experimental group, and therapy alone, without BCI, in the control group. All the included publications used the Fugl-Meyer Assessment before and after the therapy to detect the changes in the functional state of the upper limb.

The control group reported low changes in functionality of the upper extremity, ΔFMA = 3.68 SD = 4.15 (based on 10 publications). Page et al. in 2012 described that stroke patients have a clinically important improvement in the FMA when the ΔFMA is higher than 5.25 points (Minimum Clinically Important Difference, MCID). When we look in detail on the changes in the control group that every publication reported, only 4 out of 10 publications reported ΔFMA above MCID. In the case of the experimental group, the major part of the publications (6 out of 10) reported that the ΔFMA in the experimental group was above to the MCID. Moreover, the average improvement among all the publications was 7.51 points (SD = 4.83) in the FMA.

The group comparison analysis showed that the patients in the BCI groups improved 3 points [1.74 4.25] more than the patients in the control groups, see Figure 10. For the effect size, the SMD between the neurofeedback group and control group was calculated as 0.73 in Figure 11, which is consider to be a moderate (0.5) to large effect size (0.8).

Two studies reported more improvement in the control group, but it is important point out that they did not combined BCI training with physiotherapy. The other 8 papers reported higher improvement in the experimental group.

Ramos-Murguialday et al. and Wang et al. reported positive effects of the BCI group against the control group, but their improvement was lower than the ones achieved in the other publications (Ramos-Murguialday et al. reported ΔFMA = 3.4 and Wang 2018 reported ΔFMA = 3.85). Longer time after the stroke seems to cause the relatively lower improvement in this scale. The average time since stroke onset was highest in the two studies: Ramos-Murguialday 2013 was 66 months (SD = 45) and Wang 2018 was 48 months (SD = 36) considering the mean ±SD of all the studies was 26 months (SD = 34).

The reviewed data allowed us to create an effective BCI therapy protocol (Table 5). Ideally, a good protocol for a BCI therapy for motor recovery will consist on sessions of 1 hour, 4 times per week for 6 weeks. These calculations have been done considering the higher value of the IQR of Table 5, duration per session of 60 minutes (IQR= 30-60), number of sessions per week 3 (IQR = 3-4) and number of weeks 4 (IQR = 4-6). The basic time of feedback should be respected according to Table 6.

Therefore, this meta-analysis provides evidence that BCI in general significantly ($p< 0.01$) improves motor function compared to conventional training alone without neurofeedback based on high quality published literature.

Clinical improvements in stroke patients after BCI therapy

In the section "Functional assessment of stroke patients before and after BCI treatment" we evaluated the efficacy of BCI system in rehabilitation of stroke patients, but without comparing BCI-based therapy with other therapies. In fact, the relationship between BCI stroke therapy and functional outcomes has been addressed in numerous studies [123]–[127], and we also evaluated this relation in the meta-analysis (section "Effectiveness of BCI treatment for stroke recovery – systematic review with meta-analysis" of the thesis). We also observed significant improvements in stroke patients after BCI therapy that should be reported.

FMAue was the primary measure of motor function in this study. When assessing the motor function of the upper extremity by FMAue, we found the most important significant clinical improvement (ΔFMAue = 1 [0-8] and P = 0.002). On average, the stroke patients improved by 3.21 points (SD = 5.1) in the FMAue with the BCI therapy. After the therapy, the patients also presented a significant reduction in tremor (FTRS), spasticity (MAS), and increase on the grasp ability (BBT) and in the cognitive state (MOCA).

In general, the first sign that patients reported during the therapy was a reduction in spasticity, followed with improvement in motor function. The reduced spasticity might drive the improved range of motion and reduced tremor, and therefore, it could explain the improvements observed on FTRS, BBT and FMAue.

The MOCA scale also showed significant improvement, but this effect can be related to the need to mental concentration by the patient during BCI sessions in order to get positive feedback. The patients have to learn to maintain concentration during the sessions in order to improve their motor skills using BCI.

Therefore, our findings reinforce previous literature that demonstrate the effectiveness of BCI therapy to improve functional recovery in stroke patients.

EEG biomarkers for stroke diagnosis and prognosis

On the section "EEG biomarkers for stroke diagnosis and prognosis" we explored how thirteen EEG-based parameters relate to different facets of stroke diagnosis and functional prognosis during BCI-based stroke rehabilitation therapy. Better tools to analyze brain state in stroke patients would facilitate a better evaluation of different therapies, as BCI-based therapy. The use of EEG parameters is quite advantageous in BCI therapy since EEG is in fact recorded during these sessions.

Thus, we analyzed these different EEG parameters by using the EEG recorded during the training sessions. The BSI and all Band Power parameters were derived from EEG data recorded during the assessment visits in the resting state, while the LC was based on EEG data recorded during MI exercises.

Brain symmetry index

BCI ranges from 0 to 1 (being 0 maximum symmetry and 1 total asymmetry). It is assumed that in the resting state, predominates brain symmetry and thus, this index is close to 0. In contrast, an increase of this index has been described after stroke[85].

In our study we also found a small BSI in healthy patients. We did not detect a change in this index based on age, although this issue needs to be further explored in larger studies. On the other hand, we observed significant difference in BSI based on gender; males usually have higher values of BSI than females. These results could help our understanding of the BSI parameter in healthy conditions, improve detection pathological values correlated with different brain affectations that can help in the diagnosis of stroke and other conditions, and support further research involving gender differences.

To evaluate the BSI in stroke, we divided the patients into three different groups based on stroke location; Cortical, Subcortical and Cortical + Subcortical. The Cortical group was the smallest group with only 5 patients and exhibited the highest BSI variability. Prior work found similar results, with an almost identical boxplot distribution but with a smaller sample size [85]. Our results showed that healthy participants had significantly lower BSI values than stroke patients of the Subcortical group ($P = 0.001$) and the Cortex + Subcortex group ($P = 0.019$); see Table 11 and Figure 15. The high variability in the Cortical group may be due to the small size of this subgroup. Moreover, in these patients the location of the lesion is very peripheral (in the brain surface), and most of the neural activity observable via EEG originates from the cortex; consequently, the aberrant neural activity is more apparent in these patients than in the ones with other stroke locations.

Hence, despite the high variability in the Cortical group, the BSI parameter did differ significantly between the healthy control vs. stroke groups Subcortical and Cortex + Subcortex. With further research, the BSI could become a tool to support stroke diagnosis, including stroke location and severity.

We also analyzed the correlations between the values of BSI and the patient's functional state (Figure 16). The most noteworthy correlations observed showed that patients with lowest BSI have better motor function in the upper extremities (FMAue). The correlation between BSI and FMAue was also observed in prior studies; lower BSI values were correlated with higher functionality in the upper extremity [85]. Thus, the BSI could be a useful parameter to assess functional impairment during stroke assessment and rehabilitation.

Band Powers

The absolute and relative power of the classical frequency bands -delta, theta, alpha and beta- was calculate, as well as the DAR and PRI. DAR has been previously described as a useful tool to detect delayed cerebral ischemia [86] whereas PRI could be correlated with location of the injury [87]. Therefore, different studies have tried to use these parameters to correlate and predict motor functionality based on the EEG recordings [74], [88], [89].

DAR and PRI parameters seem to be unrelated to age (see Table 12, Table 13 and Figure 17), so we have been able to compare these values with those of the stroke group. We did not see any differences in these parameters related to gender. In fact, the values in all groups are very similar, see Figure 19. We cannot say that the DAR or PRI parameters can be used for diagnostic purposes as in the case of the BSI. However, they do have an important clinical function as they are related to the scores of the functional scales (see Table 16).

When analyzing the correlation between band powers and functional scales, we observed that the different parameters are related with BI, that evaluates the ability of patients to perform activities of daily living. The one with the highest correlation coefficient with BI scale is APΔ (rho = -0.692, $P < 0.001$). Since other parameters analyzed, as BSI and LC, do not present a significant correlation with this scale, this finding is important and can be a useful tool to evaluate the level of independence for a patient's activities of daily living.

The level of tremor of the paretic hand is also related to different values (APΔ, RPα and DAR). The parameter APΔ has a slightly stronger correlation than the others (rho = 0.462, $P = 0.008$). In this case, the high degree of tremor is related to high values of APΔ and DAR and low values of RPα.

The degree of spasticity of the wrist is linked to the parameter RPβ (rho = 0.395, $P = 0.023$). This relationship is positive, meaning that high values of RPβ are related to more spasticity. The APΔ parameter has also a significant but slightly weaker relationship. However, it should be noted that the correlation coefficient could change if sample size increased.

The grasp ability with the healthy hand shows a significant correlation with the APΔ, RPβ and APθ parameters. The relationship with APθ is the strongest one (rho = -0.479, $P = 0.006$). However, it was more difficult to investigate the relationship with the affected hand because many patients could not

perform the test. The correlations with fine motor skills, assessed with NHPT, are weak and often influenced by outliers.

