UNIVERZA NA PRIMORSKEM
FAKULTETA ZA MATEMATIKO, NARAVOSLOVJE IN
INFORMACIJSKE TEHNOLOGIJE

MASTER'S THESIS
(MAGISTRSKO DELO)

BRAIN-COMPUTER INTERFACE SYSTEM FOR FUNCTIONAL MOTOR REHABILITATION AFTER STROKE IN CONNECTION WITH PHARMACOTHERAPY

(VMESNIŠKI SISTEM MOŽGANI-RAČUNALNIK ZA FUNKCIONALNO MOTORIČNO OKREVANJE PO MOŽGANSKI KAPI V POVEZAVI Z ZDRAVILI)

NENSI MUROVEC

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(Vmesniški sistem možgani-računalnik za funkcionalno motorično okrevanje po možganski kapi v povezavi z zdravili)

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Izvleček: Vmesniški sistemi možgani-računalnik predstavljajo najnovejši trend za funkcionalno okrevanje po možganski kapi. Z uporabo vmesniškega sistema možgani-računalnik, ki podaja povratno informacijo preko virtualne resničnosti in funkcionalne električne stimulacije smo želeli preveriti ali lahko tak sistem pomembno pripomore k funkcionalnemu motoričnemu okrevanju in nevroplastičnosti teh bolnikov, ter hkrati preveriti ali so zdravila predpisana ob kapi vplivala na potek okrevanja. Motorični testi, ki smo jih izvedli pred in po rehabilitacijski terapiji so pokazali, da so vsi udeleženci pomembno izboljšali rezultate pri večini izmerjenih testov. Zaznali smo trend, da so udeleženci, ki so imeli predpisana zdravila s potencialnim negativnim vplivom na okrevanje slabše okrevali po možganski kapi pred pričetkom terapije, kot udeleženci s predpisanimi zdravili s potencialnim pozitivnim vplivom na okrevanje. Med obema skupinama v samem okrevanju po terapiji z vmesniškim sistemom možgani-računalnik pa nismo zaznali pomembnih razlik. Pri analizi nevroplastičnosti smo prav tako lahko pri večini udeležencev zaznali pomembne

razlike pred in po terapiji, vendar ne med samima skupinama. Študija na podlagi rezultatov kaže, da je bila terapija uspešna, ne more pa podati jasnega mnenja o vplivu zdravil na motorično okrevanje po možganski kapi.

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Abstract: Brain-computer interference systems represent the latest trend for functional motor recovery after a stroke. By using the brain-computer interface system that provides feedback via virtual reality and functional electrical stimulation, we intended to control whether such a system can significantly contribute to the functional motor recovery and neuroplasticity of these subjects, and at the same time to control whether the drugs prescribed at stroke affected the course of the recovery. Motor assessments performed before and after rehabilitation therapy showed that all participants significantly improved in most of the assessments tested. We have detected a trend that subjects who had prescribed drugs with a potential detrimental effect had worst recovery after the stroke before the start of therapy as participants who had prescribed potential rehabilitation improving drugs. There was no significant difference between the two groups in the recovery after the therapy with the brain-computer interface system. In the analysis of neuroplasticity, we also experienced significant differences in the majority of subjects before and after therapy, but not among the groups themselves. Results based on the study suggest that the therapy was successful but cannot give a clear opinion on the impact of the drugs on motor recovery after a stroke.

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DO MORE.

1 INTRODUCTION

Stroke affects 17 million people worldwide each year and it is the second most common cause of death, and a leading cause of adult disability (Stevens, Emmet, Wang, McKevitt, & Wolfe, 2017). Stroke results in multiplex of motor, sensory and cognitive impairments due to the damage of neural tissue in the brain (Remsik, Young, Vermilyea, Kiekhoefer, Abrams, Elmore et al., 2016). With that, the aim of the novel rehabilitation approaches is to increase functional recovery by promoting gradual adaptation of the brain`s remaining neural connections (Young, Nigogosayan, Remsik, Walton, Song, Nair et al., 2014), and through reorganizational and compensational processes in the damaged brain, processes of the so-called neuroplasticity (de Vries & Mulder, 2007; Hatem, Saussez & Faille, 2016).

One of the most promising novel trends in stroke rehabilitation involves electroencephalographic (EEG) monitoring method to record electrical activity of the brain associated with motor activity (Remsik et al., 2016), where Brain-Computer Interface (BCI) systems provide direct communication channel between a person's brain and a computer. This allows a person to control a computer system or a mechanical device as a natural part of their body's representation, when used for rehabilitation purpose just with imagery of specific mental task. Mental practice with motor imagery can induce reorganization of brain motor network for affected and also non-affected parts of the brain and improve regional connectivity in the motor area (Bajaj, Butler, Drake & Dhamala, 2015; Ramadan, Refat, Elshahed & Rasha, 2015). When mental practice is combined with standard therapy approach, like for example Functional Electrical Stimulation (FES), and used with BCI based therapy that can provide feedback for the specific mental task or motor imagery, and the proprioceptive feedback loop in the real time is closed, neuroplasticity and Hebbian-based motor recovery is induced (Irimia, Sabathiel, Ortner, Poboroniuc, Coon, Allison et al., 2016).

Neuroplasticity and neural connectivity, that are the concepts of neurorehabilitation and the aim of rehabilitation after stroke, can also be modulated pharmacologically. The review of the literature shows that drug therapies given at stroke as a standard therapy due to the activation of several biological pathways related to ischemic cascade, immunological, and restorative response, or for the treatment of coincident medical conditions can have profound effect on the recovery process (Engelter, 2013). Some drugs can influence specific neurotransmitter systems, and even in small doses, can enhance or have detrimental effect on functional motor recovery after stroke. This are mostly drugs used at stroke to treat accompanying symptoms due to pain, convulsions, depression, and similar biological and psychiatric symptoms, like for example antipsychotics, benzodiazepines, antidepressants, analgesics, anxiolytics, antiepileptics and some others (Cramer, 2015; Goldstein, 1993).

One of the key aspects of this thesis was to determine if the rehabilitation with the BCI based system was successful, and if we can determine if any of drugs given at stroke, influenced the rehabilitation outcome with BCI based system for functional motor recovery after stroke. In the thesis the principal biological mechanisms, the effects of stroke and rehabilitation techniques are explained with emphasis on functional motor rehabilitation and BCI technology, followed by the overview of the influence of drugs on motor recovery. The experimental part provided insight into the novel therapeutic technique efficiency and allowed the observation of the influence of drugs on this technique that, as it is known to us, has not been studied before.

1.1 CEREBROVASCULAR DISEASES

Cerebrovascular disorders are defined as "those disorders in which an area of brain is transiently or permanently affected by ischemia or bleeding, or in which one or more brain blood vessels are primarily involved in a pathological process, or a combination of both" (WHO, 1978, p. 3). Vascular disorders that affect the brain are classified as:

- Basic pathophysiological processes that consist of decreased perfusion pressure because of a cardiac or systemic circulatory problem, abnormalities of the blood or abnormalities directly impairing the vessel`s transport of blood (embolism, thrombosis, atherosclerosis, etc.).

- Pathophysiological changes in parenchymal metabolism in the brain, which can also be reversible and of a short duration, from infarction of impaired circulation or haemorrhage of the blood vessel rupture.

- Focal deficits in brain metabolism that result in neurological abnormality. They can be temporal, from a brief event, like transient ischemic attack (TIA), or produce severe permanent brain damage, from a complete stroke, that results in hemiplegia and other deficits, or even death (Good, 1990; WHO, 1978).

Stroke, a cerebrovascular disorder, characterized by neural dysfunction and apoptosis induced by cessation of blood flow as a result of clotting called ischemic stroke or rapture of blood vessels called haemorrhagic stroke. The area of the affected brain tissue, caused by blood flow obstruction, that is dead or it is dying because is no longer able to sustain homeostatic function, is called *infarct* whereas dysfunctional area surrounding the infarcted area is called *penumbra* (Seidenstein, Barone & Lytton, 2015). When blood flow is interrupted trough the small vessels, such as capillaries, the deficits are limited and have less

devastating consequences in comparison to large vessel obstruction, where the infarction and penumbra areas are usually larger (Nour, Scalzo & Liebeskind, 2013).

In the year 2015 stroke was a cause of death for around 6.2 million people in the world, according to the WHO, and for around 613 thousand people in Europe (Stevens et al., 2017). For the ones who survive, the outcomes of stroke depend on the affected brain area and its size, but are usually common and can include motor disabilities, depression and anxiety, problems with language and communication, perceptual deficiencies, declines in cognitive abilities, memory, and executive functioning (Good, Bettermann & Reichwein, 2011). About 50 to 60% of patients experience motor, neurological and cognitive impairments that have an effect on their quality of life (Patel, McKevitt, Lawrence, Rudd & Wolfe, 2007).

1.2 STROKE REHABILITATION AND RECOVERY

Stroke rehabilitation process uses three major principals of recovery: adaptation, regeneration, and neuroplasticity. Stroke rehabilitation describes the process of preventing deterioration of function, improvement of function to the highest level within the limits of the persistent stroke impairment on the physical, psychological and social level. Rehabilitation includes restoration approaches through exercises and techniques used in physio and occupational therapy. The goal of this rehabilitation techniques is to retain parts of central nervous system (CNS) to engage the functions that were lost, and by that restore function of the brain tissue that was damaged. Second approach is compensation that uses adapted behaviour technique which brings to reorganization of partly spared brain pathways and relearning. Third approach called modification alternates environmental setting to promote functionality and daily live activities (Belagaje, 2017; Cumberland Consensus Working Group, Cheeran, Cohen, Dobkin, Ford, Greenwood et al., 2009). Stroke recovery phrases the improvement across variety of outcomes, namely in biological and neurological changes that can demonstrate in improvement of performance or behavioural measurements based on activity (Belgaje, 2017).

1.2.1 Movement disorders after stroke

After stroke many types of movement disorders can be recognised, and they are mostly based on the location and extent of the lesion. Different locations within the brain are identified as responsible for movement disorders, when affected by the stroke, with basal ganglia being one the most implicated. As demonstrated on the Figure 1.01, basic function of the basal ganglia pathways is to act as a cortical feedback loop, where neo-cortex sends signals through striatum, pallidum and thalamus back to cortex. Excitatory signals are sent from cortex to striatum, striatum inhibits the pallidum and that inhibits the thalamus. The result

of cortical activation is to trigger striatum to release thalamus from pallidal inhibition, with allowing thalamic outputs to excite the cortex. These direct pathways are also modulated by other loops and these pathways are modulated by substantia nigra and subthalamic nucleus which generate neurotransmitters like dopamine and glutamate. An interruption of direct or indirect pathways by focal lesions may lead to movement disorders (Handley, Medcalf, Hellier & Dutta, 2009; Siniscalchi, Gallelli, Labate, Malferrari, Palleria & De Sarro, 2012).

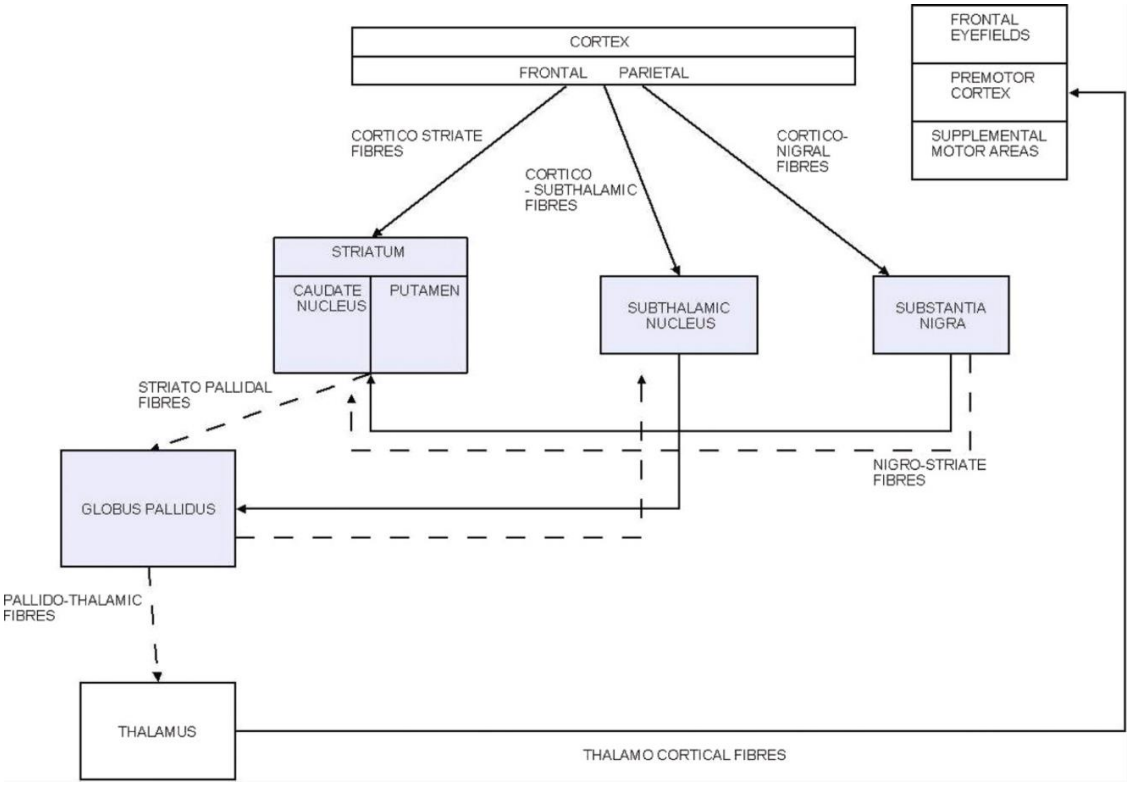


Figure 1.01. A simplified model of basal ganglia circuitry involved in movement disorders (Handley et al., 2009).

One of the most common movement disorders seen at stroke patients is upper extremity impairment with muscle weakness or contractures, joint laxity, changes in muscle tone and motor control (Hatem, Saussez, della Faille, Prist, Zhang, Dispa et al., 2016). As standard rehabilitation for movement disorders, patients after stroke have physio and occupational therapy that involves a lot of different approaches and rehabilitation techniques. And also, they can be treated with pharmacological agents (Belagaje, 2017; Brewer, Horgan, Hickey & Williams, 2012).

1.2.2 Neurobiology of plasticity after stroke

Anoxic episode as a result of stroke results in a cell death, that induces structural and functional changes in affected and also unaffected neural circuits. This process starts with

neurons failure to generate sufficient energy, which leads to ionic imbalance in depolarisation of the membrane. Glutamate, which is the major excitatory neurotransmitter in the brain is excessively released as result of oxygen deprived neurons, gamma-aminobutyric acid (GABA) as the main inhibitory neurotransmitter is released and by that the postsynaptic glutamate release is inhibited (Pamenter, Hogg, Ormond, Shin, Woodin & Buck, 2011). N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type receptors are mostly involved in overactivation, that promotes entry of calcium (Ca^{2+}) and sodium (Na^{+}) ions into postsynaptic neurons. This triggers the release of excessive glutamate from the neurons, which causes the toxic cascade to spread also to other neurons, and it triggers a death of postsynaptic neurons by a sequence of internal reactions (Clarkson, Huang, MacIsaac, Mody & Carmichael, 2010). If this process takes place 2 minutes or more, secondary damage to brain tissue due to edema, oxidative stress, excitotoxicity and inflammation is induced, and structural damage in the affected area can be seen (Murphy, Betts & Liu, 2008).