2PDT is an important test that assesses surface sensitivity. In this case we see a relation of the results of the 2PDT of both hands with several parameters, APθ, APα, RPα and RPθ. It is important to highlight the strong association with the θ band, especially with the RPθ parameter, for the healthy hand (rho = 0.530, $P = 0.002$) and the affected hand (rho = 0.651, $P < 0.001$).

The functionality of the lower limb (FMAle) has an important relationship with the parameter APθ (rho = -0.725, $P < 0.001$). So far there are not many studies that relate these parameters to motor function of the leg. There are obvious limitations of the EEG for recording the electrical activity of the motor cortex in the leg area. However, this parameter can help to know the state of the motor cortex of the lower extremity.

In general, we see that the parameters involving the frequency bands α and Δ (APΔ and DAR, for example) are the ones most related to the functional status of the patients. This is consistent with other studies that show that the relationship between both parameters seems to be decisive for having a positive or negative prognosis [74]. On the other hand, the α waves have been investigated by numerous articles and have been relate to memory, concentration or language. With these results we can assume that there is a relationship with the functional status, specifically with the coordination of movement in the affected hand, either the gasp ability evaluated with the BBT (RPα and BBT, rho = 0.452, $P = 0.011$) or the global mobility of the upper limb (RPα and FMAue, rho = 0.445, $P = 0.011$). This would also explain the above relationship with BI.

Event-related synchronization and desynchronization and Laterality Coefficient

During MI, the contralateral motor cortex will exhibit ERD, and when finishes, there is an ERS. An ERS can also occur during MI in the ipsilateral hemisphere in the μ range, related to an idle activation of these areas [33], [34], [94], [95]. After stroke, patients usually exhibit atypical ERD/ERS activation patterns [33], [34]. By combining the ERD and ERS parameters of both hemispheres, Kaiser et al. [34] defined a new parameter, the LC, and investigated the relation of this parameter with functional state and spasticity.

Here we also calculated the LC by using the event-related synchronization and desynchronization patterns generated during the MI task [34]. The LC is derived in a similar manner as the BSI, being normality close to 0, but the LC yields results from -1 to 1. We calculated the LC in two frequency bands, 8-13Hz (α band, mu frequency rhythm) and 13-30Hz (β band) and found the most relevant results in the alpha band. The alpha band has been mainly related with movement and motor cortex, whereas beta band has been related with mental concentration.

In general, LC values calculated during the MI tasks with the healthy hand (LCh) were between 0 and 1, while LC values of the paretic hand MI tasks (LCp) were between -1 and 0. The LCh in alpha band presented numerous significant correlations with functional scales. We also observed most of these significant correlations with the LCp parameter, but with the opposite sign.

The LC values for the healthy hand presented noteworthy correlations with four dependent variables. LCh values near to 0 were related with a higher BBT score in the paretic hand, which indicates better grasp function (rho = -0.616 and $P < 0.001$). The LCh was also significantly correlated with tremor, assessed by FTRS. Participants with LCh values near 1 tended to have a higher FTRS score (reflecting greater tremor) in the paretic hand (rho = 0.450 and $P = 0.008$). Finally, the LCh parameter was significantly correlated with the FMAue and FMAle. LCh values closer to 0 reflect better motor functionality for the upper extremity (FMAue, rho = -0.706 and $P < 0.001$) and for the lower extremity (FMAle, rho = -0.601 and $P = 0.006$).

The LC values for the paretic hand also presented two important correlations. LCp values near to 0 are correlated with high grasp ability (BBT, rho = 0.354 and $P = 0.043$) and general functionality of the upper extremity (FMAue, rho = 0.400 and $P = 0.019$). The correlations between the LCp and the functional scales are less common than the LCh. This could occur because the affected hemisphere does not present a normal activation pattern due the stroke, but the healthy hemisphere maintains the normal patterns of desynchronization during the ipsilateral motor movements (originated in the affected hemisphere). The ERD/ERS patterns observed in the healthy hemisphere should be more stable than the ERD/ERS patterns observed in the affected side of the brain.

The LC calculated in the β band showed similar correlations (see Table 17). It is important to point out that LCβ shows significant correlations with the scales where more mental concentration is required (FTRS and BBT). In both scales, values near 0 in LCβ (healthy and paretic) are correlated with better grasp ability and less tremor. Other studies showed correlations between the EEG activity in beta band and the concentration level [122], [123].

EEG parameters in stroke patients

The BSI parameter can be calculated in real-time using portable and practical EEG tools, and thus could be used during stroke diagnosis or ongoing monitoring of patients' brain activity during stroke rehabilitation and recovery. More broadly, the BSI, APΔ, DAR, PRI and LC parameters might contribute to other neurological assessments and ongoing monitoring of brain damage and recovery.

One limitation of this study is the absence of a healthy group that performed the same BCI training as the patient group, which prevents us from comparing LC between these groups. The study may also be limited by the unequal numbers of participants across the three stroke subgroups, and additional work is needed to identify any age differences between the control and stroke groups. Overcoming these

limitations will require substantial additional work with more participants in a larger study, which we are currently exploring.

In addition to broader work with more participants, future research could: explore variants of the different measures that we used that might be more informative; identify correlations with other types of diagnoses and therapies relating to motor (and perhaps other) impairment and recovery; evaluate these and other parameters in tandem with other methods to treat stroke, such as medications or non-invasive brain stimulation; measure long-term changes via longitudinal follow-up assessments; and compare the utility of these measures to other tools.

Improving BCI performance with gamification

The objective of this experiment was to explore how can affect the serious game in the users' concentration and in the performance of a BCI system for stroke functional rehabilitation. Thus, a game-based rehabilitation instrument has been developed as an improvement of the existing recoveriX system for post-stroke upper limb rehabilitation. A pilot study has been carried out to test the impact of the game in the rehabilitation process. Sixteen subjects were recruited (6 healthy and 10 stroke patients) to perform 2 sessions of BCI therapy using different visual feedback modalities. The first run (80 trials) of each session was used to calibrate the system creating a personal LDA classifier. In the second run of the first session (T1-S1) all participants performed 80 trials using the 'standard' VR avatar. In the third run of the first session (T2-S1) the participants used a new animated version based on the standard avatar. In the second run of the second session (T2-S2) users trained with the new avatar combined with a pop-up window that was appearing for a short period every ten minutes showing the score. In the third run of the second session (T2-S2) the appearance was similar to the T2-S2, but the score window was appearing all the time. The objective of these last two runs was to add more cognitive responses to improve the concentration without harm the MI accuracy.

Although the Healthy and Stroke groups presented significant differences in age, this unevenness seems not to be harmful to the analysis, because there is no correlation between age and accuracy (Pearson's test; rho = -0.195, P = 0.505). Furthermore, there was no differences in the MI accuracy between the Healthy group and the Stroke group (t-test, t-value = |1.475| and P = 0.166).

The BCI performance has been studied through a multiple comparison analysis using the MI accuracy calculated after each run using different avatar versions. The comparison using repeated measures ANOVA test, showed no significant differences, neither in the mean accuracy nor in the maximum accuracy (Table 18, Table 19 and Figure 29). The results of this first analysis demonstrate that there is no negative effect in the BCI performance when it is combined with a new gamified avatar. In spite of the results of the multiple comparison, the point cloud of T1-S2 and T2-S2 are slightly higher than T1-S1 (MI accuracy baseline measure, see Figure 29.A). This difference is more evident in the mean accuracy plot (Figure 29.C). Probably, the pop-up scoring window is encouraging the user to be more focused in the MI task.

The results obtained from the questionnaire show a high satisfaction level from the users (see Figure 30). In one hand, the easiness of use and the clarity of the rules are the best scored features of the game for both groups. Is important to point out that previous experience on gaming is not related with better user experience or better BCI performance. All users also reported that this new avatar helps them to improve the concentration (Q6) and reduce the boredom (Q7), and thus explain the tendency to higher accuracy when using this avatar. On the other hand, all participants gave the lowest score to the entertainment level (Q1) and visual attractiveness (Q2). The visual attractiveness can be solved easily

by changing the appearance of the game, the more difficult part could be improving the entertainment level without increase the cognitive task and consequently decrease the BCI performance. In order to apply all these changes, more patients and more sessions are needed. Some improvements of the game can be done following this seminal work. In particular, we could adapt the game's difficulty level to the user performance: the better the results, the higher the correct response threshold. The hypothesis to be evaluated would be thus, if this extra challenge affects users' mental imagery. Then, other narrative threads could be tested and stratified into levels in order to evaluate how story impacts on user performance and motivation. Nevertheless, the idea of introducing games combined with BCI therapy seems to be an indispensable step to take in order to improve the user experience, increase adherence to treatment and improve the functional outcomes of patients.

The results show that there is no significant difference in the MI accuracy baseline between healthy group and stroke group. Moreover, there were no significant differences between training with or without game. Results also show that there are no significant differences in the accuracies using the different forms of scoring feedback. Thus, the added stimuli of scoring and time does not affect performance. Concerning the users' opinions, they were all positive about the game level of entertainment, clarity of rules, narrative and visual attractiveness. Participants declared not having been affected by the game to create a mental image but having felt less bored. Finally, there was a consensus about the interest of gamifying stroke rehabilitation sessions.

Conclusions

Technology is bursting into daily clinical practice with increasing force. Today we have more advanced medical devices that allow us to achieve better results. This thesis has been based on the study of brain-computer interfaces for the rehabilitation of patients with motor impairments due to stroke. Through the systematic review of the literature the effectiveness of BCI treatment against conventional treatment is shown and these results are consistent with the results obtained in clinical trial I, where patients obtained a significant improvement in motor functionality. Rehabilitation is a long process, so it is very difficult to follow patients' improvements on a day-to-day basis. Functional scales have certain limitations in assessing these changes from one day to the next. However, from a neurophysiological point of view we can assume that during the therapy, small changes in the central nervous system occur, often at a subclinical level, undetectable for common functional measures. Technology could be a good ally in tracking these changes. Thirteen EEG biomarkers have been studied that are related to the most common functional scales. These markers can be of great help to follow changes in the nervous system, they can be faster, more accurate and more objective than conventional methods, where inter-rater variability can be reduced almost completely. This is undoubtedly an open research line, which can generate very beneficial advances for the patient and the physician.

Finally, it is necessary to consider how neurotechnology can help in the adherence to treatment. In clinical study II, it has been possible to investigate the impact of serious games in reinforcing concentration in therapy. Providing the patient with entertaining and accurate feedback can improve the user experience, increase concentration, improve task performance and prevent loss of patients during treatment.

It is time that we learn those new methods, provide scientific evidence and introduce them in our clinical practice looking the patient’s welfare.

Conclusions summary

1. In stroke patients, BCI improves motor function compared to conventional training alone without neurofeedback based on a meta-analysis of high-quality published literature.
2. BCI therapy effectively improves functional recovery in stroke patients, being the first positive sign reported a reduction in spasticity, followed by improvement in motor function.
3. EEG biomarkers can be a useful tool for stroke diagnosis and prognosis.
4. In healthy subjects, males have higher values of BSI than females.
5. Healthy participants had significantly lower BSI values than stroke patients with Subcortical or cortical and subcortical stroke.
6. In stroke patients, lower values of BSI correlate with better motor function in the upper extremities.
7. In stroke patients, different parameters related with band powers, APΔ the most, correlates with the ability of patients to perform activities of daily living.
8. In stroke patients, the level of tremor of the paretic hand is also related to APΔ, RPα and DAR.
9. In general, we see that the parameters involving the frequency bands α and Δ (APΔ and DAR, for example) are the ones most related to the functional status of the stroke patients.
10. In stroke patients, LC values for the healthy hand close to 0 correlated with better grasping function, lower tremor, and better motor functionality of the affected upper and lower extremity.
11. In stroke patients, LC values close to 0 for the paretic hand also correlated with high grasp ability and general functionality of the upper extremity.
12. Regarding gamification of BCI, the added stimuli of scoring and time neither affect performance nor accuracy of MI.
13. Users of a gamified BCI related that this new avatar helps them to improve concentration and were all positive about level of entertainment, clarity of rules, narrative and visual attractiveness.

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Publications

Correlations between The Laterality Coefficient and functional scales in stroke patients

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Abstract

Motor impairments are the most common and incapacitating consequences for stroke survivors. As of today, the effects of this pathology in the central nervous system as well as the brain proprieties to restore the function are still not fully understood. The conventional physical therapy techniques are limited and sometimes have an innocuous effect for non-cooperative or strongly impaired patients who only can receive passive movement treatments. Brain Computer Interface (BCI) systems are adding new possibilities for the stroke patient's rehabilitation, helping the patients in the relearning process of lost movements, and inducing neuroplastic changes in the affected motor cortex. The electrical brain signals can provide valuable information about the brain functions, thence the BCI systems can process these signals to understand what is happening in each situation. The event-related synchronization and even-related desynchronization (ERD/ERS) calculated with the brain signals during the motor imagery tasks, could be related with the functional state of the stroke patients. The Laterality Coefficient (LC) is a parameter calculated using the ERD/ERS changes in the mu wave. Twenty-six stroke patients with hemiparesis in the upper limb have been enrolled in this study and performed 25 sessions of BCI therapy. All of them performed assessment sessions before and after the therapy. The results showed significant correlation between the LC and functional scales like the Fugl-Meyer Assessment (FMA) or Box and Block Test (BBT). The findings of this experiment suggest that the LC parameter could be a good biomarker for the functional state of stroke patients.

Introduction

Stroke is one of the most prevalent pathologies around the world, with severe effects to the motor and sensory system that hinder the daily living activities. The major part of the stroke patients needs a long rehabilitation process to overcome the hemiplegia and adapt again to the environment. The conventional rehabilitation techniques have a roof effect to get a complete degree of rehabilitation. New technologies like the Brain Computer Interfaces (BCI) are important tools to improve the functional results of the rehabilitation process. The BCI systems are able to measure the brain activation and to generate a

control signal for external devices in real-time [1], [2]. After the stroke, the brain signals do not follow a normal activation, usually the affected cortex presents less excitability due to the change in the cortical representation areas and other physiological alterations on the nervous tissue [3], [4]. However, BCI systems can help the stroke survivor to relearn the lost movements, using EEG signals during Motor Imagery (MI) exercises [5]. The detected brain oscillations can be used to move a virtual reality avatar or trigger a functional electrical stimulator device to reproduce the imagined movement with the paretic limb (e.g.[6],[7]). This way it provides the patient a closed loop feedback to ease the motor learning process.

During the MI tasks the patient should concentrate on performing an indicated movement mentally. At this moment typical brain waves appear in the EEG. During MI, the contralateral motor cortex produces a desynchronization (event-related desynchronization or ERD) of motor neurons, showing a decrease in the EEG amplitude in the frequency of 8-13 Hz (mu frequency rhythm). When the imagery period is finished, the contralateral motor cortex restores the synchronization state (event-related synchronization or ERS) and increases again the amplitude of the EEG ([3], [4], [8], [9]). Considering the stroke patients do not present normal brain signals, the ERD and the ERS patterns could be atypical as well. Kaiser et al. [4] investigated the relation between these patterns versus the patient's functional state and spasticity, using a new parameter, the Laterality Coefficient (LC). For functional assessment they used the European Stroke Scale (ESS), the Medical Research Council (MRC) and the Modified Ashworth Scale (MAS). The LC presented significant correlations with the MRC scale and MAS. The findings of Kaiser and colleagues showed that strong ERD patterns on the contralesional hemisphere are related to a high degree of impairment [4].

The objective of this study is to find correlations between the LC parameter in alpha and beta band, calculated using the ERD/ERS patterns, with other functional scales like the Fugl-Meyer Assessment (FMA).

Materials and methods

Study design: Twenty-six stroke patients with upper extremity hemiparesis were recruited for this study. All these patients have been classified in four groups based on their stroke diagnosis: Cortical, Subcortical, Cortical + Subcortical and Unknown. The inclusion criteria were: i) able to understand written and spoken instructions, ii) residual hemiparesis, iii) beeing in the subacute or chronic stroke phase (more than 2 months), iv) functional restriction in the upper extremities, v) stable neurological status, vi) willing to participate in the study and to understand and sign the informed consent, vii) have the opportunity to attend meetings. All these patients that did not present stable neurological situation have been excluded from the study for example persons with uncontrolled epilepsy.

All patients have completed between 23 and 25 sessions of BCI therapy, two sessions per week. Two assessment visits have been performed by an expert clinician before and after the therapy to track the

therapy effect in the functional patient state. The Pre1 assessment is performed 1 month before starting the therapy, and Pre2 assessment is performed just before the therapy starts. Post1 is performed just after the last session, and Post2 is performed one month after the last session.

The main scale used for the motor function assessment is the Fugl-Meyer Assessment (FMA). The FMA has an excellent internal consistency [10] and very good interrater and intrarater reliability [11], [12]. These are some reasons explaining why FMA is one of the most used scales for the motor assessment in stroke patients [5], [10]–[13]. The FMA scale contains two different parts; the first part (up to 66 points) is for the motor assessment, and the other part is for the assessment of the sensation (up to 12 points). Table 1 shows the used scales for the assessments. In the first column appears the scales name, the second column is the short name of each scale, the column number three shows a short description of each scale and the last column presents the worst and best possible score. For the Fahn Tremor Rating Scale (FTRS) and BBT we have assessed both hands. For the BBT, the patient is asked to move as many blocks as possible from one box to the contralateral box in less than 1 minute. In the case that the patient cannot move any block, the final score would be 0.

BCI System: The BCI system used on this study is recoveriX® (g.tec medical engineering GmbH, Austria). The recoveriX system combines the visual feedback using a virtual reality avatar with a proprioceptive feedback using functional electrical stimulation (FES).