The most important neurobiological mechanisms that are involved in the protection and reparatory processes caused by stroke are neurotrophicity, neuroprotection, neuroplasticity and neurogenesis (Muresanu, Buzoianu, Florian & von Wild, 2012). As reverse process an increase in synthesis of neurotrophic factors starts. One of the most important which promotes the neural survival is brain-derived neurotrophic factor (BDNF) (Tamatani, Ogawa, Nunez & Tohayama, 1998). Important to note is that some neurobiological mechanisms share common biological background. N-methyl-D-aspartate receptors (NMDAR), can have deleterious role by overactivation induced excitotoxicity that generates pathological cascade, but it is also involved in physiological activation which generates neurotrophicity and neuroplasticity, depending on the magnitude of stimulation and location of the receptors. With that, the more pathophysiological processes are modulated, the better are the chances for rehabilitation and recovery (Muresanu et al., 2012).

Even if the stroke damage can be devastating, many patients survive and experience some spontaneous recovery and often exhibit continued functional recovery for years following the stroke. In cerebral cortex functional and structural reorganization in happening for weeks and months after injury with measurable compensatory changes. Importantly, later recovery depends on the central nervous system (CNS) reorganization and plasticity, with first fast initial phase of spontaneous recovery can be observed in the first six weeks after stroke (Figure 1.02) (Hatem et al., 2016; Murphy & Corbett, 2009).

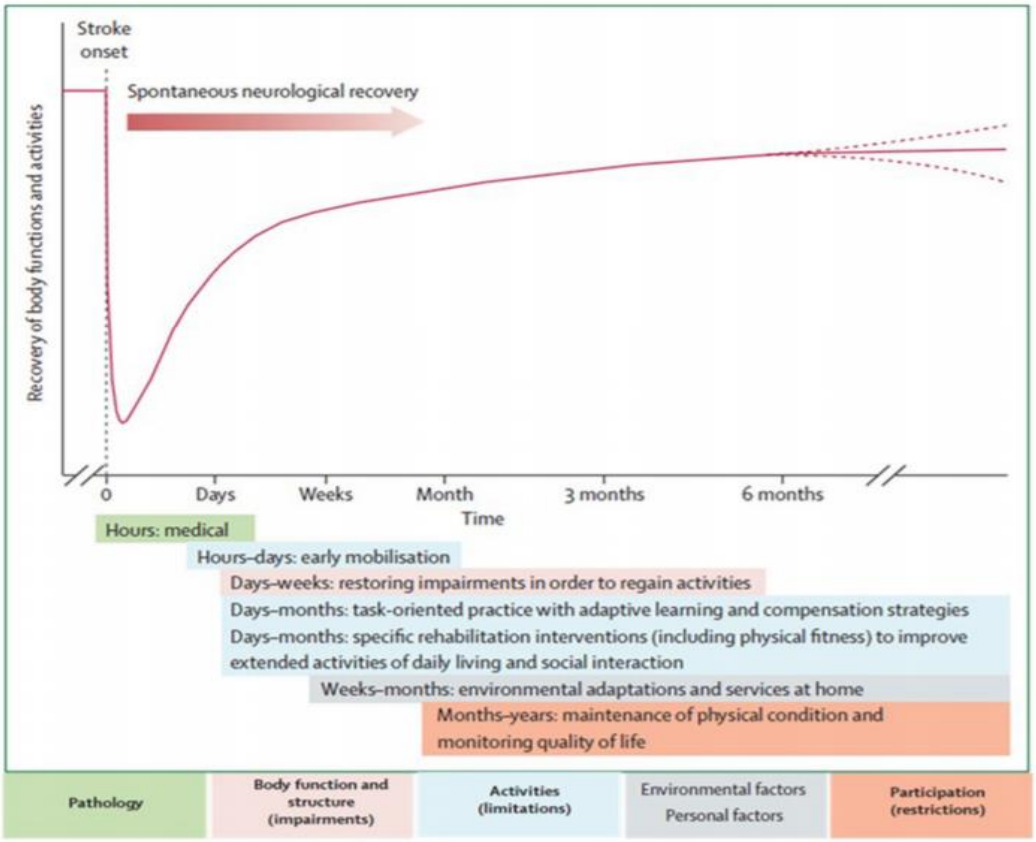


Figure 1.02. Hypothetical pattern with timing of intervention strategies for recovery after stroke (Hatem et al., 2016).

Neuronal plasticity variously attributes to redundancy (parallel distributed pathways), changes in synaptic strength, axonal sprouting, formation of new synapses, assumption of function by contralateral homologous cortex, and substitution of uncrossed pathways. These mechanisms can be noticed as cortical reorganization, which includes increased recruitment of contralateral motor areas, increased activity in non-primary motor areas, and recruitment of ipsilateral sensorimotor areas (Cramer, 2015; Hatem et al., 2016; Tran, Pajaro-Blazquez, Daneault, Gallegos, Pons, Fregni et al., 2016). Especially motor and sensory cortices are organized into somatotopic functional maps, that exhibit high levels of use-dependent plasticity, which means that they can be modified by experiences (Nudo, Wise, SiFuentes & Milliken, 1996).

All these neurobiological processes can be endogenously or exogenously activated and modulated. Normally they are regulated endogenously, but to successfully overcome the pathological processes and generate neural recovery to the biggest extent possible, these processes should be exogenously enhanced with pharmacotherapeutic, physiotherapeutic, psychotherapeutic interventions, environmental support and any other intervention which is needed to regain the functionality (Muresanu, 2012). From pharmacological perspective first

72 hours represent the early time window, but pharmacological agents are the most effective if given during early hours from the stroke onset (Cramer, 2015). Whereas onset of other therapies to improve recovery, like for example physiotherapy after stroke remains unclear. Some studies show, that very early and intense training, with less than 48 hours from stroke may lead to increased damage in brain tissue, whereas late onset of rehabilitation with more than 30 days after stroke is less effective in terms of brain plasticity and outcome (Belagaje, 2017; Krakauer, Carmichael, Corbett & Wittenberg, 2012).

1.3 BCIs

BCIs are a fast-growing engagement technology that enable the communication between brain and computer by relying on the brain activity (Wolpaw & Winter Wolpaw, 2012). BCI utilizes the brain and nervous system functions, by processing and integrating incoming sensory stimuli that it is received via peripheral nerves and gives impulses back to muscles or glands which cause automatic or voluntary actions. The imagination of specific movement or task performance produces specific patterns of electroencephalographic (EEG) activity that can be detected with BCI and translated into actions and commands that control the computer or a mechanical device. Most applications are related to disable people and this helps them ease their daily leaving activities, and it goes to the extent of Artificial and Computational Intelligence (Ramadan et al., 2015).

1.3.1 BCI types

BCI techniques can be divided into two types. Invasive BCI acquisition techniques which are based on detecting signal from single or multiple areas of brain cells and are devices that are inserted directly into the human brain with a surgery. The electro-corticogram (ECoG) obtains the signals from inserted electrodes and provides the highest quality human brain signal, but it is also the riskiest technique (He, 2013).

Second type of BCIs are non-invasive BCI acquisition techniques which measure electroencephalographic activity (EEG) from the electrodes that are placed on the scalp. These devices can achieve a resolution from 16 to 256 electrodes on the whole scalp. Placement of the electrodes is easy and not harmful (Wolpaw, 2003).

1.3.2 BCI signals

The brain generates an amount of neural activity or signals, which can be divided into two classes. First class is called spikes, which reflect the action potentials of individual neurons and can be acquired only through microelectrodes that are implanted with invasive

techniques. The second class is called field potentials, this are combined synaptic, neural, and axonal activity signals that can be measured with EEG or implanted electrodes (Wolpaw, 2003).

1.3.2.1 EEG signals

The following classification represents the EEG signals that are based on their frequencies or bands. Graphic representation for all of the signals is presented on the Figure 1.03 below.

- *Delta signal:* It has the highest amplitude and slowest waves, with frequency range of 0.5-3.5 Hz. Normally it is observed in slow wave sleep cycle, but can also be present in awake state, especially with babies and children (He, 2013).

- *Theta signal:* The frequency ranges from 3.5-7.5 Hz. When the signal is mostly present in central and temporal lobe parts, it is connected with awake state of an adult person. Lower posterior amplitudes appear between the state of being awake and sleeping and are also linked to daydreaming. Frontocentral theta activity appears in different cognitive and behavioural processes (He, 2013; Mitchell, McNaughton, Flanagan & Kirk, 2008).

- *Alpha signal:* The frequency range is from 7.5-12 Hz. This signal can be seen in the posterior regions on both sides of the brain, with higher amplitude on dominant side at a state of relaxation when the eyes are closed (He, 2013).

- *Beta signal:* Beta waves range is from 12-30 Hz. It can be most evidently seen on frontal-central lobe with symmetrical distribution on both sides. These waves can be detected in awaked state and they are connected with active mental tasks and attention or at movement performance (He, 2013).

- *Gamma signal:* This wave amplitude is rarely noticeable and it reflects the consciousness in connection with cognitive and perceptual processes with the frequency range from 30 Hz and up (He, 2013).

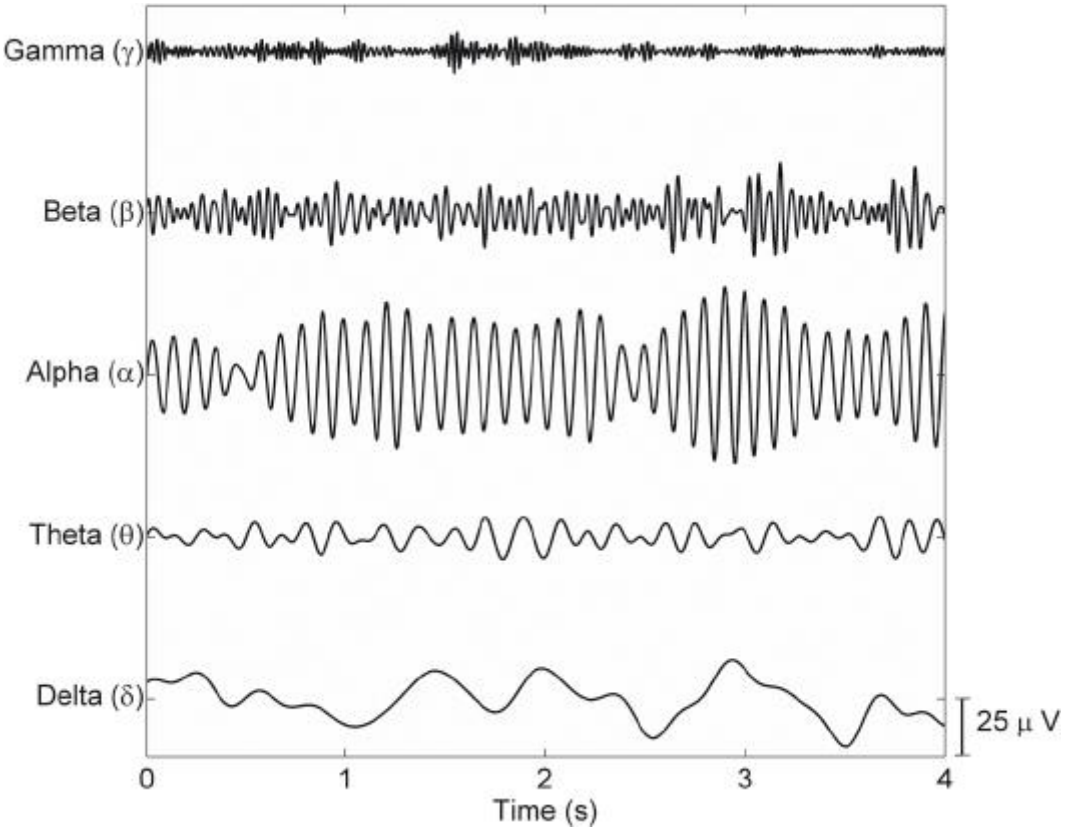


Figure 1.03. EEG signal amplitude (Scarano, Rocca & Campisi, 2012).

1.3.2.2 Components of interest for BCI

Components we can measure with BCI devices and are of interest for the efficient BCI use are:

Oscillatory EEG activity which is caused by complex neuronal networks that create feedback loops with synchronised firing. The two distinctive oscillations are *Rolandic mu-rhythm* that ranges from 10-12 Hz and *central beta rhythm* in the 14-18 Hz range, and they can be seen in resting state (He, 2013). Increases in oscillatory activity are therefore often referred to as *event-related desynchronization* (ERD), which means decrease in signal amplitude, and *event-related synchronisation* (ERS), showing increase of power in specific band frequencies during physical motor execution and mental motor imagery (Figure 1.04) (Ramadan et al., 2015).

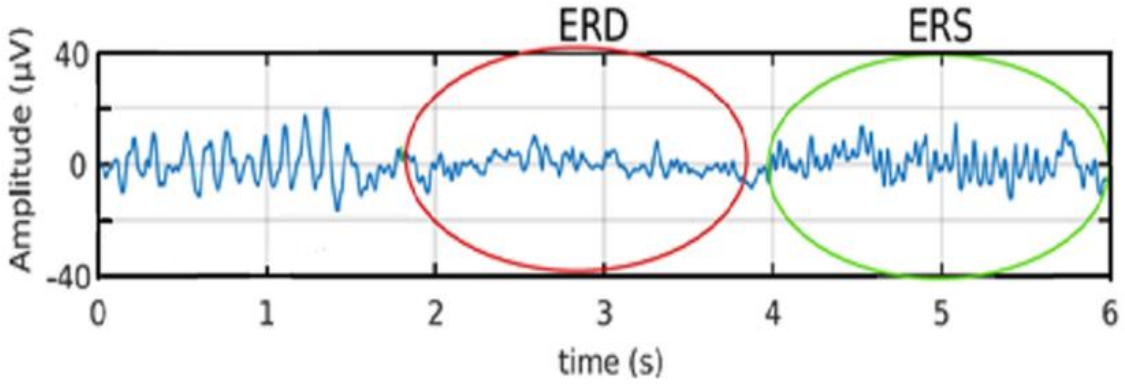


Figure 1.04. ERD and ERS demonstration during movement imagery.

Event-Related Potentials (ERPs) are time-locked responses that occur at a fixed time point after particular internal or external sensory or mental stimulus. Exogenous ERP components are connected to the external events and are independent to the role of the stimuli in the information processing. Endogenous ERP occur with internal event processing. The ERP events can be further classified by occurrence of:

- *Visual-Evoked Potentials* (VEPs) depend on P300 component which is elicited in the process of decision making, it reflects the processes involved in the stimulus evaluation or categorisation by visual stimulus. It normally uses the oddball paradigm, which involves low-probability targets and high-probability nontargets, and when the rare targets are displayed, large positive wave occurs approximately 300 milliseconds after the onset of the target (Tamara & Howard, 2013).

- *Slow Cortical Potentials* (SCP) are caused by the shifts of depolarisation levels of certain dendrites. Positive SCP represent the reduction of synchronised potentials, whereas negative SCP show the sum of potentials synchronisation (Ramadan et al., 2015).

- *Neural Potential* is a voltage spike from individual neurons and can be measured for a group of neurons or particular neuron itself on an average rate, correlation and temporal pattern of neuron firing (Kameswara, Rajyalakshmi & Prasad, 2013).

1.4 PLASTICITY SHAPING AFTER STROKE WITH BCI SYSTEM TECHNIQUES

Behavioral recovery is supported through reorganization of surviving CNS elements. This happens through changes in interhemispheric lateralization, active association of areas linked to injured zones and reorganization of cortical representation maps. Models that

include motor learning or cortical stimulation techniques can alter intracortical inhibitory circuits and can facilitate long-term potentiation (LTP) and cortical remodeling which include activity-dependent rewiring and synapse strengthening mechanisms (Hara, 2015).