Every patient performed 25 sessions of BCI training. The patient was seated in a comfortable chair with the arms on the table. In front of the patient was a computer screen, showing two hands in virtual reality. The total time of one session was about 60 minutes, including preparation and cleaning. Every session was composed by up to 3 runs of 80 trials, depending of the patient's fatigue. Patients wore EEG caps with 16 active electrodes (g.LADYbird or g.Scarabeo, g.tec medical engineering GmbH). The electrode positions were according to the international 10/10 system (extended 10/20 system): FC5, FC1, FCz, FC2, FC6, C5 C3, C1, Cz, C2, C4, C6, Cp5, Cp1, Cp2, Cp6. A reference electrode was placed on the right earlobe and a ground electrode at position of FPz. Two FES electrodes were placed on the skin over wrist extensors of the left and right forearms. The stimulation parameters (g.Estim FES, g.tec medical engineering GmbH, Austria) were adjusted for each patient and session individually, to find the optimal passive movement without pain. The frequency was set to 50 Hz, the pulse-width to 300µs. Then, the therapist increased the current amplitude until the optimal stimulation point was observed.

The sequence of trials (motor tasks) was specified by the recoveriX software in pseudo random order. One single motor task is depicted in Figure 1. The patients first heard an attention beep. Two seconds later, an animated arrow with spotlight to the expected hand for motor imagery indicated the task of each trial with an auditory instruction saying either "left" or "right" in the patient's mother tongue. The patient started to imagine the movement and recoveriX processed the EEG using the features from a Common Spatial Patter (CSP) filter and using a Linear Discriminant Analysis (LDA) classifier to infer

which hand the patient is imagining. If recoveriX detected the appearance of the expected hand side, FES and avatar feedback were activated during the feedback phase. Feedback was otherwise deactivated. Updating the feedback was carried out five times per second. The animated forearm movement in avatar simultaneously performed the similar wrist dorsiflexion as produced by FES. The full recoveriX system is described in Figure 2.

Figure 1. Timing of one trial

Figure 2. Components of the BCI System.

Both hands are trained, the patient should learn the strategy used with the healthy hand to move the affected one. This is a key point for a correct embodiment and activate the motor learning process.

Laterality coefficient analysis: The EEG raw data recorded during the recoveriX sessions has been used to calculate the LC parameter. The LC coefficient (1) is calculated for each session twice: one time for trials of MI of the paretic (p) hand and another time for the trials of the healthy (h) hand.

$$LC_{p/h} = (C-I) / (C+I) \qquad (1)$$

Where C and I refer to the contralateral and ipsilateral values of the ERD/ERS patterns during the MI. C and I are calculated following these steps: 1) band filtering (8-13 Hz or 13-30Hz) of the EEG signal on the C3 and C4 electrodes. 2) Artifact rejection. 3) Laplacian derivation using the surrounding electrodes. 4) Calculate ERD/ERS patterns according to [9]. 5) Summation of all ERD/ERS values from second 2 until the end of the ERD map (second 8). And 6) apply the formula to obtain the LC coefficients.

Results

Participant baseline information: The mean age of the participants was 61.5 years (±12.8), the maximum age was 86 years, and the minimum was 33 years old. The mean time since the stroke was 4.2 years (±4.8), the maximum time since stroke was 24 years, and the minimum 10 months. In terms of kind of stroke; fourteen patients had a subcortical stroke, one had a cortical stroke, five a mixed cortical+subcortical and for six of them the kind of stroke is not clear. From the total number of patients, eight of them presented a hemiparesis on the right side, and eighteen on the left side.

LC during BCI therapy: Fig. 3 shows the delta of the LC parameter calculated in the alpha band during the BCI therapy. Typically, the ΔLC in both hands goes to values near 0 through the therapy. ΔLCh was -0.290 (pvalue = 0.191), and ΔLCp was 0.411 (pvalue = 0.059).

Functional scales: The FMA mean before the therapy was 23.08 points, with an SD of ±16.99 points. The highest possible FMA score is 66. The BI mean was 78.46 (±21.45) points, the mean FTRS of the healthy hand was 0.53 (±2.00) points, the of the paretic hand 8.98 (±4.83) points. The mean of the MAS scale of the wrist was 1.76 (±1.34) points, the MAS of the fingers 2.11 (±1.12) points. The mean of the BBT of the healthy hand was 56.67 (±14.38) boxes, and the same scale with the paretic hand was 4.96 (±11.90) boxes.

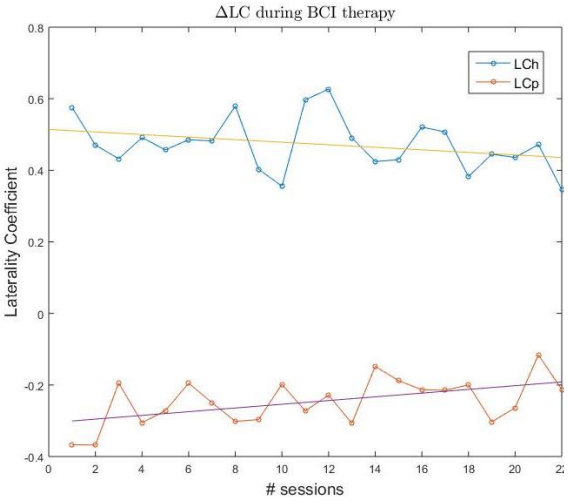

Figure 3. LC parameter in alpha band during BCI

Functional results after the therapy: The FMA mean after the therapy was 26.27 points (±19.58). The BI mean was 80.39 points (±21.40). The FTRS mean for the healthy hand was 0.42 points (±1.77), and FTRS mean for the paretic hand was 7.92 points (±5.57). The MAS of the wrist was 1.40 points (±1.55), and the MAS of the fingers was 1.50 points (±1.21). Finally, the BBT score of healthy hand was 64.73 (±15.96), and BBT for the paretic hand 6.58 (±13.14).

Functional scales improvement: ΔFMA was 3.46 (±4.89). 18 patients (69.23%) improved at least by one point in the FMA of motor part (ΔFMA = 5.39, SD = ±4.64), 4 patients (15.39%) did not present any change in the FMA scale (ΔFMA = 0, SD =0), and the others 3 patients (11.54%) decreased by at least one point in this scale (ΔFMA = -2.33, SD = 1.16).

The ΔBI was 2 (±3.82). 10 patients (38.46%) increased by at least one point (ΔBI = 6.00, SD = ±2.11), 13 patients (50.00%) did not present any change (ΔBI = 0, SD = ±0), and 3 patients (11.54%) decreased by at least one point (ΔBI = -5, SD = ±0).

The ΔMAS on the wrist was -0.23 (±0.77), 9 patients (34.61%) decreased the spasticity (ΔMASwrist = -1.06, SD = ± 0.39), 14 patients (53.85%) did not present any change (ΔMASwrist = 0, SD = ±0), and 3 patients (11.54%), increased the spasticity in the wrist (ΔMASwrist = 1.17, SD = ±0.76). The ΔMAS in the fingers was -0.52 (±1.03). 12 patients (46.15%) reduced the spasticity (ΔMASfingers = -1.38, SD = ±0.71), 12 patients (46.15%) did not change the punctuation in the MAS score (ΔMASfingers = 0, SD = ±0), and 2 patients (7.69%) increased the spasticity (ΔMAS fingers = 0.08, SD = ±0.27).

The ΔBBT in the healthy hand was 4.52 (±4.63). 20 patients 76.92%), increased in the BBT performance with the healthy hand (ΔBBThealthy = 5.40, SD = ±4.31), and 3 patients (11.54%) decreased the BBT score (ΔBBThealthy = -1.33 SD = ±0.58). The ΔBBT for the paretic hand was 1.30 (±2.95). 7 patients (26.92%) improved the BBT score with the paretic hand (ΔBBTparetic = 4.29 SD =

±4.11), 16 patients (61.54%) did not change the original score (ΔBBTparetic = 0, SD = ±0). The data from 3 patients in the preassessments was missing.

The ΔFTRS of the healthy hand was -0.039 (±0.34). 2 patients (7.69%) decreased the punctuation on the FTRS of the healthy hand (ΔFTRShealthy = -1, SD = ±0), and 1 patient (3.85%) increased the punctuation (ΔFTRShealthy = 1, SD = ±0). The other patients did not present changes on FTRS for the healthy hand. The ΔFTRS of the paretic hand was -0.92 (±2.28). 9 patients (34.62%) decreased the punctuation on the FTRS of the paretic hand (ΔFTRSparetic = -2.67, SD = ±3.32). 17 patients (65.39%) did not presented any chang in this scale.

No significant changes have been detected in the scales after treatment using the Wilcoxon Test.

Correlation with the functional scales: Statistical analysis was performed using MATLAB R2015a. The Kolmogorov-Smirnov Test showed that this data does not follow a normal distribution. Hence, for the statistical analysis we have used a non-parametrical method, the Spearman Test. The analysis was based on the calculation of the mean LC parameters (LCh and LCp) obtained in the therapy sessions. The correlations existing between the LC (of each hand, LCh and LCp) and the functional results of the evaluations have been calculated. These correlations have been performed separately, not using the multiple correlation technique.