In a typical EEG-based non-invasive BCI setting detection of movement intention, execution or motor imagery is performed, these techniques are also known as motor learning techniques. As presented on the Figure 1.05 below, the ongoing EEG analysis is performed in real time, which triggers a contingent sensory feedback to the user. The feedback can be presented in abstract form like for example as a moving cursor, or as embodied feedback with visual representation of a body or a body part through virtual reality (VR) avatar on a computer screen. Feedback can also be delivered through a robotic movement, or FES that reproduces intended movement, which enhances motor learning process (Alimardani, Nishio & Ishiguro, 2016; Buch, Weber, Cohen, Braun, Dimyan, Ard et al., 2008; Hara, 2015; Pfurtscheller & Neuper, 2006).

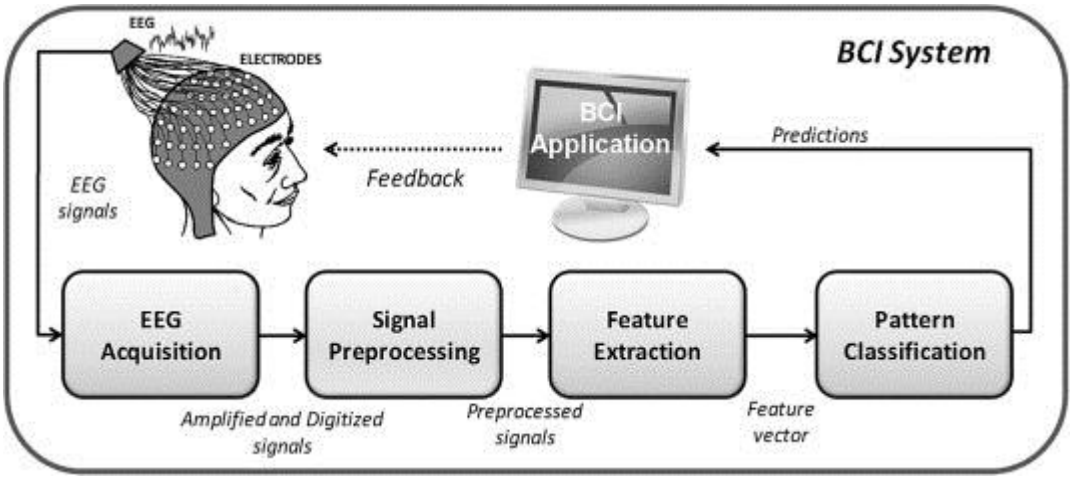


Figure 1.05. General block diagram of a EEG-based BCI system (García-Laencina, Rodríguez-Bermudez & Roca-Dorda, 2014).

When BCIs are used as a rehabilitation technology they are referred as neurofeedback or rehabilitative BCIs. They aim to foster neuroplasticity through self-regulation of neurophysiological activity or through manipulation, and with that facilitation of motor recovery can occur (Sitaram, Ros, Stoeckel, Haller, Scharnowski, Lewis-Peacock et al., 2017). Rehabilitative BCIs that use motor learning aim to promote activity in ipsilesional and/or contralesional hemisphere, predominantly to influence the cortical reorganization of the affected hemisphere (Bundy, Souders, Baranyai, Leonard, Schalk, Coker et al., 2017). This motor learning techniques are shown to influence the increase in excitability, neurotransmitters, receptor and neurotrophin levels, and cause changes in synaptic activity, gene expression in the motor areas of the brain (Hara, 2015). Studies using BCI technology

as therapeutic technique show, that neuroplasticity changes can reflect on significant motor function improvements that can be measured with different motoric assessments (Cervera, Soekadar, Ushiba, Millan, Liu, Birbaumer et al., 2017).

1.4.1 Hebbian plasticity

Hebbian plasticity theory proposes an explanation for the neuron adaptations in the brain during the learning and memory process and it describes a basic mechanism for synaptic plasticity (Murphy et al., 2009). Once homeostatic mechanisms are engaged to restore synaptic structural elements, Hebbian or correlative mechanisms could reinforce presynaptic and postsynaptic elements. When presynaptic and postsynaptic neurons are coincidently active, neurotransmitter release occurs within milliseconds, which causes synaptic straightening and modifications takes place (Brown, Zhao & Leung, 2009) in forms of LTP and depression (LTD) (Abbot and Nelson, 2000). LTP is a form of activity-dependent plasticity which results in a persistent enhancement of synaptic transmission, whereas LTD is a process, in which the efficacy of synaptic transmission is reduced. LTP process requires postsynaptic Ca^{2+} entry through NMDA receptor. Activation of metabotropic glutamate receptors and generation of diffusible intercellular messengers also has to occur, that alters the AMPA receptors function and synaptic efficacy is enhanced. On the other hand, LTD works through a process of depotentiation, by reduction of AMPA receptors efficiency (Lee, Barbarosie, Kemaya, Bear & Huganir, 2000). Into these processes also initiated novel gene transcription is involved by cAMP-dependent signalling cascade that involves cAMP-dependent protein kinase (PKA), transcription of factor cAMP-responsive element binding protein (CREB) and mitogen activated protein kinases (MAPK) (Huang, Martin & Kandel, 2000). In the regulation of longevity of synaptic plasticity also modulatory neurotransmitters such as dopamine (DA), noradrenaline (NA), serotonin (5-HT) and acetylcholine (ACh) play a role, by acting on their respective receptors to activate cAMP-dependent signalling in neurons (Bliss & Cooke, 2011).

Paired Associative Stimulation (PAS) paradigm is a crucial element in BCI technology that allows the Hebbian plasticity to occur. BCIs with VR and/or FES real-time rewarding feedback, that gets activated when MI or other mental task is correctly performed and the accurate neural activation occurs, allow the sensorimotor loop to close and at that time both presynaptic and postsynaptic neurons are activated (Cho, Sabathiel, Ortner, Lechner, Irimia, Allison at al., 2016). Mental Practice (MP) with MI by itself shows reorganisation or the brain networks for affected and non-affected hemisphere and it improves regional connectivity (Bajaj et al., 2015), as does VR with the activation of mirror neurons (Hatem et al., 2016), FES provides also functional muscle restoration through electrical activation of intact lower motor neurons. This stimulation can elicit action potentials in the innervating

axonal growth and can regulate the strength, the muscle contracture (Peckham & Knutson, 2005) and it also changes the axonal conduction velocities and myelination of peripheral nerves (Hara, 2015).

1.5 PHARMACOTHERAPY AND STROKE

After stroke there are a variety of drugs that are administered to patients in the acute phase for supportive treatment. The aim of these drugs is to treat frequent concomitant somatic conditions to ensure restoration and homeostasis of vital functions, but they can also have an influence on modification of motor recovery by influencing the modulation of neurotransmitters important for plasticity.

Present medications for the management of stroke can be assigned into the following categories: anticoagulants, reperfusion improving drugs, antiplatelet and neuroprotective drugs. Many of these drugs are used in stroke patients to treat symptoms due to decreased life quality, pain, convulsion, depression etc. These are for example antipsychotics, benzodiazepines, antidepressants, analgesics, anxiolytics and opioids, and they act on different neurotransmitter systems which can influence functional recovery after stroke (Belagaje, 2017; Conroy, Zorowitz, Horn, Ryser, Teraoka & Smout, 2005; Viale, Catoria, Di Girolamo & Gonzales, 2017). Studies show that there are drugs that can have a negative, or detrimental effect on functional motor recovery and drugs that can have an effect of improvement on functional motor recovery after stroke. Detrimental effect is seen as significantly slower motor recovery, longer hospitalization compared with recovery of similar groups of patients who did not receive these drugs. (Belagaje, 2017; Conroy et al. 2005; Engelter, 2013; Goldstein, 1993; Goldstein, 1998; Viale et al., 2017).

1.5.1 Pharmacotherapeutic agents with potential improving effect on motor recovery after stroke

In the studies that were conducted in previous years many drugs showed increased synaptic excitability, synaptic transmission and other acute effects. Some others showed more long-term effects that facilitate neuroplasticity and brain connectivity and by that motor recovery after stroke (Belagaje, 2017, Cramer, 2015; Shin & Dixon, 2015; Viale, 2017).

Drugs that showed improvement in motor functions are most often linked to monoamines regulation since they are involved in processes of arousal, motivation and attention (Cramer, 2015; Shin et al., 2015; Vitrac & Benoit-Marand, 2017). These are drugs that influence dopaminergic neurotransmission, serotonergic neurotransmission or work in combination of dopaminergic, serotonergic, noradrenergic and cholinergic transmission, and drugs that

enhance brain derived neurotrophic factor (BDNF) release (Björkholm and Monteggia, 2016; Cramer, 2015; Shin et al., 2015; Tran, Pajaro-Blazquez, Daneault, Gallegos, Pons, Fregini, Bonato et al., 2016).

1.5.1.1 Dopaminergic agonists

Mechanism and role of dopamine in motor activity is well established. DA is regulating many aspects of neural functioning, such as excitability, synaptic transition, plasticity, protein trafficking and gene transcription (Tritsch, Ding & Sabatini, 2012). Therefore, DA has a key role in the process of movement, reward system, learning, motivation and brain plasticity (McAllister, 2009). Since dopaminergic terminals in motor cortex contribute to cortical plasticity are also important for motor skill learning (Hosp, Pekanovic, Rioult-Pedotti & Luft, 2011). In the term of neuroplasticity dopamine D_1 receptor (D1R) signaling cascade which impacts the acetylcholine is mediating the mechanism of LTP induction (Calabresi, Picconi, Tozzi & Filippo, 2007). Li, Dabrowska, Hazra & Rannie, (2014) suggest that temporal interaction between metabolic glutamate receptors and D1Rs may regulate the direction of LTP or LTD showing and importance of dopamine in neuroplasticity. Dopamine can affect LTD through several different mechanisms. Most important being the dopamine D_2 receptors (D2R) that influences the endocannabinoid system (Kreitzer & Malenka, 2005) and modulates the signaling cascade of LTP and LTD within many cerebellar synapses (Grasselli & Hansel, 2014). One of the possible mechanisms also explains LTD formation between cortical pyramidal neurons and striatal medium spiny neurons, that is taught to be depended upon D2R localized in the postsynaptic membrane explaining the theory of motor plasticity and associative learning in connection to dopamine (Wang, Kai, Day, Yin, Ding, Tkatch, Lovinger et al., 2006). Tran et al. (2016) summarizing that dopaminergic signaling between the substantia nigra and striatal medium spiny neurons is pruning the LTP and LTD process that can form new motor memories. Explaining that dopaminergic signaling is mediating the motor learning system, connecting the dorsolateral prefrontal cortex, the striatum and the cerebellum that are essential for effective motor therapy (Tran et al., 2016).

1.5.1.2 Selective serotonin reuptake inhibitors/Serotonin–noradrenaline reuptake inhibitors

The mechanism of selective-serotonin reuptake inhibitors (SSRI) regarding the rehabilitation after stroke is not completely understood. There are few possible mechanisms of action since serotonin plays a role in modulating multiple cognitive functions, especially in memory consolidation, response inhibition and it modulates the impact of punishment related signals on learning and emotions (Cowen & Sherwood, 2013). The central mechanism in major depression treatment with SSRI is via high affinity for the serotonin

transporter with drug binding to the transporter inhibiting serotonin removal from the synaptic cleft. The effect of long-term SSRI administration is down regulation and desensitization of the essential serotonin receptors, thereby dampening negative feedback on serotonin release (Walker, 2013). Other suggested mechanisms of SSRI action work by reduction of neural inflammation, enhancement of neurotrophin activity and neurogenesis with migration of newly generated neurons from neurogenerating brain areas toward damaged regions (Siepmann, Penzlin, Kepplinger, Illigens Weidner, Reichmann et al., 2015). Serotonin also modulates spinal motor control through multiple effects on spinal motor circuits, regulating rhythmic activity and control of excitability with the action on the intrasynaptic and extra synaptic receptors that can help locomotor function and also affect the spasticity. Animal studies also suggest that SSRI influences enhancement of neuroplasticity, anti-inflammation mediated neuroprotection, improves cerebral blood flow autoregulation and modulates adrenergic neurohormonal system (Mead, Hsieh, Lee, Kutlubaev, Claxton, Hankey et al., 2012). Primary psychopharmacological effect is lowering the severity and frequency of post stroke depression and anxiety, improving sleep and alertness and improving stroke recovery (Siepmann et al. 2015). Whereas SNRIs are monoamine reuptake inhibitors of serotonin and noradrenaline (NA) and they modulate serotonin and noradrenaline neurotransmitter systems (Perry & Cassagnol, 2009).

1.5.1.3 Cholinergics

Cholinergic neurotransmitter system is involved in executive functions. There are two classes of cholinergic receptors, muscarinic and nicotinic (nAChRs). The role of muscarinic receptors in executive function is not as well established as nicotinic receptor is. However, studies on rats show that disruption of muscarinic signaling via the muscarinic selective antagonist scopolamine is disrupting cognitive flexibility by disrupting set-shifting and reversal learning (Chen, Baxter & Rodefer, 2004). NAChRs are ligand-gated ion channels and act as excitatory receptors (Taly, Corringer, Guedin, Lestage & Changeux, 2009). Most nAChRs are presynaptically located and are involved in regulation of neurotransmitter release (Gotti, Zoli & Clementi, 2006) either as auto receptors or as heteroreceptors modulating release of DA, NA and 5-HT. The role of nAChRs as heteroreceptors in the prefrontal cortex in conjunction with the nAChRs expressed in the ventral tegmental area (VTA), locus coeruleus (LC) and dorsal Raphe nucleus (DR) put the cholinergic system in position to serve as a crucial modulator of the three neurotransmitter systems that are necessary for cognitive processes mediated by the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC). The neural mechanisms responsible for the effects of nicotine on executive functions, especially on attention, are difficult to determine because nicotine can either act directly on cholinergic signaling or can modulate other neurotransmitters. Most likely, the effects of nicotine on executive functions involves a complex balanced regulation

of multiple neurotransmitter systems such as DA, NA and 5-HT (Logue & Gould, 2014). Also important are the cortex acetylcholine alternations that are positively enabling neural plasticity by selectively amplifying only anticipated and selectively weakening non-anticipated inputs in learning induced behavior (Merzenich, Van Vleet & Nahum, 2014).

1.5.1.4 Noradrenergics

NA is the only neurotransmitter system that is involved in all four cognitive processes. This are working memory, attention, cognitive flexibility and impulse control (Logue et al., 2014). Noradrenergic nucleus LC has strong projections to serotonergic DR, the midbrain dopaminergic neurons of the VTA, substantia nigra and cholinergic nuclei in the brainstem (Jones, 2008). Noradrenaline is acting on the adrenergic receptors alpha 2 that are located in all four neural types and it inhibits the release of their transmitters. By that, the specific role of noradrenergic locus coeruleus in modulating forebrain networks mediating cognitive activity can be observed. LC sends projections to thalamic nuclei, septum, hippocampus and basal lateral amygdala as well as to all cortical regions showing the involvement of noradrenergic neurotransmitter system in the arousal and behavioral state, regulation of synaptic plasticity, amplifying neural activity, memory consolidation particularly by interacting with opioids and other neuropeptides and is essential in frontal cortex for working memory and focusing in attention (Sara & Bouret, 2012).

1.5.1.5 Stimulants

Amphetamines are non-catecholamine sympathomimetic amines that are stimulating CNS activity by mimicking the structures of the catecholamine neurotransmitters, noradrenaline and dopamine. Amphetamines are modulating monoamine release, reuptake, and signaling within the brain (Fleckenstein, Volz, Riddle, Gibb & Hanson, 2007; Wolf, Martin, Kartje & Farrer, 2014). At higher dosages, they cause a release of DA from mesocorticolimbic system and nigrostriatal DA systems and they can also act as a direct agonist on central 5-HT receptors and they may inhibit monoamine oxidase (MAO). One of the central mechanisms of amphetamines is believed to cause the release of noradrenaline by acting on the adrenergic nerve terminals, and alpha- and beta-receptors (Rothman & Baumann, 2003). Preclinical studies are showing the evidence that fibroblast growth factor-2 (FGF-2), that is one of the neurotropic factors that is upregulated as a response due to the brain injury, has a protective and restorative role, and it is induced by amphetamine administration. Since the cellular action of FGF-2 includes the promotion of cellular proliferation, differentiation, migration and induction of neural fiber outgrowth, this could be the underlying mechanism of amphetamine induced neuroplasticity (Wolf et al., 2014).

Methylphenidate is a potent dopamine and noradrenaline reuptake inhibitor. Methylphenidate-modulated neural activity during the cognitive task performance could be mediated predominantly by DA and NA mechanisms, as it enhances DA and NA neurotransmissions by blocking DA and NA transporters, and by increasing DA and NA levels in the brain (Kuczemski & Segal, 1997). Methylphenidate effects on blood-oxygenation-level dependent (BOLD) responses related to cognitive tasks could be complicated by its effects on blood pressure, and heart rate by increasing the bioavailability of DA (Volkow, Wang, Fowler, Logan, Gerasimov, Maynard et al., 2002). And similarly, like amphetamine it is shown that it increases caudate putamen (CP) and nucleus accumbens (NAc) extracellular DA in a dose-dependent manner. Methylphenidate also binds to the NA transporter and it is an effective inhibitor of NA uptake and, therefore it increases extracellular NA (Kuczemski & Segal, 1997). Both of these mechanisms are explained and are connected with possibility of enhancement of motor recovery after stroke.

1.5.2 Pharmacotherapeutic agents with potential detrimental effect on motor recovery after stroke

For a number of drugs, where mechanisms of action involve mechanisms opposite to the action of the drugs that enhance motor recovery, particularly classical neuroleptics, and GABA agonists like benzodiazepines, some evidences suggest that administration of these drugs in the acute faze after stroke can impede motor recovery and thereby reduce motor rehabilitation outcome. Studies show that these drugs can impair functional motor recovery after focal brain injury and that even single doses may have long-term harmful effects on motor recovery because they interfere with plasticity proves (Conroy et al., 2005; Cramer, 2015; Goldstein, 1993; Goldstein, 1998; Viale et al., 2017; Vitrac et al., 2017).

1.5.2.1 GABA allosteric modulators

GABA allosteric modulators are drugs that act as an agonist on one or more GABA sites on receptors. They usually have sedative effects, and may also cause other effects such as anxiolytic, anticonvulsant, and muscle relaxant effects. GABA-α and GABA-ρ receptors are ion channels that are pervious to chloride ions that reduce neuronal excitability. The GABA-β receptors are from G-Protein class of coupled receptors that inhibit adenylyl cyclase, therefore leading to decreased cAMP. GABA-α and GABA-ρ receptors produce sedative, hypnotic effects and they have anti-convulsive properties. GABA-β receptors also produce sedative effects, but also lead to changes in gene transcription (Dragovich & Cohen, 2009).

Benzodiazepines (BZD) are one of the drugs that act as GABA allosteric modulators, and indiscriminately target the entire brain, because GABA receptors are distributed throughout

all of the CNS. This has a negative effect on every area of the brain including motor, sensory, speech, cognitive and respiratory impairments (Guina & Merrill, 2018; Guina, Rossetter, DeRhodes, Nahhas & Welton, 2015; Longo & Johnson, 2000). Acute effects of BZDs are DA release and synthesis and have a negative effect on AMPA/kinate receptors (Choi & Kim, 2007). BZD produce transient facilitation of recovery by LTP suppression and with that they impair learning and memory processes (Schallert, Jones, Weaver, Shapiro, Crippens & Fulton, 1992).

1.5.2.2 Classical neuroleptics

Antipsychotics from the first-generation act as dopaminergic D_2 antagonists and they influence four dopamine pathways. This are mesocortical pathway, mesolimbic pathway, nigrostiatal pathway and tuberoinfundibular pathway (Grunder, Hippius & Carlsson, 2009). They have an impact on the impairment of motor recovery, when administered shortly after brain injury (Cramer, 2005; Goldstein, 1993; Viale et al., 2017). Many atypical antipsychotics are not selective and they act on D_1 and D_2 receptors, 5-HT receptors, histamine H_1 receptors or disinhibit striatal cholinergic interneurons and increase acetyl choline release. They depend on stimulation of muscarinic M_1 and M_4 receptors on striatal neurones that have an influence on reduction of cAMP formation and by that have extrapyramidal effects, effects on CNS and on cardiovascular system (Miller, 2009).

1.5.2.3 Anticholinergics

Anticholinergic drugs are used for different indications that occur at stroke. Literature shows that due to of physiological and pathophysiological changes that are often accompanying the aging process especially elderly patients can be particularly sensitive to the anticholinergic drugs. Also, use of multiple drugs can result in pharmacodynamic and pharmacokinetic drug interactions that heighten anticholinergic effects (Feinberg, 1993). Anticholinergics are potent anamnestic acetylcholine (ACh) agents that act on CNS through blockade of muscarinic and nicotinic receptors, and this causes neuromuscular blockade. Acetylcholine is known to enhance LTP and is involved in learning and memory processes, and with blockade of that, they can impair motor recovery after cortical injury (Goldstein, 1993; Hasselmo, 2009).

2 RESEARCH QUESTIONS AND HYPOTHESES

The aim of this Master`s thesis was to investigate if there is a difference in the functional motor recovery of stroke patients after 25 therapy sessions with BCI based technology system, and if there is a difference between groups that these subjects were divided into, based on the drugs that were prescribed when stroke occurred. As a research question we wished to investigate "If the BCI therapy will be effective, if and how different drugs which were prescribed at stroke influenced the recovery."

To do this, we have set the following goals. Firstly, before the therapy sessions were performed, we assessed their motor function score, to be able to investigate the changes in recovery based on the therapy training. We performed the assessment 1 month before the therapy sessions and repeated the assessment right before the therapy sessions started to make sure, that their motor score status is stable. Secondly, we performed 25 therapy sessions, lasting 1 hour, about twice a week, and repeated the motor function score evaluation at the end of the therapy training.

2.1 HYPOTHESES

Based on literature review and the empirical evidence, we have formed following hypotheses for our research:

H1 Therapy with BCI system will have positive effect on subjects' motor function rehabilitation.

H2 Subjects treated with drugs with potential detrimental effect will have lower motor recovery, than subjects treated drugs with potential rehabilitation improving effect applied before the therapy with BCI based system.

H3 Subjects treated with drugs with potential detrimental effect will have lower motor recovery, than subjects treated with drugs with potential rehabilitation improving effect applied within the BCI based system therapy.

3 METHOD

3.1 PARTICIPANTS

For this study we recruited stroke patients who were willing to participate in the study and had expressed this by signing the informed consent. Subjects were eligible for inclusion if they:

- were 18 years old or more;
- were able to understand written and spoken instructions;
- had residual hemiparesis;
- stroke occurred at least four days before beginning of the study;
- had a restriction of the upper extremities, which prevent the persons from activities of everyday life;
- had stable neurological status;
- were able to understand and sign the informed consent.

Subjects were excluded from the study if they:

- were pregnant;
- had active or passive implanted medical devices such as pacemakers which do not allow the use of FES;
- had implanted metallic fragments in the upper extremities which can limit the use of FES;
- had cerebellar lesions;
- had elevated intracranial pressure;
- had hemispatial neglect;
- had a history of disordered aneurism;
- had a history of epilepsy or seizures that is uncontrolled by proper treatment;
- had cognitive impairments, so that the task stated could not be understood;
- did not adequately understand the given instructions as well as the informed consent;
- had fractures or lesions in the upper extremities;
- had severe lung diseases, infections, renal insufficiency, liver damage, heart diseases;
- had severe pusher syndrome;
- had significant circulatory disturbances of the upper limbs;
- were not able to independently maintain the seated position (without assistance) for about 60 minutes;
- had sensory disorders which can significantly affect the subjects' ability to feel pain and to react to unsuitable proprioceptive stimuli;
- had diseases of the peripheral nervous system affecting the upper limbs (brachial plexus palsy, cervical radicular syndromes or truncal syndromes);

- had botulinum toxin treatment of his/her paretic limb during this study.

Overall 25 subjects had met the criteria out of 31, then we retrospectively checked the diagnosis of these subjects to see which pharmacotherapy was prescribed as a standard therapy at stroke, to test the hypotheses. The final sample consisted of 19 subjects, afterwards divided into two groups. Based on literature, one group has had prescribed a class of drugs with potential detrimental effects on the functional motor recovery outcome (n=10), these were BZDs and classical neuroleptics. Second group has had prescribed drug class with potential rehabilitation improving effect (n=9), these were SSRIs and SNRIs.

Groups did not exactly match by gender; there were 3 males and 7 females in group with potential detrimental drugs activity, and 6 males and 3 females in group with drugs with potential rehabilitation improving effect. The factor of paretic hand being the dominant or non-dominant was also controlled, and there were 4 subjects with paretic hand being the dominant in both groups. For factors age and time after stroke the variables are presented in Table 3.01 below.

Table 3.01
Demographic information for age and time after stroke factors at the start of the therapy

	n	***M***	***mdn***	***SD***	***Min***	***Max***
Potential detrimental activity drug group	10					
Age		60.8	67	17.0	33	80
Months since stroke		71.2	70	50.1	18	158
Potential rehabilitation improving drug group	9					
Age		68	64	11.1	53	86
Months since stroke		44.7	33	33.6	16	123

Note: n, numerus; M, mean; mdn, median; SD, standard deviation; Min, minimum; Max, maximum.

Both groups matched by lesion location, there were 5 subjects with subcortical stroke location, 1 subject with cortical and 4 subjects with cortical and subcortical location in the group with drugs with potential detrimental effect. And 5 subjects with subcortical stroke, 1 subject with cortical and 3 subjects with cortical and subcortical location in the group with drugs with potential rehabilitation improving effect. Subjects also matched by the factor whether the stroke was ischemic or haemorrhagic. There were 9 subjects in both groups with ischemic stroke and only 1 with haemorrhagic stroke in the group with potential detrimental effect drugs. Furthermore, in both groups there was one subject who had multiple strokes, and all others who suffered from a single-point stroke.

3.2 MEASURES

3.2.1 Motor function assessments

Motor function assessments were performed by 2 physiotherapists in German language. We used 6 different motoric assessments to get information about overall motor function of the subjects.

To assess the physical performance, motor and sensory impairment of upper extremity we used *Fugl-Meyer Assessment* (FMA). This score consists of volitional movement assessment that includes flexor synergy, extensor synergy, movement combining synergies, movement out of synergy, wrist, hand and coordination/speed. During the assessment the subject is seated, and the therapist asks the subject to perform certain movements with the affected hand, or the therapist passively moves the affected hand of the subject. The score for upper extremity motor function goes from 0, which means no motor function up to 66 points, full motor function of upper extremity (Fugl-Meyer, 1980; Fugl-Meyer, Jaasko, Leyman, Olsson & Steglind, 1975).

To assess the ability to perform daily activities we used *Barthel Index* (BI). This score assesses how independent are they at feeding, bathing, grooming, dressing, how are they able to use toilet and how mobile they are. The therapist asks the subject about their ability to perform these activities, if they are totally dependent and need help, need moderate help or are completely independent. The score goes from 0 to 100, where score 100 means they are independent at performing these daily activities (Mahoney & Barthel, 1965).

For spasticity assessment *Modified Ashworth scale* (MAS) was used, which scores the spasticity for the wrist (MAS_W) and for the fingers (MAS_F) separately. To assess the wrist spasticity, the therapist tries to move the affected hand and perform the wrist dorsiflexion. And to assess the finger spasticity, the therapist tries to straighten the subjects' fingers and determines the spasticity shown at movement performance. Score 0 means no spasticity, and score 4 means maximum spasticity (Bohannon & Smith, 1987).

Evaluation of gross motoric activity was assessed with *Box and blocks test* (BBT). The subject is sited, the box with the wooden blocks is placed in front of the subject. The box where the blocks are, is placed on the side that is being tested. The subject is told to try to move as many blocks, one by one from one box to another in 1 minute. First 15 second trial is done, then the assessment is performed. If the blocks fall out of the box on the other side, if the subject grabs more than 1 block or does not move the hand enough toward the other

side of the box, the blocks are not counted. If the subject is not able to perform the task the result is noted with a 0 score (Mathiowez, Volland, Kashman & Weber, 1985a).

For assessment of the fine motoric activity, *Nine-hole peg test* (NHPT) was used. The subject is seated, the peg board is placed in front of the subject, with the peg pull on the side that is being tested. The subject is instructed to try to pick up the 9 pegs from the pull, one by one, and insert them into the holes. When the subject inserts all of the pegs, subject has to pick them back out form the holes, one by one, and return them to the pull as fast as possible. The task has to be performed without the assistance of the healthy hand. If the subject is not able to perform the task the result is noted with a 0 score (Mathiowetz, Weber, Kashman, & Volland, 1985b).

3.2.2 BCI system

System combines BCI based MI with avatar and FES feedback as shown on the Figure 3.01. The user is asked to imagine movement of either right or left hand according to visual and auditory cues in each trial. This produces specific patterns of brain activity in the EEG signal called ERD and ERS, and the system can detect which hand the user imagined moving with data pre-processing and usage of linear discriminant analysis (LDA). When the MI matches the task, the avatar and FES feedback are activated. With that the feedback loop is closed, which promotes neural plasticity.

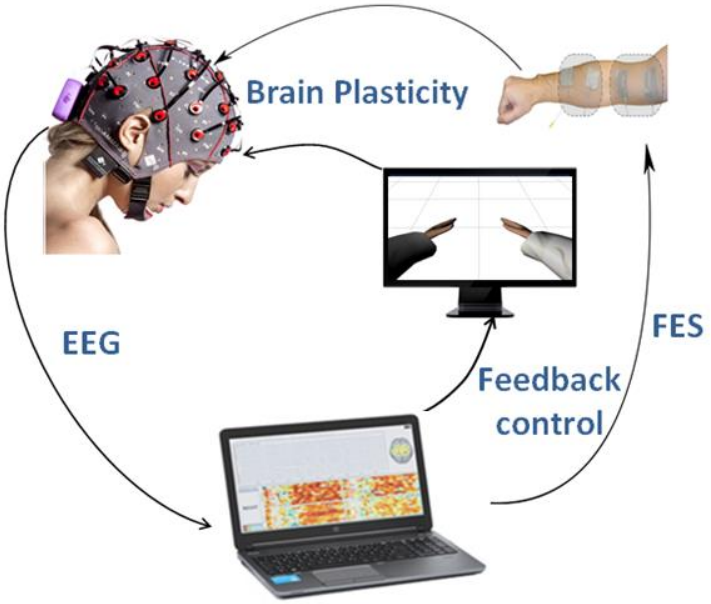


Figure 3.01: BCI system.

EEG cap, which is placed on the subjects head, uses active electrodes (g.LADYbird, g.tec medical engineering GmbH). The electrode positions are placed according to international 10/10 system: FC5, FC1, FC2, FC2, FC6, C5 C3, C1, Cz, C2, C4, C6, Cp5, Cp1, Cp2, Cp6. A reference electrode is placed on the right earlobe and a ground electrode at position of FPz, graphically presented on Figure 3.02 below.