Laterality Coefficient in alpha band: In general, the patients had positive LCh values during therapy, 0.4523 (SD = ± 0.33), while LCp values were negative, -0.2635 (SD = ± 0.35), as shown in Figure 3. LCh and LCp showed significant correlations with the FTRS score of the paretic hand, also with the BBT score of the paretic hand, and the FMA of the motor part and the FMA of the sensation part. No significant correlations have been found between LC and BI or MAS.

Laterality Coefficient of the healthy hand: LCh was moderate correlated with the tremor degree of the paretic hand assessed with FTRS (Figure 4.A). This positive correlation is present in all the assessments (pre and post) less on Pre2 assessment, where the p-value is near to 0.05. The second significant correlation has been with the FMA scale (Figure 4.B and 4.C). In this case the correlation is with negative sign, values near to 0 were correlated with better motor functional score (FMA motor) and better sensation degree (FMA sens). The correlation coefficients and pvalue's of each analysis are shown in Table 2. We did not find significant correlations between LCh and the daily living activities performance (BI) or with the spasticity degree (MAS).

Laterality Coefficient of the paretic hand: LCp was moderately correlated with the grasp ability in the paretic hand, assessed with the BBT (Figure 5.A). This correlation is stable in almost all the assessments but not in the Pre2, where the p-value is slightly above 0.05. The second important correlation is between the LCp and the FMA scale (Figure 5.B and 5.C). In this case the correlation is with positive sign, values near to 0 were correlated with better motor functional score (FMA motor) and better sensation degree (FMA sens). The correlation with the FMA motor is significant in the Post1 and Post2

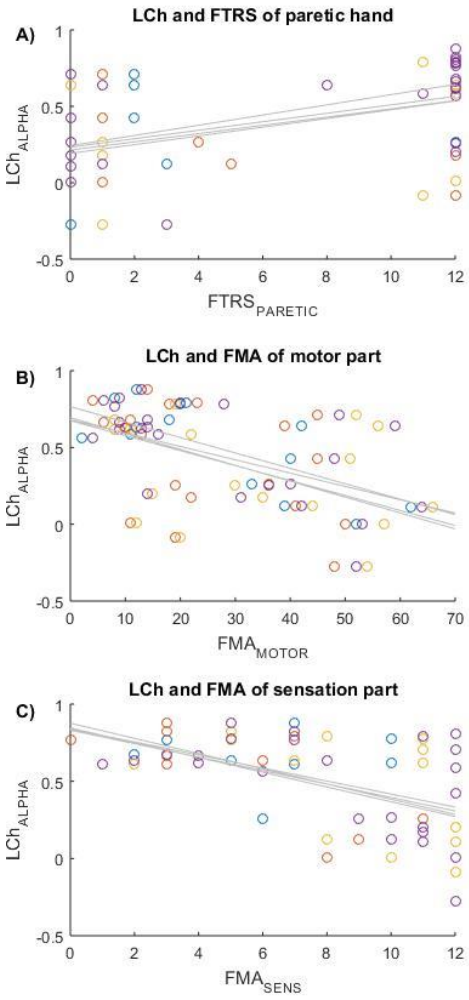

Figure 4. Correlation of LCh and functional scales

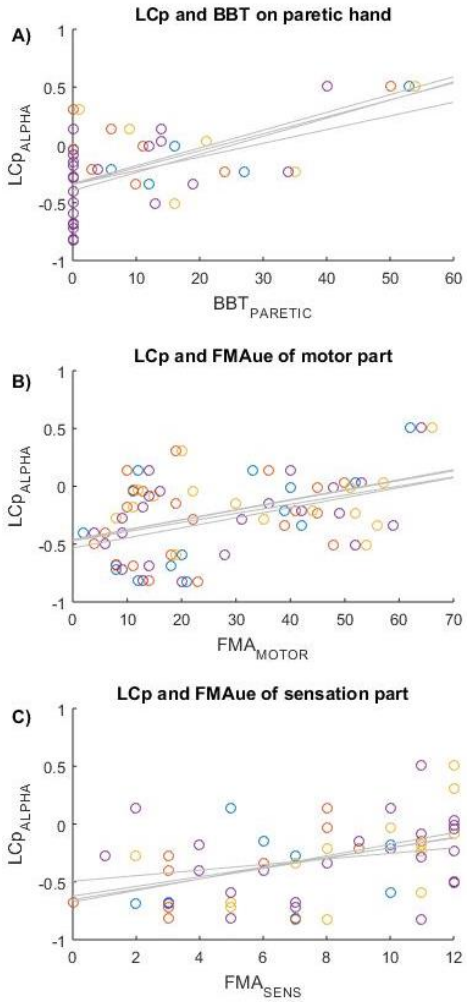

Figure 5. Correlation of LCp and functional scales

assessments, not in Pre1 and Pre2. The correlation coefficients and p-values of each analysis are shown in Table 2. We did not find significant correlations between LCh and the daily living activities performance (BI) or with the spasticity degree (MAS).

The correlations present coherence amongst them. The correlation coefficients express that the high levels of functionality were related with LCp values near to 0, and the low functional levels were related with very negative LCp values. Furthermore, the LCh have the opposed sign on the correlation coefficient with the scales.

In terms of the used functional scales, the high scores are related with values near to 0 in LCh and LCp, and the low scores with values near to 1 of LCh, and -1 in LCp. The FTRS is a special case of this typical positive or negative trend related with the LCh or LCp, because on the FTRS the high score is related with high degree of tremor.

Laterality coefficient in beta band: No significant correlations have been found between the functional scales and the LC of the beta band.

Table 2. Significant correlations between LC and functional scales (Spearman test)

Alpha band						
Scale	***Laterality Coefficient***	***Assessment session***	***Pre1***	***Pre2***	***Post1***	***Post2***
FTRSp	LCh	rho	0.401	0.385	0.418	0.574
		pval	0.042	0.052	0.034	0.003
FMAmotor	LCh	rho	-0.470	-0.486	-0.508	-0.561
		pval	0.015	0.012	0.008	0.004
FMAsens	LCh	rho	-0.415	-0.532	-0.500	-0.370
		pval	0.035	0.005	0.009	0.075
BBTp	LCp	rho	0.501	0.403	0.445	0.459
		pval	0.015	0.057	0.023	0.024
FMAmotor	LCp	rho	0.351	0.358	0.459	0.459
		pval	0.078	0.072	0.018	0.024
FMAsens	LCp	rho	0.415	0.559	0.449	0.262
		pval	0.035	0.003	0.021	0.215

Discussion

The objective of this study was to find correlations between the LC parameter in the alpha band, calculated using the ERD/ERS patterns with the functional state of stroke patients. For this, we analyzed 26 stroke patients who performed 25 sessions of therapy with BCI system.

The LCh in alpha band shows significant correlations with the tremor degree, with the global functionality of the upper extremity and with the sensation part of the FMA. In the other hand, the LCp in alpha band shows a marked correlation with the grasp functionality (Figure 5.A), with the global motor function in the upper extremity (Figure 5.B) and the sensation degree (Figure 5.C).

The general rule that can be applied to all these correlations is: LC values near to 0 points are related with high functional degree. LCh values near to 1 and LCp values near to -1 are related with poor functional degree.

The first important result to point out is that our results of the LC against the MAS are not similar to the results presented by Kaiser et al. The different kind of stroke patient, or the sample size could explain this.

Another important finding is the correlation with the FMA motor score. The FMA is a very extended scale, used to evaluate the patient's functional state. FMA has been validated many times by many researchers, and the correlations between this scale with EEG features are not common. This correlation is especially interesting because it could mean that the quantification of the cortical activation, using the LC parameter is related to the peripherical motor performance. The FMA and LC relationship is consistent with the relation of BBT and LC. Many studies demonstrate the strong correlation of the FMA and BBT scale [13]. In the light of this fact, it seems probable to find correlations with both scales at the same time, demonstrating the good quality of the data collected during the assessments. This relation is present in the affected hemisphere and also in the healthy hemisphere. The healthy hemisphere is not related directly to the motor activity of the paretic side, but for the LC calculation it is necessary using and compare the signals of both hemispheres. This is a reason why the LCh are important values for the assessment of the paretic side. Even though the sample size in our study is too small to give conclusive results, it is worth to point out the significance of this finding.

And last but not least, the LC alpha also presented a strong correlation with the FMA sensation scale part.

The superficial sensation and the proprioception are essential players on the BCI systems. The patients should feel as much as possible the feedback that the system provides for a correct closed loop interaction. Only if a correct synchronization between the intention of movement and the real feeling of this movement is provided the motor learning process is optimal [14]. This is only possible with BCI, and this is the greatest limitation of the conventional therapy techniques like the mirror therapy.