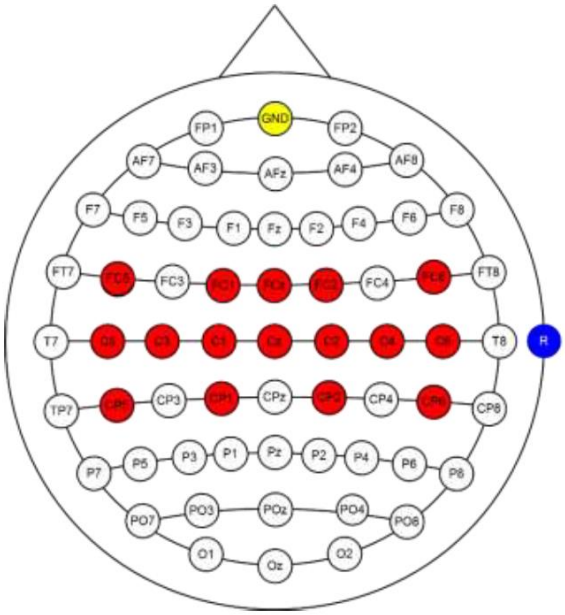


Figure 3.02: Graphic presentation of EEG electrodes position.

FES (g.ESTIM, g.tec medical engineering GmbH) parameters are adjusted to find the individual threshold to perform the dorsiflexion of the wrist. Subjects are sitting and are asked to place their arms on a table. Two FES electrodes are applied across the wrist extensor muscles of the left and right forearms, respectively. The FES stimulation is set to a frequency of 50 Hz and a pulse width of 300 μs.

Movement intention is analyzed in real time with Common Spatial Patterns (CSP) and LDA, and it classifies left or right hand movement imagery. When the software algorithm detects the appearance of the correct hand movement imagery in the EEG, FES (g.Estim, g.tec medical engineering GmbH, Austria) induces passive wrist dorsiflexion, and the avatar of upper limbs is displayed on a screen and simultaneously performs the same movement. A session contains 240 trials random left and right hand movements, 120 each.

Each movement starts with an attention sound, telling the subject to concentrate on the upcoming task. Two seconds later, the command to imagine the dorsiflexion of either the left or right wrist is triggered. It is provided auditorily in the subjects' language, and visually

via an arrow pointing to the left or right. Subject is asked to start the MI immediately after receiving the command. The feedback phase starts 1.5 seconds after the command presentation and it lasts 4.5 seconds. The feedback devices can only be activated during this phase. Graphic representation on the Figure 3.03.

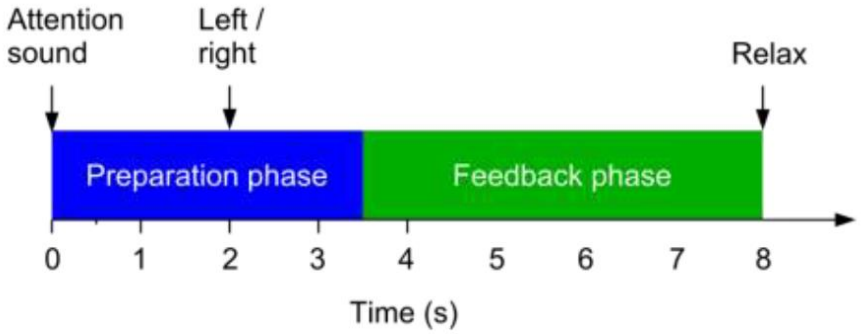


Figure 3.03: Trial protocol.

3.3 RESEARCH DESIGN AND PROCEDURES

Data collection and assessments lasted approximately 6 months, from June until November 2017 at g.tec medical engineering company in Austria. Before the first assessment, subjects were asked to provide the diagnosis and were asked about their health condition so we were able to evaluate if they fit the inclusion criteria. The assessments and therapy sessions were performed individually in calm and controlled environment. All of the assessments that were used and the therapy procedure were designed according to literature-based data and pre-study measurements performed with the same BCI system.

3.3.1 Assessments procedure

With every subject 3 assessments were performed by a physiotherapist, each assessment lasted about 1 hour and half. First and second pre-assessment were performed 4 weeks apart, with therapy sessions starting right after the second assessment. After the 25 therapy sessions were finished the post-assessment was performed. Each assessment was performed in the same way, with determine order of assessments. Procedure started with BI, continued with MAS for wrist and then fingers, FMA, BBT and ended with NHPT.

3.3.2 Therapy sessions procedure

Subjects were seated on the chair or in the wheelchair in comfortable position in front of the screen with forearms laying on the table. They were explained the therapy session procedure and instructed to sit still without talking during the period of task performing. They were explained, that each run last about 8 minutes, with a 2-minute break in between. Each run

was consisted out of 80 trials and 3 runs were done in each therapy session. Subjects were asked to imagine wrist dorsiflexion movement of the left or right hand, dependent on the instructions given by the system through audio and visual channel. Afterwards we started with the preparation of the subject. Hands were disinfected in the part where we placed FES electrodes. If needed the gel was used on the skin surface for better conductivity. Pillows and towels were used to get the appropriate hand position. FES pads were mounted on the subjects left and right forearm, on the muscle called *Extensor digitorum communis*. Therapist increased the intensity of stimulation as much as possible to induce wrist dorsiflexion without causing pain of the subject, or until muscle contraction was observable. Then EEG cap was mounted on the subjects' head. To ensure that location of the electrodes was correct, the position of the electrodes was controlled, and EEG gel was then injected into the electrodes to get good quality signal. When the EEG signal was appropriate and FES set, the subjects were asked if the instructions were clear. If the answer was confirmative the headphones were placed on the subjects' head and the therapy session started. In the pause and after each run the subject was asked about their feeling and was given a short feedback about the task performance. After session was finished, the EEG cap and FES electrodes were removed, and the excess gel was cleaned. The whole process lasted about 1 hour, each subject had about 2 sessions per a week over the period of 3 months, respectively.

3.3.3 Data analysis

3.3.3.1 Motoric assessments

After subjects completed with the therapy sessions and post-assessments, changes in motor performance were analyzed by IBM SPSS 22 software. Because all of the subjects were in chronic stage after stroke and their motor performance was stable in the 2 pre-assessments, statistical significance difference for all of the assessments that were measured in pre-assessments was controlled with the *Wilcoxon-Signed Ranked test*. Based on results, the average of those assessments was done for further analysis to avoid the influence of subjectivity of the physiotherapists in assessment and changes in subjects feeling on the assessment day, that could influence the results. Then, we controlled the Normality of Distribution where *Shapiro-Wilk test* was used for all subjects together and separate by the groups. Age and time after stroke factors at the time of the start of the therapy were also examined for significance. Homogeneity of Variances with *Levene Statistic* was performed between the groups and *one-way ANOVA* was used to analyze the statistical difference between the groups for these factors. Afterwards statistical analysis for both groups was performed, and statistically significant difference between the groups with *Mann-Whitney U test* of the pre and post-assessment results was examined. First the Normality of Distribution with *Shapiro-Wilk test* and Homogeneity of Variances with *Levene Statistic* were controlled for all assessments. The assessments that did not show statistical significance in Normality of

Distribution with $p > .05$, *ANOVA for repeated measures* with the *Tests of Within-Subjects Contrasts test* was performed. For assessments which showed significance in Normality of Distribution with $p < .05$, nonparametric *Wilcoxon-Signed Ranked test* was used for statistical analysis.

3.3.3.2 EEG data analysis

BCI system software performs the offline classification accuracy of MI, and the EEG data is bandpass filtered between 8Hz and 30Hz. It uses CSP method to transform the pre-processed data to a matrix with minimal variance of one class and maximal variance of the other class. These features are normalized, log transformed and classified with LDA. Then, the variance and the accuracy are calculated via cross validation in steps of half a second for left and right hand MI in the testing pool within a time-window of 1.5 second.

The panels with ERD and LDA plots were calculated separately for the MI of the left and right hand for motor areas on the left (C3) and right hemisphere (C4) of the brain. Data were analysed with MATLAB – The MathWorks, Inc. (2016) and compatible program for EEG data analysis g.BSanalyze (g.tec medical engineering GmbH, Austria). Raw EEG data was imported, frequency was set to range between 8Hz and 30Hz, with Butterworth filter realization, and scaling to 100 μV. Artefacts from small muscle movements, teeth grinding and eye blinking were manually removed. The data from the first 3 sessions was merged together and plots were created for visual representation for each subject to show the neural activation and MI from the beginning of the therapy sessions. Same, the data from last 3 sessions was merged together to show the neural activation and MI from the end of the therapy sessions.

4 RESULTS

4.1 MOTOR FUNCTION ASSESSMENTS

4.1.1 First pre-assessment and second pre-assessment analysis

The results for the first pre-assessment and the second pre-assessment that were analysed first for Normality of Distribution with *Shapiro-Wilk test* are presented in the Table 4.01 below and are showing significant result for all of the motoric assessments.

Table 4.01
Normality of Distribution for the first and second pre-assessment

		Shapiro-Wilk test			
		First pre-assessment		**Second pre-assessment**	
	n	***F***	***p***	***F***	***p***
FMA	19	.871	**.015***	.853	**.007***
BI	19	.852	**.007***	.844	**.005***
MAS_W	19	.841	**.005***	.839	**.004***
MAS_F	19	.818	**.002***	.866	**.012***
BBT	19	.579	**.000***	.601	**.000***
NHPT	19	.549	**.000***	.468	**.000***

Note; n, numerus; F, test statistic for Shapiro-Wilk test; p, significance; * statistically significant difference; FMA, Fugl-Meyer Assessment; BI, Barthel Index; MAS_W, Modified Ashworth Scale for wrist; MAS_F, Modified Ashworth Scale for fingers; BBT, Box and Blocks test; NHPT, Nine-Hole Peg test.

4.1.2 Analysis of the results before and after the therapy

Following results for all of the motoric assessments, for results measured before and after the therapy are presented in the Table 4.02 below. Analysis for Normality of Distribution with *Shapiro-Wilk* test shows significant result for all of the motoric assessments for results measured in pre and post-assessment, except the assessment that measures spasticity for the fingers MAS_F, which is not significant, but it shows a trend to significance.

Table 4.02
Normality of Distribution for motoric assessment results before and after the BCI based therapy

		Shapiro-Wilk test			
		Pre-assessment		**Post-assessment**	
	n	***F***	***p***	***F***	***p***
FMA	19	.856	**.008***	.864	**.011***
BI	19	.854	**.008***	.794	**.001***
MAS_W	19	.862	**.010***	.819	**.002***
MAS_F	19	.868	**.013***	.903	.054
BBT	19	.620	**>.001***	.625	**>.001***
NHPT	19	.530	**>.001***	.595	**>.001***

Note; n, numerus; F, test statistic for Shapiro-Wilk test; p, significance; * statistically significant difference; FMA, Fugl-Meyer Assessment; BI, Barthel Index; MAS_W, Modified Ashworth Scale for wrist; MAS_F, Modified Ashworth Scale for fingers; BBT, Box and Blocks test; NHPT, Nine-Hole Peg test.

The same assessment results were also analyzed for Homogenitiy of Variance with *Levene Statistic test* demonstrated in the Table 4.03 below.

Table 4.03
Homogeneity of Variances analysis of the results before and after the BCI based therapy

		Pre-assessment		**Post-assessment**	
	n	**Levene Statistic**	***p***	**Levene Statistic**	***p***
FMA	19	1.702	.209	2.135	.162
BI	19	3.285	.088	12.961	**.002***
MAS_W	19	.234	.635	2.024	.173
MAS_F	19	1.968	.179	.026	.875
BBT	19	18.728	**>.001***	20.250	**>.001***
NHPT	19	29.715	**>.001***	52.245	**>.001***

Note; n, numerus; Levene Statistic, test statistic for Homogeneity of Variance test; p, significance; * statistically significant difference; FMA, Fugl-Meyer Assessment; BI, Barthel Index; MAS_W, Modified Ashworth Scale for wrist; MAS_F, Modified Ashworth Scale for fingers; BBT, Box and Blocks test; NHPT, Nine-Hole Peg test.

Statistical comparison of the results for the motoric assessments shows, that subjects significantly improved in assessment that measures physical performance, motor and sensory impairment of upper extremity FMA with Z = -3.072, p = .002, spasticity for wrist MAS_W with Z = -2.777, p = .005, and fingers MAS_F with Z = -2.630, p = .009, and gross motoric activity assessment BBT with Z = -2.032, p = .042. The results for ability to perform daily activities BI, and fine motoric abilities with NHPT, did not show statistical differences with Z = -1.425, p = .154 and Z = -1.826, p = .068, but did show improvement, a better result

at the assessment after the therapy when compared to results measured at the pre-assessment. The descriptive statistic results for these measures are displayed in Table 4.04 below.

Table 4.04
Demonstration of descriptive results before and after the BCI based therapy

		Pre-assessment			**Post-assessment**		
	n	***mdn***	***25th***	***75th***	***mdn***	***25th***	***75th***
FMA	19	15	9.5	32	20	12	42
BI	19	85	70	95	85	65	100
MAS_W	19	3	1	4	2	0	4
MAS_F	19	3	2	4	2	1	3
BBT	19	0	0	7	0	0	13
NHPT	19	0	0	0	0	0	3

Note; n, numerus; mdn, median; 25th, 25th percentile; 75th, 75th percentile.

4.1.3 Analysis for the factors of age and time after stroke at the start of the therapy

On the Figure 4.01 below, first the difference for factors A) age and B) time after stroke are presented for between the groups comparison. Homogeneity of Variance was calculated with *Levene Statistic*, showing factor age is not significant with F (1,17) = 2.581, p = .127. Statistical analysis with *one-way ANOVA* for significance between groups for factor age showed non-statistically significant difference with F (1,17) = 1.161, p = .296. Analysis for Homogeneity of Variance was performed also for the factor time after stroke and is showing similar non-statistically significant results with F (1,17) = 1.895, p = .186, and *one-way ANOVA* with F (1,17) = 1.793, p = .198.

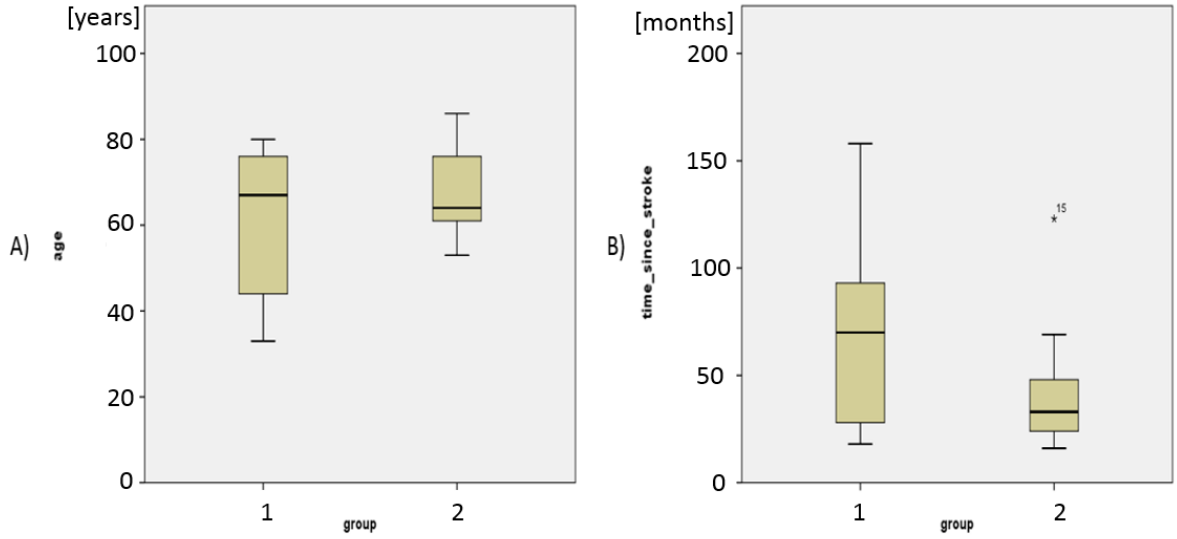


Figure 4.01: Age and time after stroke factors between the groups at the start of the therapy. A) age factor, B) time after stoke factor. Group 1 represents the results for the group with drugs with potential detrimental effect, group 2 for the group with potential rehabilitation improving drugs.

4.1.4 Analysis of the motoric assessment results between the groups for the pre-assessment

Following below, the results for two separate groups are presented, to compare the difference in the outcome of the results after the therapy sessions. First, we controlled if there is significant difference in the motor performance status between the two groups at pre-assessment results with *Mann-Whitney U test*. The results are presented in the Table 4.05 below and are not showing statistical significance. Group 1 represents the results for the group with drugs with potential detrimental effect, and group 2 for the group with potential rehabilitation improving drugs.

Table 4.05
Descriptive results and statistical comparison with Mann-Whitney U test for the results between the groups for pre-assessment

	Pre-assessment group 1		**Pre-assessment group 2**		**Mann-Whitney U**		
	n	***mdn***	***N***	***mdn***	***Z***	***U***	***p***
FMA	10	16	9	17	-1.716	78.5	.082
BI	10	85	9	85	-1.370	83	.167
MAS_W	10	3	9	3	-.454	106	.645
MAS_F	10	3	9	3	-.499	106.5	.615
BBT	10	0	9	0	-1.650	82	.099
NHPT	10	0	9	0	-2.232	80	.065

Note; n, numerus; mdn, median; Z, test statistic for Mann-Whitney U test, U, effect size for Mann-Whitney U test; p, significance; FMA, Fugl-Meyer Assessment; BI, Barthel Index; MAS_W, Modified Ashworth Scale for wrist; MAS_F, Modified Ashworth Scale for fingers; BBT, Box and Blocks test; NHPT, Nine-Hole Peg test.

The results of *one-way ANOVA* for the Homogeneity of Variance are presented in the Table 4.06 below, showing there is statistically significant difference between the groups for the fine motoric abilities measured with NHPT for the pre and post-assessment. Other assessments do not show significance between the group with drugs with potential detrimental effect (n = 10), and group with potential rehabilitation improving drugs (n = 9).

Table 4.06
Significance in Homogeneity of Variance differences between the groups for results before and after the BCI based therapy

	Homogeneity of Variance: one-way ANOVA			
	Pre-assessment		**Post-assessment**	
	F	***p***	**F**	***p***
FMA	2.888	.107	1.869	.189
BI	2.528	.130	2.271	.150
MAS_W	.039	.845	.086	.773
MAS_F	.520	.481	.226	.641
BBT	3.117	.095	3.733	.070
NHPT	5.354	**.033***	5.374	**.033***

Note; F, test statistic for one-way ANOVA; p, significance; * statistically significant difference; FMA, Fugl-Meyer Assessment; BI, Barthel Index; MAS_W, Modified Ashworth Scale for wrist; MAS_F, Modified Ashworth Scale for fingers; BBT, Box and Blocks test; NHPT, Nine-Hole Peg test.

4.1.5 Analysis of the group with drugs with potential detrimental effect for the pre and post-assessments

On the Table 4.07 below the Normality of distribution with *Shapiro-Wilk* statistics results for the assessments measured before and after the therapy, are presented. The results show significance in Normality of Distribution for all motoric assessments, except for assessment that measures spasticity in the fingers MAS_F. The results for the fine motoric ability assessment NHPT at the pre-assessment could not be calculated, none of the subjects was able to perform this assessment, as shown in the Table 4.08 that demonstrates the descriptive and statistic results for this group.

Table 4.07
Normality of Distribution analysis for the group with drugs with potential detrimental effect for the results before and after the BCI based therapy

	Shapiro-Wilk test			
	Pre-assessment		**Post-assessment**	
	F	***p***	***F***	***p***
FMA	.767	**.006***	.836	**.039***
BI	.864	.086	.080	**.011***
MAS_W	.850	.058	.760	**.005***
MAS_F	.898	.209	.905	.249
BBT	.529	**>.001***	.519	**>.001***
NHPT			.366	**>.001***

Note; F, test statistic for Shapiro-Wilk test; p, significance; * statistically significant difference; FMA, Fugl-Meyer Assessment; BI, Barthel Index; MAS_W, Modified Ashworth Scale for wrist; MAS_F, Modified Ashworth Scale for fingers; BBT, Box and Blocks test; NHPT, Nine-Hole Peg test.

The statistical analysis of the results measured at the pre and post-assessment show, that subjects in the group with drugs with potential detrimental effect significantly improved in assessment that measures physical performance, motor and sensory impairment of upper extremity FMA, spasticity of the wrist MAS_W and fingers MAS_F. Other assessments also show improvement, better results after the BCI based therapy compared to results at the pre-assessment for this group as shown in Table 4.08 below.

Table 4.08

Statistical comparison of the results for the group with drugs with potential detrimental effect for results before and after the BCI based therapy

		Pre-assessment			**Post-assessment**			**Within-Subjects contrast test**	
	n	***M***	***SD***	***SEM***	***M***	***SD***	***SEM***	***F***	***p***
MAS_F	10	2.85	1.13	0.36	2.3	1.42	0.45	5.76	**.040***
								Wilcoxon Signed-Ranks test	
	n	***mdn***	***25th***	***75th***	***mdn***	***25th***	***75th***	***Z***	***p***
FMA	10	12	8.63	19.25	14	10.5	31.25	2.295	**.022***
BI	10	75	51.88	95	85	45	100	.898	.369
MAS_W	10	2.88	0.88	4	1.5	0	4	-2.032	**.042***
BBT	10	0	0	1.63	0	0	3	.447	.655
NHPT	10	0	0	0	0	0	0	1.000	.317

Note; n, numerus; M, mean; mdn, median; SD, Standard deviation; SEM, Standard mean error; 25^{th}, 25th percentile; 75^{th}, 75th percentile; Z, test statistics for Wilcoxon Signed Ranks test; F, test statistic for Within-Subjects contrast test; p, significance; * statistically significant difference; FMA, Fugl-Meyer Assessment; BI, Barthel Index; MAS_W, Modified Ashworth Scale for wrist; MAS_F, Modified Ashworth Scale for fingers; BBT, Box and Blocks test; NHPT, Nine-Hole Peg test.

4.1.6 Analysis of the group with potential rehabilitation improving drugs for the pre and post-assessments

Same statistical tests were performed for the group with potential rehabilitation improving drugs. In the Table 4.09 below the results for the Normality of Distribution with *Shapiro-Wilk test* are presented.

Table 4.09

Normality of Distribution analysis for the group with potential rehabilitation improving drugs for the results before and after the BCI based therapy

	Shapiro-Wilk test			
	Pre-assessment		**Post-assessment**	
	F	***p***	***F***	***p***
FMA	.909	.306	.873	.134
BI	.856	.088	.829	**.044***
MAS_W	.860	.095	.897	.232
MAS_F	.860	.097	.745	**.005***
BBT	.713	**.002***	.718	**.002***
NHPT	.775	**.011***	.763	**.008***

Note; F, test statistic for Shapiro-Wilk test; p, significance; * statistically significant difference; FMA, Fugl-Meyer Assessment; BI, Barthel Index; MAS_W, Modified Ashworth Scale for wrist; MAS_F, Modified Ashworth Scale for fingers; BBT, Box and Blocks test; NHPT, Nine-Hole Peg test.

Statistical comparison of the results presented in the Table 4.10 that were measured before and after the therapy for this group shows, that subjects had significantly improved in assessment that measures physical performance, motor and sensory impairment of upper extremity FMA, spasticity of the wrist MAS_W and gross motoric abilities BBT. Results also show improvement in ability to perform daily activities BI and fine motoric abilities NHPT. Results for the assessment of fingers spasticity MAS_F shows improvement at percentile results, but deterioration at median result.

Table 4.10
Statistical comparison of the results for the group with potential rehabilitation improving drugs for results before and after the BCI based therapy

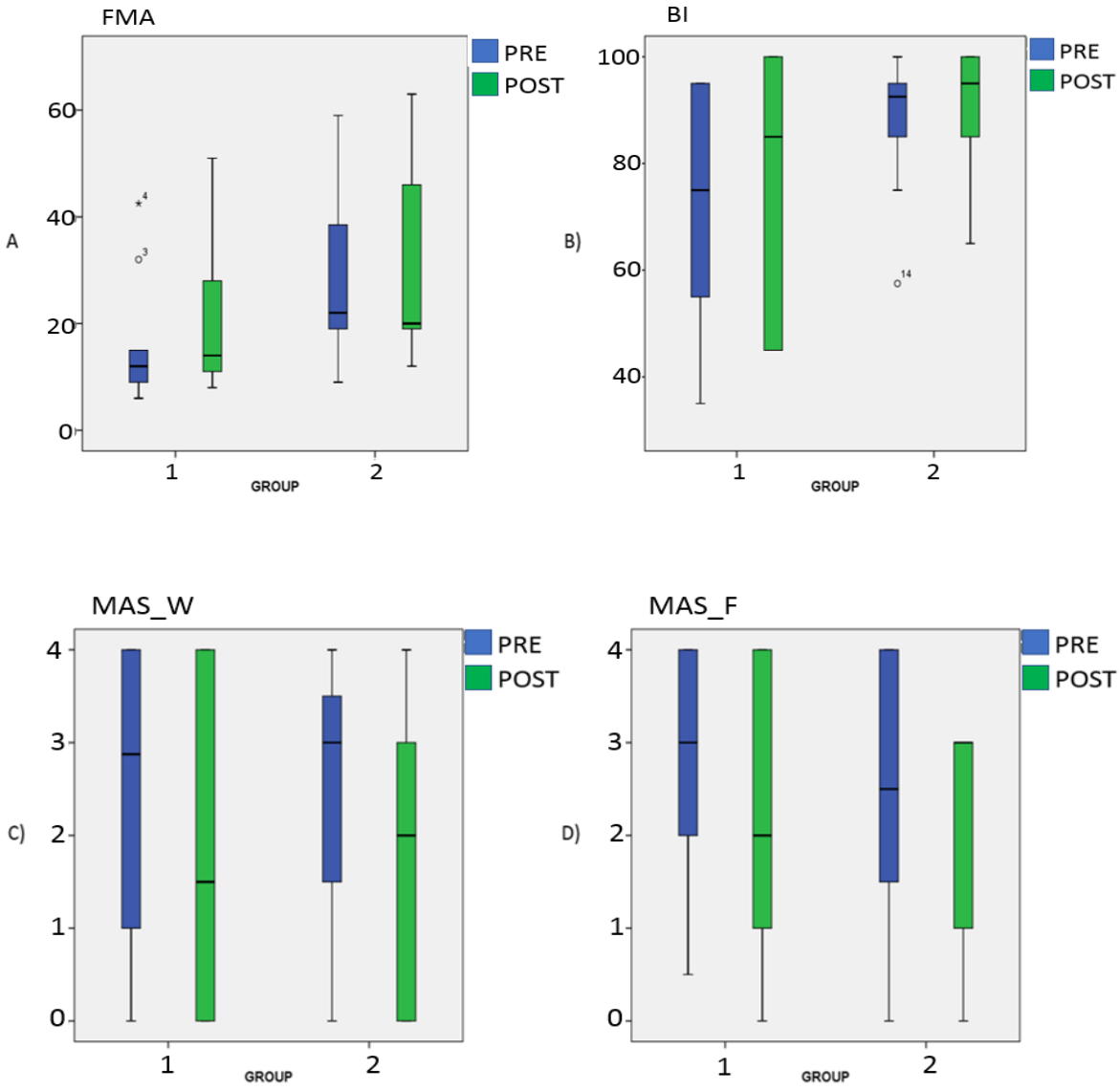
		Pre-assessment			**Post-assessment**			**Within-Subjects contrast test**	
	n	***M***	***SD***	***SEM***	***M***	***SD***	***SEM***	***F***	***p***
FMA	9	27.3	16.8	5.6	31.9	18.9	6.3	5.984	**.040***
MAS_W	9	2.3	1.5	0.5	1.7	1.5	0.5	5.33	**.050***
								Wilcoxon Signed-Ranks test	
	n	***mdn***	***25th***	***75th***	***mdn***	***25th***	***75th***	***Z***	***p***
BI	9	92.5	80	97.5	95	80	100	1.633	.102
MAS_F	9	2.5	0.75	4	3	0.50	3	1.734	.083
BBT	9	0.5	0	25.25	1	0	34.5	2.023	**.043***
NHPT	9	0	0	6.25	0	0	9	1.604	.109

Note; n, numerus; M, mean; mdn, median; SD, Standard deviation; SEM, Standard mean error; 25^{th}, 25th percentile; 75^{th}, 75th percentile; Z, test statistics for Wilcoxon Signed Ranks test; F, test statistic for Within-Subjects contrast test; p, significance; * statistically significant difference.

4.1.7 Mann-Whitney U analysis between the groups for pre and post-assessment results

Graphic comparison between the groups is presented on Figure 4.02. for the difference in the results measured before and after the therapy for all assessments separately. As group 1, group with drugs with potential detrimental effect is shown and group with potential rehabilitation improving drugs is shown as group 2. To address statistical differences, we used *Mann-Whitney U* test. Significant difference between the groups for the results measured at pre and post-assessment was noticed on Figure 4.02 E for gross motoric ability measured with BBT with U = 76.5, Z =-2.171 and p = .038. The figure shows how many blocks the subjects were able to move from one box into another at the pre and post-assessment. Other results do not show statistical difference. On Figure 4.02 A results for assessment of physical performance, motor and sensory impairment of upper extremity FMA is shown with U = 108, Z = 0.613 and p = .548. Figure represents for how many points the subjects improved from pre to post-assessment after the therapy, where the maximum score on this assessment is 66 points. Figure 4.02 B is showing ability to perform daily activities measured with BI with U = 108, Z = 0.634 and p = .525 and it shows for how many points the performance of daily activities was more independent after the therapy. The maximum score is 100 points. On Figure 4.02 C results for wrist spasticity measured with MAS_W are presented with statistical results U = 102.5, Z =0.170 and p = .846. Figure 4.02 D presents results for fingers spasticity measured with MAS_F, with U = 96, Z = -0.296 and p = .780. These two figures show how much the spasticity improved where the range on this

assessment is from 4 to 0 points, with 0 meaning no spasticity. Figure 4.02 F shows results for fine motoric abilities NHPT, also with not significant difference between the groups for pre and post-assessment results with U = 89, Z = -1.201 and p = .229 and represents how many pegs the subjects were able to insert and take out of the holes in 100 seconds.