The other used scales of this study did not present significant correlations with the LC parameter. Again, the sample size of our study could be a limitation to find such correlations. No significant changes have been detected in the scales before-after the therapy. The study was described to analyze the correlation of LC with the functional scales, not to evaluate the effectiveness of the treatment. To do that, other

statistical analysis is needed, with other patient's subclassifications, keeping in mind the different stroke location, or the time since the stroke. Nevertheless, the major part of these patients presented important improvements with this BCI therapy, but the bad functional results from a few patients made it impossible detecting significant changes.

The meta-analysis of Cervera et al. [5], suggest that BCI can induce neuroplastic changes at subclinical level, sometimes it is difficult for clinicians to detect improvements in a short term with the current rehabilitation scales. The results of our study suggest that LC could be a good indicator of improvements, because could it could detect changes related directly to cortex activations.

Concerning the LC of the beta band, it shows only some isolated significant correlations with the scales.

Further studies with more patients will be needed to confirm these correlations and to find out how useful the LC parameter is in the daily clinical practice.

CONFLICT OF INTEREST

Christoph Guger is CEO of g.tec medical engineering GmbH, who developed and sells the system used for data assessment in this study.

Conclusion

The results of this study suggest that the LC parameter, calculated using the ERD/ERS of the stroke patients could be related with the Fugl-Meyer Assessment scale. This study opens the door to find more correlations between the EEG parameter with the patient's functional state.

Acknowledgment

We appreciate the collaboration of the Ministry of Business and Knowledge of the Government of Catalonia that partially supported this study (ACCIO RD15-1-0020 project and the Industrial Doctorates Plan). This study was also supported by the H2020-ESCEL Project Astonish (692470-1), the EC SME Phase 2 project recoveriX, and the MSCA-RISE grant Progait (agreement No 778043).

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Laterality Coefficient: An EEG parameter related with the functional improvement in stroke patients

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Abstract— Stroke is one of the most prevalent pathologies around the world, with severe effects to the motor and sensory system that hinder the daily living activities. Brain Computer Interface (BCI) systems can help the stroke survivors to relearn the lost movements inducing neuroplastic changes in the affected motor cortex. The event-related synchronization and even-related desynchronization (ERD/ERS) calculated with the brain signals during the motor imagery tasks, could be related with the functional state of the stroke patients. The Laterality Coefficient (LC) is a parameter calculated using the ERD/ERS changes in the mu wave. The goal of this study is to test how useful the LC is for the functional assessment of stroke patients. Fifteen stroke patients with hemiparesis in the upper limbs have been enrolled on this study and performed 25 sessions of BCI therapy. All of them performed assessment sessions before and after the therapy. The results showed significant correlation between the LC and functional scales, like the Fugl-Meyer Assessment (FMA) or Box and Block Test (BBT). The LC could be a good biomarker for the functional assessment in stroke patients.

Keywords — Brain Computer Interfaces, BCI, EEG, Stroke, Rehabilitation, FMA, Laterality Coefficient, LC, ERD, ERS.

Introduction

Stroke is one of the most prevalent pathologies around the world, with severe effects to the motor and sensory system that hinder the daily living activities. The major part of the stroke patients needs a long rehabilitation process to beat the hemiplegia and adapt again to the environment. New technologies like the Brain Computer Interfaces (BCI) are important tools to improve the functional results of the rehabilitation process. The BCI systems are able to measure the brain activation and to generate a control signal for external devices in real-time [1], [2]. After the stroke the brain signals do not follow a normal activation, usually the affected cortex presents less excitability due to the change in the cortical representation areas and other physiological alterations on the nervous tissue [3], [4].

However, these systems can help the stroke survivor to relearn the lost movements, using EEG signals during Motor Imagery (MI) exercises. The detected brain oscillations can be used to move a virtual reality avatar or trigger a functional electrical stimulator device to reproduce the imagined movement

with the paretic limb. This way it provides the patient a closed loop feedback to ease the motor learning process.

During the MI tasks the patient should concentrate on performing an indicated movement mentally. At this moment typical brain waves appear in the EEG. During MI, the contralateral motor cortex produces a desynchronization (event-related desynchronization or ERD) of motor neurons, showing a decrease in the EEG amplitude in the frequency of 8-13 Hz (mu frequency rhythm). When the imagery period is finished, the contralateral motor cortex restores the synchronization state (event-related synchronization or ERS) and increases again the amplitude of the EEG [3]–[5].

Considering the stroke patients do not present normal brain signals, the ERD and the ERS patterns could be atypical as well. Kaiser et al. investigated the relation between these patterns versus the patient's functional state and spasticity using a new parameter, the Laterality Coefficient (LC) [4]. For functional assessment they used the European Stroke Scale (ESS), the Medical Research Council (MRC) and the Modified Ashworth Scale (MAS). The LC presented significant correlations with the MRC scale and MAS. The findings of Kaiser and colleagues showed that strong ERD patterns on the contralesional hemisphere are related to a high degree of impairment [4]. Other recent studies have analyzed this LC parameter with similar results [6], [7].

The objective of this study is to find correlations between the LC parameter in alpha and beta band, calculated using the ERD/ERS patterns, with other functional scales like the Fugl-Meyer Assessment (FMA) [8].

Materials and Methods

Study design

Fifteen stroke patients with upper extremity hemiparesis were recruited for this study. All these patients have been classified in four groups based on their stroke diagnosis: Cortical, Subcortical, Cortical + Subcortical and Unknown. The inclusion criteria were: i) able to understand written and spoken instructions, ii) residual hemiparesis, iii) the stroke occurred at least four days before the beginning of the study, iv) Functional restriction in the upper extremities, v) stable neurological status, vi) willing to participate in the study and to understand and sign the informed consent, vii) have the opportunity to attend meetings.

All patients have completed 25 sessions of BCI therapy, two sessions per week. Two assessment visits have been performed by an expert clinician before and after the therapy to track the therapy effect in the functional patient state. The Pre1 assessment is performed 1 month before starting the therapy, and Pre2 assessment is performed

just before the therapy starts. Post1 is performed just after the last session, and Post2 is performed one month after the last session.

Table 1 shows the used scales for the assessments. In the first column appears the scales name, the second column is the short name of each scale, the column number three shows a short description of each scale and the last column presents the worst and best score. For the Fahn Tremor Rating Scale (FTRS) and BBT we have assessed both hands. For the BBT the patient is asked to move as many blocks as possible from one box to the contralateral box in less than 1 minute. In the case that the patient cannot move any block, the final score would be 0.

Assessment scales				
Scale name	***Short name***	***Description***	***Score***	
			Worst	***Best***
Barthel Index	BI	Daily living activities	0	100
Fahn Tremor Rating Scale	FTRS	Degree of tremor	12	0
Modified Ashworth Scale	MAS	Spasticity	4	0
Box and Block Test	BBT	Grasp	Block's number	
Fugl-Meyer Assessment	FMA	Motor function on upper limb	0	66

Table I. Scales used in the assessment visits.

BCI System

The BCI system used on this study is recoveriX® (g.tec medical engineering GmbH, Austria). The recoveriX system combines the visual feedback using a virtual reality avatar with a proprioceptive feedback using functional electrical stimulation (FES) [9].

Every patient performed 25 sessions of BCI training. The patient was seated in a comfortable chair with the arms on the table. In front of the patient was a computer screen, showing two hands in virtual reality. The total time of one session was about 60 minutes, including preparation and cleaning time. Every session was composed by up to 3 runs of 80 trials, depending of the patient's fatigue. Patients wore EEG caps with 16 active electrodes (g.LADYbird or g.Scarabeo, g.tec medical engineering GmbH). The electrode positions were according to international 10/10 system (extended 10/20 system): FC5, FC1, FCz, FC2, FC6, C5 C3, C1, Cz, C2, C4, C6, Cp5, Cp1, Cp2, Cp6. A reference electrode was placed on the right earlobe and a ground electrode at position of FPz.

Two FES electrodes were placed on the skin over wrist extensors of the left and right forearms. The stimulation parameters (g.Estim FES, g.tec medical engineering GmbH, Austria) were adjusted for each patient and session individually, to find the optimal passive movement without pain for patients with mild or moderate muscle spasm, or until muscle contraction was observed in the target muscle of their paretic side for patients with severe muscle spasm. The frequency was set to 50 Hz, the pulse with to 300 μs. Then, the therapist increased the current amplitude until the optimal stimulation point was observed.

The sequence of trials (motor tasks) was specified by the recoveriX software in pseudo random order. One single motor task is depicted in Fig 1. The patients first heard an attention beep. Two seconds later, an animated arrow with spotlight to the expected hand for motor imagery indicated the task of each trial

with an auditory instruction saying either "left" or "right". When the recoveriX detected the appearance of the correct hand side, FES and avatar feedback were activated during the feedback phase. Feedback was otherwise deactivated. Updating the feedback was carried out five times per second. The animated forearm movement in avatar simultaneously performed the similar wrist dorsiflexion produced by FES. The full recoveriX system is described in Fig. 2.

Figure 1. Timming of one trial.

Figure 2. Components of recoveriX system

Laterality Coefficient analysis

The EEG raw data recorded during the recoveriX sessions has been used to calculate the LC parameter.

The LC coefficient is calculated for each session twice: one time for trials of MI of the paretic (p) hand and another time for the trials of the healthy (h) hand.

$$LCp/h = (C-I) / (C+I)$$

Where C and I refer to the contralateral and ipsilateral values of the ERD/ERS patterns during the MI. C and I are calculated following these steps: 1) band filtering (8-13 Hz or 13-30Hz) of the EEG signal on the C3 and C4 electrodes. 2) Artifact rejection. 3) Laplacian derivation using the surrounding electrodes. 4) Calculate ERD/ERS patterns according to [10]. 5) Summation of all ERD/ERS values from second 2 until the end of the ERD map (second 8). And 6) apply the formula to obtain the LC coefficients.

Results

Participant baseline information

The mean age of the participants was 55.27 years (±15.8), the time since the stroke was 7.43 years (±5.07). In terms of kind of stroke; six patients had a subcortical stroke, three had a cortical stroke, four a mixed cortical+subcortical and for two of them the kind of stroke is not clear. From the total number of patients, six of them presented a hemiparesis on the right side, and nine on the left side.

Functional scales

The FMA mean before the therapy was 31.63 points, with an SD of ±20.46 points. The highest possible FMA score is 66. The BI mean was 88.33 (±16.86) points, the mean FTRS of the healthy hand was 0.13 (±0.39) points, the one of the paretic hand 7.27 (±5.15) points. The mean of the MAS scale of the wrist was 2.00 (±16.65) points, the MAS of the fingers 2.27 (±1.50) points. The mean of the BBT of the

healthy hand was 60.08 (±15.39) boxes, and the same scale with the paretic hand was 9.92 (±11.59) boxes.

LC variance

Fig. 3 shows the variance of the LC parameter in alpha and beta band. In both bands, the LC of healthy hand (LCh) is strongly related with the results of the LC of paretic hand (LCp).

Correlation with the functional scales

Statistical analysis was performed using MATLAB R2015a. The Kolmogorov-Smirnov Test showed that this data does not follow a normal distribution [11]. Hence, for the statistical analysis we have used a non-parametrical method, the Spearman Test [12].

No significant correlations have been found between the LC of the beta band, or between the scales and the LCh in alpha band.

The average of the LC calculated during these 25 sessions in the paretic hand (LCp), shows significant correlations with the MAS scale, also with the BBT score of the paretic hand, and the FMA score.

Fig. 4 shows the correlation between the spasticity level of the fingers using the MAS, against the LC parameter of the paretic hand. Fig. 5 shows the correlation between the BBT score with the paretic hand and the LC parameter of the paretic hand. Fig. 6 shows the correlation between the FMA score and the LC parameter of the paretic hand.

The correlations present coherence amongst them. The results express that the high levels of functionality are related with LCp values near to 0. In the case of BBT and FMA, the correlations have a positive trend, as less negativity of the LCp, better results in the grasp and general function of upper limb. Nevertheless, the significant results of the MAS scale show a negative trend, that means the patients that have less spasticity (values near to 0 points) have LCp values near to 0.

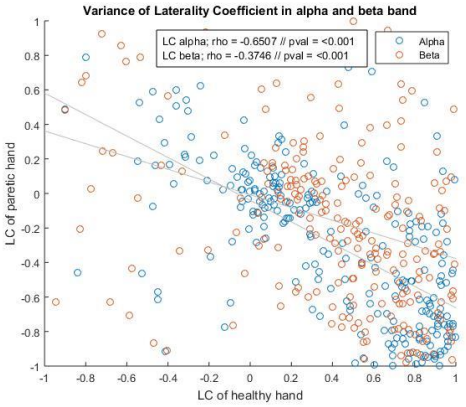

Figure 3. Variance of LC parameter in Alpha and Beta band.

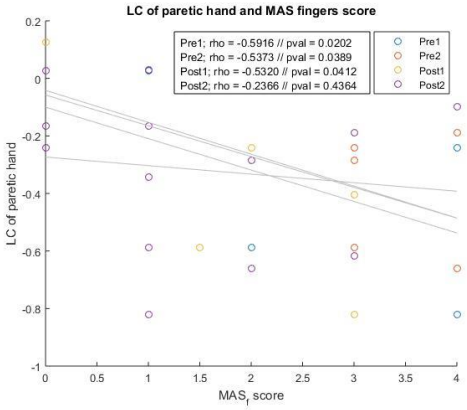

Figure 4. Correlation between the LC of the paretic hand and the Modified Ashworth Scale of fingers.

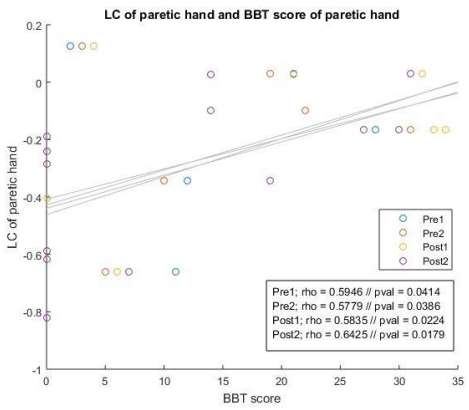

Figure 5. Correlation between the LC of the paretic hand and the Box and Block Test.

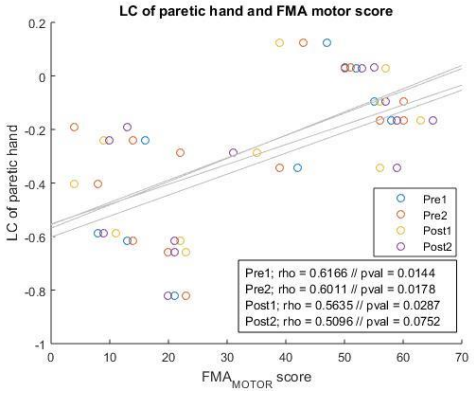

Figure 6. Correlation between the LC of the paretic hand and the Fugl-Meyer Assessment of motor part.

Two of these correlations are not present in the Post2 assessment. MAS and FMA present good significance in Pre1, Pre2 and Post1 but not in the last assessment. No significant correlations have been found with the other functional scales.

Discussion

The objective of this study was to find correlations between the LC parameter in the alpha band, calculated using the ERD/ERS patterns with the functional state of stroke patients. For this, we analyzed 15 stroke patients who performed 25 sessions of therapy with BCI system.

Usually the EEG parameters present high variability, but this is not the case for the LC parameter, as Fig.3 shows.

The LCp in alpha band show significant correlations with the level of spasticity, with the grasp function and with the global functionality of the upper extremity.

The first important result to point out is that our significant results of the LC against the MAS could reproduce the results presented by Kaiser et al. Our sample size is smaller than in the previous study, but the LC show a similar behavior on the same kind of patients. Our study results are also consistent with Park et al, and Belfatto et al, where the high values of FMA are related with a decrease of the LC [7].

Furthermore, the LCp is directly correlated with the grasp functionality of the affected hand (Fig. 4). These patients, having an LCp value near to 0, had better scores in the BBT. This correlation could be directly related to the last finding of the experiment, the relationship between the LCp parameter and the FMA score. The FMA is a very extended scale, used to evaluate the patient's functional state. FMA has been validated many times by many researchers, and the correlations between this scale with EEG features are not common. Even though the sample size in our study is too small to give conclusive results, it is worth to point out the significance of this finding.

The other used scales of this study did not present significant correlations with the LC parameter. Again, the sample size of our study could be a limitation to find such correlations.

Concerning to the LC of the beta band, and the LCh: they showed only some isolated significant correlations with the scales. After the analysis, the low values of the LCh parameter seems to be related with the high scores in the functional scales, but the correlations did not show significance of these relations.

Further studies with more patients will be needed to confirm these correlations and to find out how useful the LC parameter is in the daily clinical practice.

Conclusion

The results of this study suggest that the LC parameter, calculated using the ERD/ERS of the stroke patients could be related with the Fugl-Meyer Assessment scale. This study opens the door to find more correlations between the EEG parameter with the patient's functional state.

Acknowledgment

We appreciate the collaboration of the Ministry of Business and Knowledge of the Government of Catalonia that partially supported this study (ACCIO RD15-1-0020 project and the Industrial Doctorates Plan). This study was also supported by the H2020-ESCEL Project Astonish (692470-1), the EC SME Phase 2 project recoveriX, and the MSCA-RISE grant Progait (agreement No 778043).