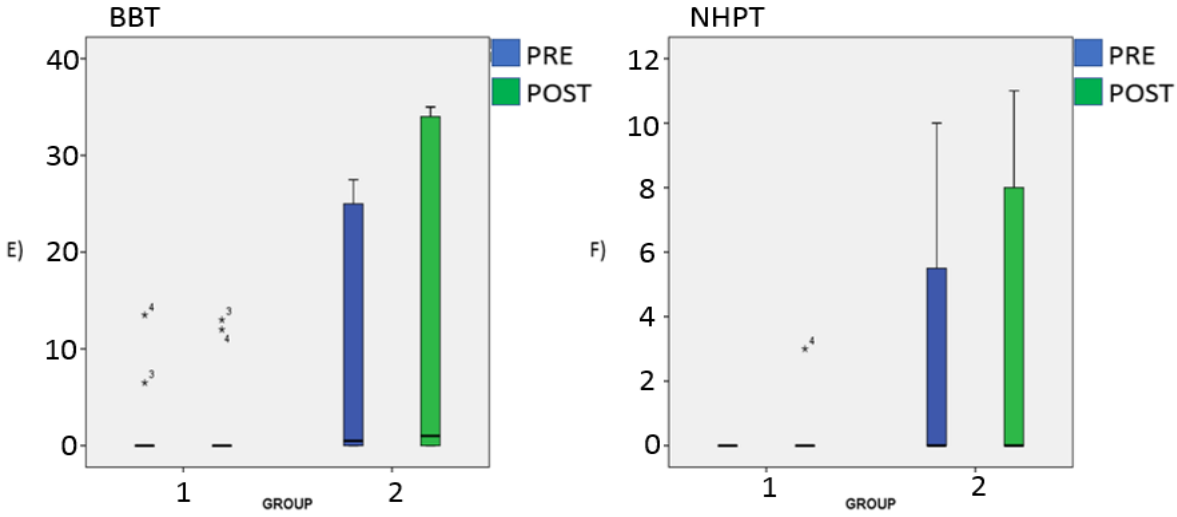
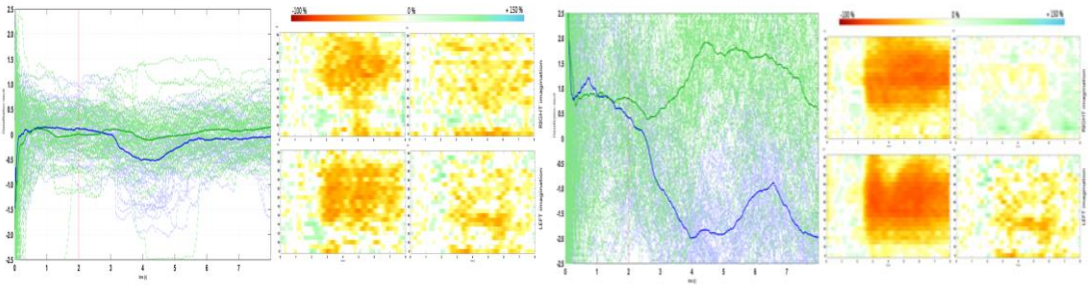


Figure 4.02: Differences between the groups for the pre and post assessment results for each assessment, A) FMA, B) BI, C) MAS_W, D) MAS_F, E) BBT and F) NHPT. Group 1 represents the results for the group with drugs with potential detrimental effect, group 2 for the group with potential rehabilitation improving drugs.

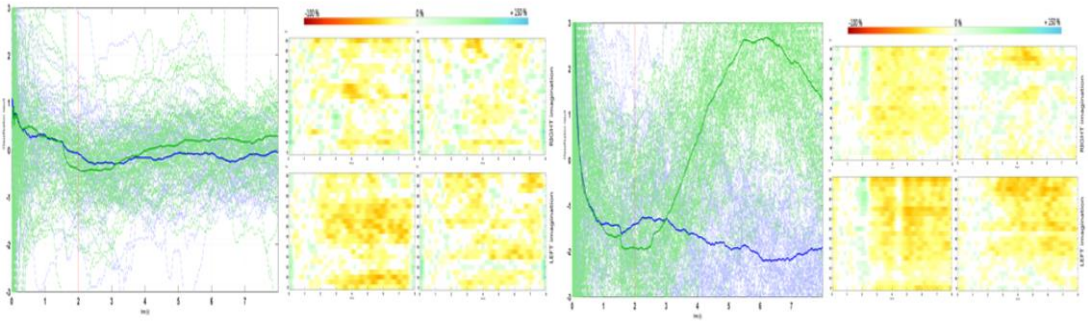
4.2 EEG DATA ANALYSIS

The analysis of neural activity for MI was analyzed and it is presented on LDA and ERD plots. Plots show the difference in ability to imagine left and right hand movement and neural activity that appears when this task is performed for each subject from the beginning and the end of the therapy. Figure 4.03 shows the plots for the subjects in the group with drugs with potential detrimental effect. We can observe that subjects S1 – S3, S5, S6, S8 – S10 show increase in MI and neural activity, whereas plots for subjects S4, S7 and S10 show greater ability to imagine left and right hand movement already in the beginning of therapy and the difference in ability to perform MI in the end of the therapy is not so substantial compared to other subjects.

S1



S2



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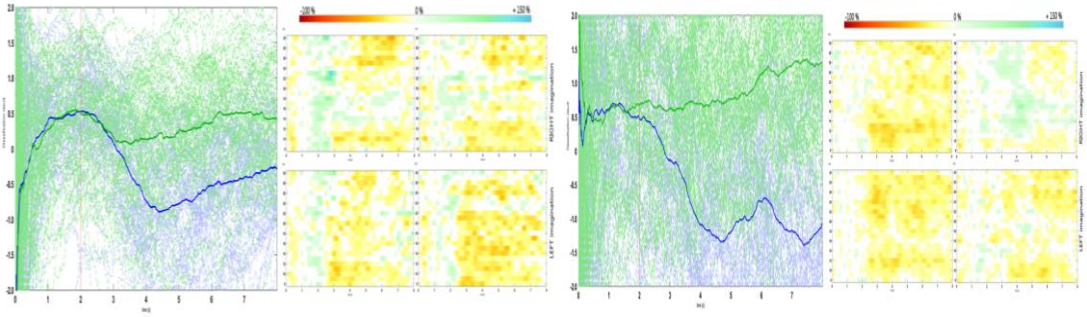
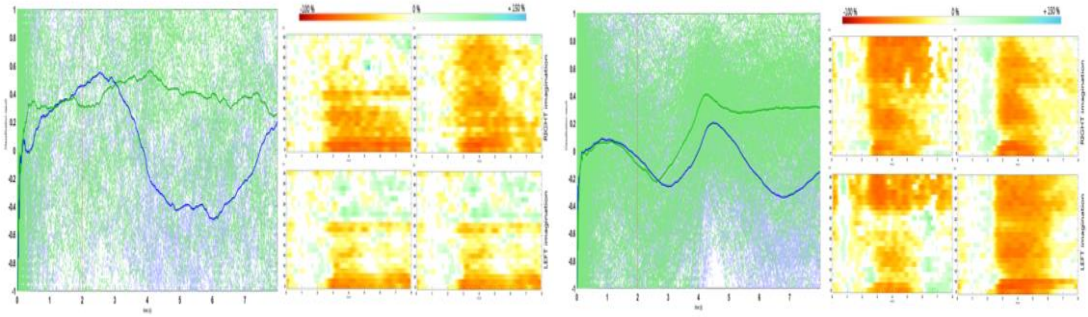


S4



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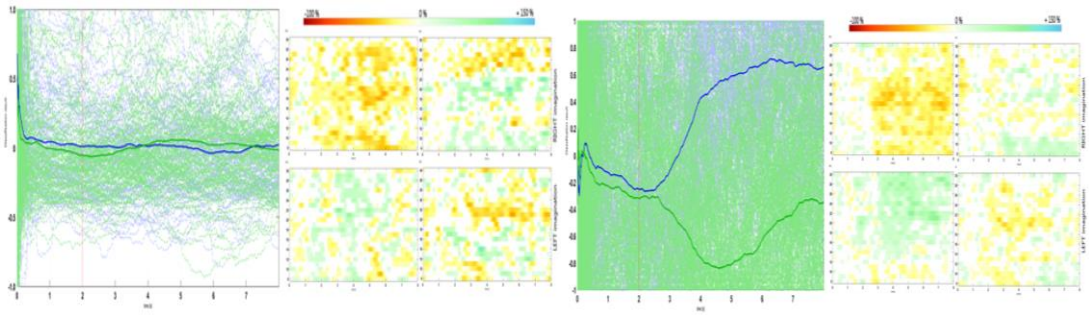

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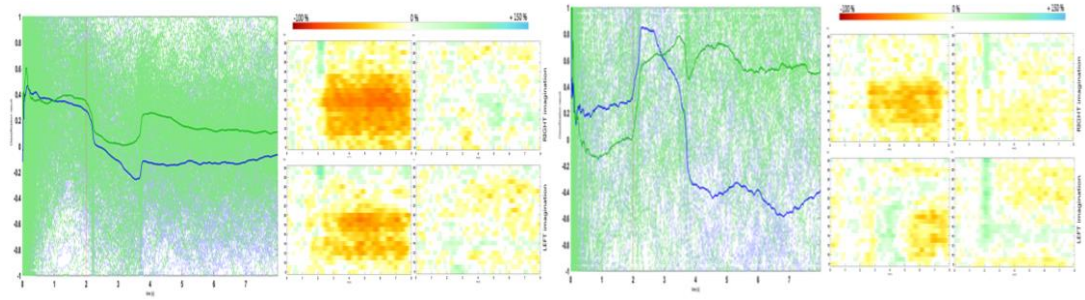


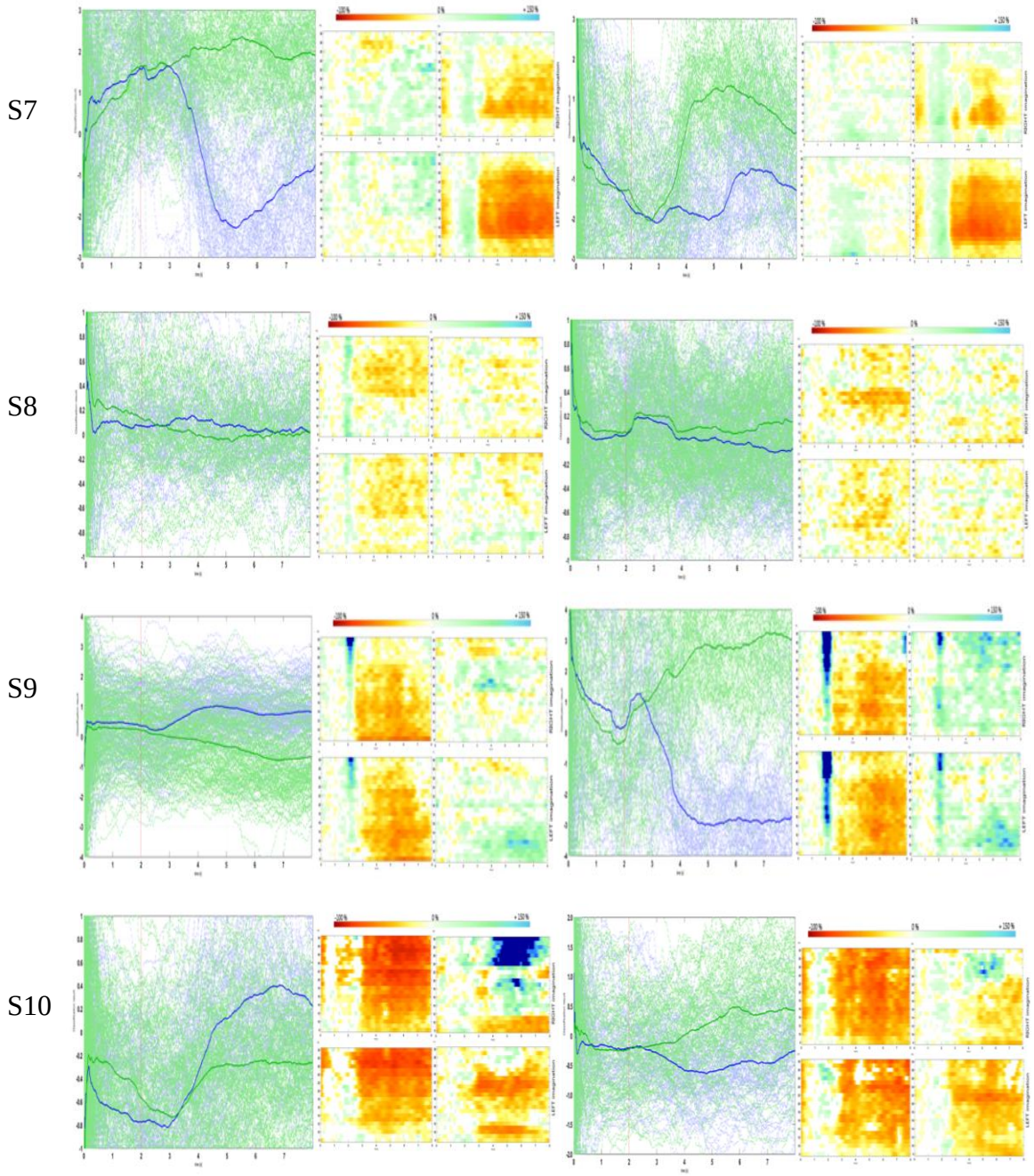
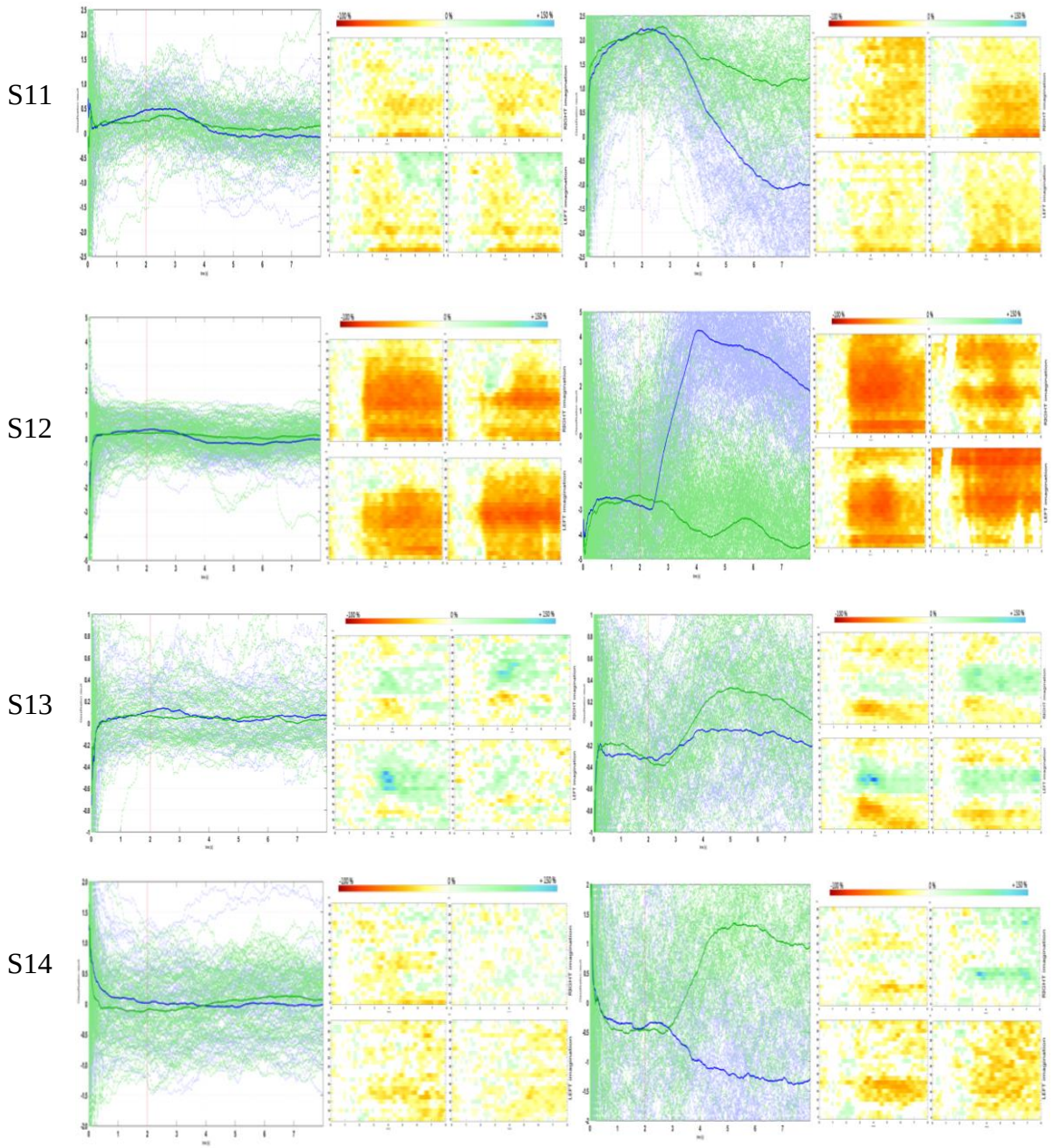


Figure 4.03: LDA and ERD plots for group with drugs with potential detrimental effect for each subject. On the left side the LDA and ERD plots from the beginning of the training are presented, on the right side the LDA and ERD plots from the end of the training are presented.