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Appendix

Appendix A

Search terms

Term	Date	Result
(((cerebrovascular disorders[mh]) or (basal ganglia cerebrovascular disease[mh]) or (brain ischemia[mh]) or (carotid artery diseases[mh]) or (intracranial arterial diseases[mh]) or (intracranial embolism and thrombosis[mh]) or (intracranial hemorrhages[mh]) or (stroke[mh]) or (brain infarction[mh]) or (vertebral artery dissection[mh])) OR ((stroke[tiab]) or (poststroke[tiab]) or ("post-stroke"[tiab]) or (cerebrovasc*[tiab]) or (cva*[tiab]) or (apoplex*[tiab]) or (SAH[tiab])) OR ((hemiplegia[mh]) or (paresis[mh])) OR ((hemipleg*[tiab]) or (hemipar*[tiab]) or (paresis[tiab]) or (paretic[tiab]))) AND (((brain computer interface[mh]) or (neurofeedback[mh])) OR ((“brain$computer interface”[tiab]) or (“brain$machine interface”[tiab]) or (neurofeedback[tiab]) or (“brain$machine interface”[tiab]) or (“brain$actuated”[tiab]))	01.03.2019	442 Hits*

*One review paper included 15 publication; another review paper included 9 publication. Total = 466.

Table with included articles

First author	Title	Year	DOI
Kai Keng Ang	Brain-computer interface-based robotic end effector system for wrist and hand rehabilitation: results of a three-armed randomized controlled trial for chronic stroke	2014	0.3389/fneng.2014.00030
Kai Keng Ang	A Randomized Controlled Trial of EEG-Based Motor Imagery Brain-Computer Interface Robotic Rehabilitation for Stroke	2015	10.1177/1550059414522229
A.Biasiucci	Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke	2018	10.1038/s41467-018-04673-z
TaeHoon Kim	Effects of Action Observational Training Plus Brain–Computer Interface-Based Functional Electrical Stimulation on Paretic Arm Motor Recovery in Patient with Stroke: A Randomized Controlled Trial	2016	10.1002/oti.1403
Mingfen Li	Neurophysiological substrates of stroke patients with motor imagery-based brain-computer interface training	2014	10.3109/00207454.2013.850082
Masahito Mihara	Near-infrared Spectroscopy–mediated Neurofeedback Enhances Efficacy of Motor Imagery–based Training in Poststroke Victims: A Pilot Study	2013	10.1161/STROKEAHA.111.674507
Anaïs Mottaz	Modulating functional connectivity after stroke with neurofeedback: Effect on motor deficits in a controlled cross-over study	2018	10.1016/j.nicl.2018.07.029
Floriana Pichiorri	Brain–Computer Interface Boosts Motor Imagery Practice during Stroke Recovery	2015	10.1002/ana.24390
Ander Ramos-Murguialday	Brain-Machine-Interface in Chronic Stroke Rehabilitation: A Controlled Study	2013	10.1002/ana.23879
Xin Wang	Differentiated Effects of Robot Hand Training With and Without Neural Guidance on Neuroplasticity Patterns in Chronic Stroke	2018	10.3389/fneur.2018.00810

Effectiveness of intervention

Summary of the included trials in the meta-analysis (n = 10).

Study	Evidence level	N – Experimental	N – Control	Age (years)	Stroke stage	Biofeedback principle	Feedback type	Control group intervention method	intervention time (in minutes)	Number of interventions	Outcome measures	Level of impairment *	BCI change	Control change
Wang et al	Ib	13	11	54 (9)	Chronic	Motor imagery + BCI	Robot	Sham feedback	60	20	FMA-UE	Moderate to severe	3.85 (5.51)	2.82 (4.0)
Mottaz et al	IIa	10	10	57.10 (8.9)	Chronic	EEG MI BCI	Visual	Contralesional EEG during MI	50 min NFT + 10 min resting state EEG + 30min PT	8	FMA-UE	Severe, Moderate and Mild	5.3 (3.0)	2.0 (2.6)
Biasiucci et al	Ib	14	13	57.6 (11.0)	Chronic	Motor attempt + BCI	FES + visual	Sham feedback FES	60 min NFT + 45min PT	10	FMA-UE	Moderate to severe	6.6 (5.6)	2.1 (3.0)
Li et al	Ib	7	7	67.07(5.24)	Subacute	MI; BCI; FES	FES+visual +auditory	FES + conventional therapy	60~90min NFT + 30min PT	24	FMA-UE	Severe	12.71 (12.2)	6.71 (4.46)
Ang et al	Ib	11	14	51.4(11.6)	Subacute, Chronic	MI; BCI; Robot	Robot + visual	MANUS (Robot assisted)	90min NFT	12	FMA-UE	Severe, moderate	4.55 (6.07)	6.21 (6.33)
Kim et al	Ib	15	15	Exp: 59.1 (8.1) Control: 59.9 (9.6)	Chronic <12 months	EEG MI BCI	FES	Conventional therapy only	30min NFT + 30min PT	20	FMA-UE	Not mentioned.	7.87 (2.42)	2.93 (2.74)
Pichiorri et al	Ib	14	14	Exp: 64.1 (8.4) Control: 59.6 (12.7)	Subacute	EEG MI BCI	Visual	Sham feedback	30min NFT + 180min PT	12	FMA-UE	Spasticity <5 MAS	13.67 (8.87)	6.5 (7.0)
Ang et al (a)	Ib	6	8	54.2 (12.4)	Subacute, chronic >4 months	EEG MI-BCI	haptic knob	Haptic knob	90min NFT	18	FMA-UE	FMA 10-50	7.2 (2.3)	7.3(4.7)
Ramos-Murguialday et al	Ib	16	16	Exp: 49.3 (12.5) Control: 50.3 (12.2)	Subacute, Chronic >10months	EEG MI BCI	Orthosis	MI with random feedback	60min NFT + 60min PT	20	cFMA (max 54)	Not mentioned.	3.4 (2.2)	0.36 (4.2)
Mihara et al	Ib	10	10	58.1 (8.3)	Subacute, Chronic >2.8months	NIRS MI BCI	Visual	MI with random feedback	20min NFT + 150min PT	6	FMA-UE	FMA 0-50	4.8 (2.57)	2.3 (1.77)

Abbreviations: ARAT, action research arm test; FMA, Fugl-Meyer Assessment; UE, Upper Extremity; MI, Motor Imagery; NFT, neurofeedback training; FES, functional electrical stimulation; cFMA, combined hand and modified arm FMA; NIRS, near-infrared spectroscopy; PT: Physiotherapy. * Moderate (FM-UE 29-42); Mild: (FM-UE 43-66); Severe: (FM-UE 0-28).

Appendix B

Full text questionnaire of Clinical trial 2.

Enquestes de dades demogràfiques i valoració del joc

Estudio del impacto de la gamificación en la rehabilitación con BCI

Fecha : / /2019

Encuesta demográfica

- Fecha de nacimiento
- Sexo
- Lado afectado: [ ] derecho [ ] izquierdo
- Fecha del ictus (mes y año):
- Localización del ictus:

  [ ] Cortical [ ] Subcortical [ ] Cortical y Subcortical (mixto) [ ] Desconocido

Encuesta de opinión

1. ¿Has utilizado con anterioridad un dispositivo BCI? [ ] si [ ] no

En caso afirmativo, ¿con qué finalidad? ……..

2. ¿Juegas a algún video-juego?

[ ] Nunca [ ] Casi nunca [ ] Algunas veces [ ] Frecuentemente [ ] Muy frecuentemente

3. Evalúa el nivel de diversión del juego:

[ ] nada divertido [ ] poco divertido [ ] indiferente [ ] divertido [ ] muy divertido

Explica porque:……...

4. Evalúa el aspecto visual del juego:

[ ] muy malo [ ] malo [ ] indiferente [ ] bueno [ ] muy bueno

Explica porque: ……

5. Evalúa la facilidad de uso del juego:

[ ] muy difícil [ ] difícil [ ] normal [ ] fácil [ ] muy fácil

Explica porque: ……

6. Evalúa las reglas de juego:

[ ] muy confusas [ ] confusas [ ] indiferente [ ] claras [ ] muy claras

Explica porque: ……

7. Con respecto a la trama narrativa (la lucha contra el ratón para proteger el queso), te ha parecido:

[ ] muy inadecuada [ ] inadecuada [ ] indiferente [ ] adecuada [ ] muy adecuada

Explica porque: ……

8. Con respecto al nivel de concentración necesario para realizar el ejercicio, en tu opinión, añadir el juego a la sesión de rehabilitación ha contribuido a:

[ ] despistarte mucho [ ] despistarte [ ] no me ha influido [ ] me ha ayudado a concentrarme [ ] me ha ayudado mucho a concentrarme

Explica porque: ……

9. Con respecto a la posible sensación de aburrimiento al realizar el ejercicio, en tu opinión, añadir el juego a la sesión de rehabilitación ha contribuido a:

[ ] me ha aburrido mucho más [ ] me ha aburrido más [ ] ni me ha influido [ ] me ha animado más [ ] me ha animado mucho más

Explica porque: ……

10. En general, la idea de introducir un juego (no necesariamente éste) en la terapia de rehabilitación, te parece:

[ ] nada acertada [ ] poco acertada [ ] indiferente [ ] acertada [ ] muy acertada

Explica porque: ……