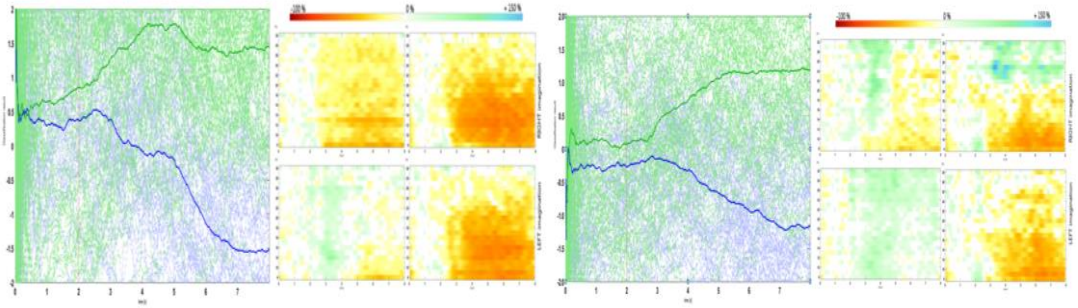
For the LDA plot, dotted green lines represent MI of the left hand movement for each trial, and the full green line shows the average, whereas blue lines represents the right hand MI. X-axis shows the time, the red line presents the cue for left or right hand MI, Y-axis shows the activity of MI. The scale is the same for each subject, but it is not the same for all of them.

The ERD plots are showing neural activity of MI on the C3 and C4 electrode for right hand on top and left hand on bottom for each subject from beginning of the training on the left, and end of the training on the right side, corresponding to the LDA plots. On each on 4 blocks X-axis represent the time of 8 seconds, and Y- axis represent a measure of significant ERD/S activity from 8-30 Hz.

Figure 4.04 shows same parameters for the group with potential rehabilitation improving drugs. It can be observed that subjects S11 – S14, S16 and S18 show increase in MI and neural activation, whereas subjects S15, S17 and S19 do not demonstrate substantial greater improvement when compared at the beginning and the end of the therapy.



S15



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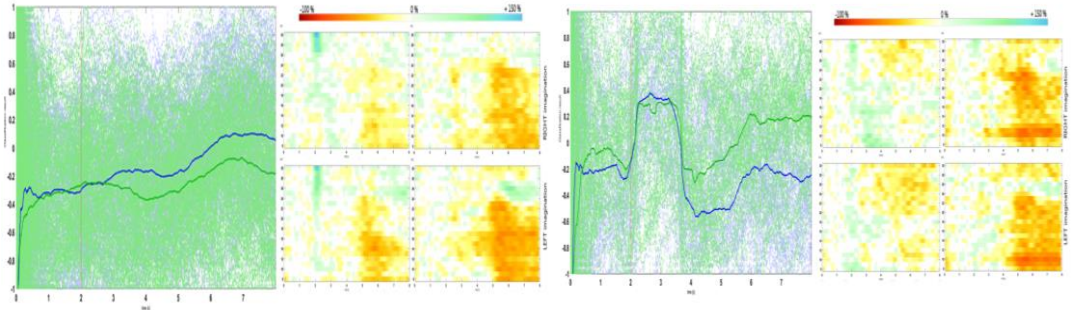

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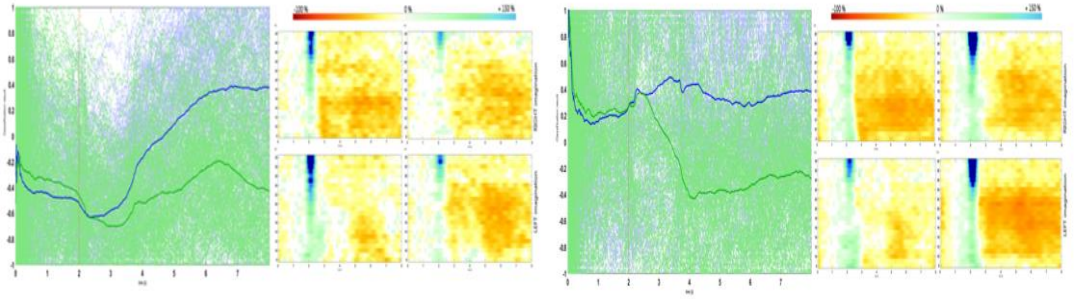

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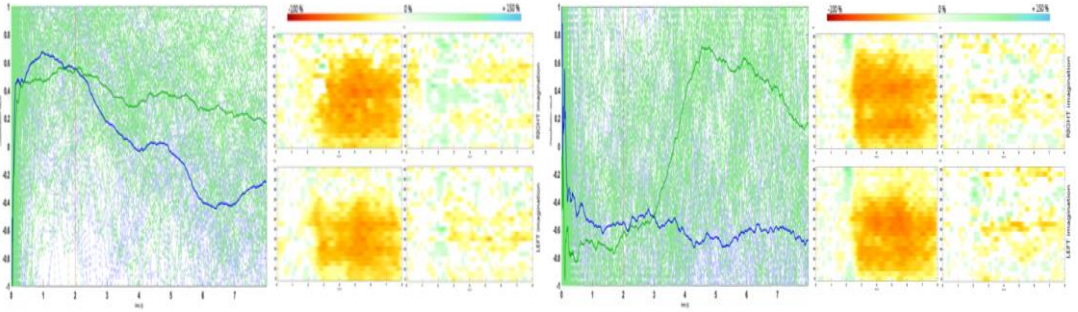

S19

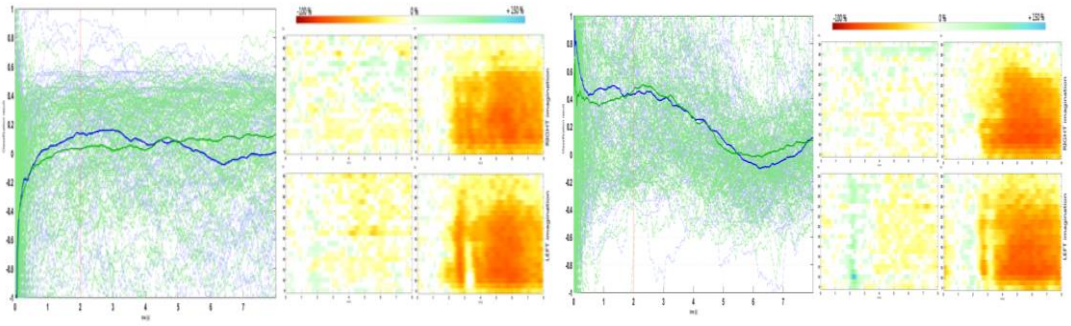

Figure 4.04: LDA and ERD plots for group with drugs with potential rehabilitation improving effect for each subject. On the left side the LDA and ERD plots from the beginning of the training are presented, on the right side the LDA and ERD plots from the end of the training are presented.

5 DISCUSSION

In this thesis we wanted to study the rehabilitation effect of the BCI based stroke rehabilitation technique. Also, we wanted to evaluate if there is a difference in rehabilitation result between the subjects that had prescribed drugs with possible detrimental effect or potential rehabilitation improving drugs used after the stroke. We compared the results for all subjects together for the results before and after the BCI based therapy and separated by the groups for differences in the pre-assessments, and before and after the BCI based therapy. We measured their physical performance, motor and sensory impairment of upper extremity with Fugl-Meyer Assessment, ability to perform daily activities with Barthel Index, spasticity for wrist and fingers with Modifies Ashworth Scale, gross motoric abilities with Box and Blocks test and fine motoric abilities with Nine-Hole peg test. These assessments are often used as standard measures after stroke, to assess the motor recovery of this subjects.

5.1 THERAPY WITH BCI BASED SYSTEM AND IMPROVEMENT IN RECOVERY

Comparison of the results for all subjects together (n = 19) for the pre and post-assessment results reveal that the therapy with BCI system statistically significantly improved motor recovery in 4 out of 6 motor assessments, respectfully. Significant improvement can be seen in Fugl-Meyer Assessment ($p = .002$), that shows that subjects improved in volitional movements and experienced lower sensory impairment of the affected hand after the therapy sessions. The median difference in 5 points, and the mean difference from 21.4 to 26.3, on the scale from 0 – 66 points, between pre and post-assessment shows that the subjects also clinically improved based on Clinically Important Difference (CID) that ranges from 4.25 to 7.25 points for chronic stroke patients (Page, Fulk & Boyne, 2012). Significant improvement is shown also for spasticity of the wrist with $p = .005$, and spasticity for the fingers with $p = .009$ and median of 1-point difference in the scale from 4 – 0 points. This shows that subjects' spasticity in the wrist and fingers decreased. Significant improvement can also be seen in ability to perform gross motoric movements measured with Box and blocks test with $p = .042$. The median improvement is not noticeable, but the results demonstrate the improvement in 75^{th} percentile, which had raised from 7 to 13 blocks. Subjects also demonstrated better ability to perform daily activities measured with Barthel Index and ability to perform fine motoric movements measured with Nine-Hole Peg test. The descriptive results of the median and percentiles show that subjects did not statistically improve the ability to perform daily live activities. Mean score was compared for the Barthel Index and it went from 79.9 to 81.1, and since the minimal clinically important difference (MCID) for Barthel Index is improvement for 1.85 point (Hsieh, Wang, Wu, Chen, Sheu & Hsieh, 2007), we cannot say the subjects clinically improved based on this assessment. The starting point of this subjects on the Barthel Index assessment was relatively high with

median of 85 points on the scale from 0 – 100 points, which limited the improvement possibility. For the fine motoric ability assessment Nine-Hole peg test shows that the majority of the subjects could not perform this fine motoric movements. Result of the 75th percentile show, that some subjects who were not able to perform this assessment in the beginning, were able to insert pegs in the holes after the therapy training with improvement from 0 to 3 pegs in 100 seconds. We were not able to find CID score for these assessments to control if the improvement is clinically important. Based on these results we can confirm the hypothesis H1, that states that the BCI based therapy will improve subjects motoric functioning.

5.1.1 Group differences before BCI based therapy

Demographic data were examined first to see if there were any patterns for the group comparison that would indicate bias were apparent. Since there was the same number of subjects in both groups with dominant hand being the affected one and the same number of ischemic stroke subjects we believe that these factors could not have an influence on the results of the recovery in either of the groups. Study by Harris & Janice (2006) shows, that rehabilitation outcome could be influenced by these factors, since individuals with the dominant hand affected following stroke demonstrate less impairment than those with the nondominant hand affected, and haemorrhagic strokes are generally more severe then ischemic (Andersen, Olsen, Gehlendorff & Kammersgraard, 2009). Age of the subjects could also influence the outcome of the rehabilitation, since studies show that learning and rehabilitation processes by itself are lower with greater age (Bagg, Pombo & Hopman, 2002). Our results show non-statistically significant difference between the groups ($p = .296$) for the factor of age when the therapy started. The same result was demonstrated for the factor time after stroke ($p = .198$) when the therapy started for these subjects, so there were none of the factors that could have bias influence for any of the groups.

Hypothesis H2 states that the group with drugs with potential detrimental effect had lower recovery after stroke before our BCI based therapy sessions, than the group with potential rehabilitation improving drugs. To control this, we analyzed the results of the pre-assessments between the groups to see if there was a difference in the motor function. This difference was described in the literature as pharmacological influence on motor recovery after stroke (Belagaje, 2017; Cramer, 2005; Goldberg, 1993; Goldberg, 1998; Viale, 2017). The results calculated with *Mann-Whitney U test* did not show statistically significant difference, so the hypothesis H2 has to be dismissed. Nevertheless, the group with drugs with potential detrimental effect had in all of the assessments worse results than the group with potential rehabilitation improving drugs applied before the therapy. We noticed that fine motoric ability assessment Nine-Hole Peg test showed a trend toward significance with $p = .065$, median does not show difference in ability to move the pegs from the pool to the holes, but result shows that fine motoric movement difference

between this two groups is detectable. In the group with drugs with potential detrimental effect none of the subjects could perform the assessment, whereas in the group with rehabilitation improving drugs there were 4 subjects who could complete the assessment before our therapy started. Also, physical performance, motor and sensory impairment of upper extremity measured with Fugl-Meyer Assessment showed that group with drugs with potential detrimental effect had lower recovery then the group with drugs with rehabilitation improving drugs applied before the therapy. Median for this measure shows 1 point of a difference with p = .085. The difference can also be seen in the ability to perform gross motoric movements measured with Box and Blocks test with p = .099, but no difference in median. In the group with drugs with potential detrimental effect, there were just 2 out of 10 subjects that were able to perform this gross motoric movements, when compared to the group with potential rehabilitation improving drugs, where there were 5 out of 9 subjects who were able to perform the assessment that measures gross motoric movements. Barthel Index used to measure the ability to perform daily activities, and Modified Ashworth Scale for spasticity did not show difference between the groups, with p = .162 and median of 85 points for Barthel Index and p = .645 for spasticity of the wrist, p = .615 for spasticity of the fingers and median of 3 points for both assessments. Since subjects are chronic patients, and all of them received physio and occupational therapy as a standard rehabilitation after stroke, we believe that the significant difference in affected hand function and performance in daily activities could not be seen because of this, but the long-term effect of drugs used showed more in specific and fine hand movements.

5.1.2 Group differences after the BCI based therapy

Followed that, separate results for both groups were analyzed and compared to confirm or dismiss the hypothesis H3, that states that the group with drugs with potential detrimental effects will improve less with the BCI based therapy than the group with potential rehabilitation improving drugs. Looking at the results, we can see that both groups improved significantly in 3 out of 6 assessments, respectfully.

In the group with drugs with potential detrimental effect, significant improvement in physical performance, motor and sensory impairment of upper extremity measured with Fugl-Meyer Assessment (p = .022) can be seen. The median shows improvement of 2 points, whereas mean score of the pre-assessment was 16.1 and the post-assessment score was 21.3, that shows that the improvement was clinically important for this assessment. Spasticity for the wrist with p = .042 and the fingers p = .040 also improved significantly for this group. Assessment of the ability to perform daily activities BI, showed that the group achieved MCID with the increase in mean from 73.3 to 75.5 points. In the gross and fine motoric movement abilities assessments Box and Block test and Nine-Hole Peg test the subjects in this group did not significantly improved.

The group with potential rehabilitation improving drugs also experienced improvement in physical performance, motor and sensory impairment of upper extremity measured with Fugl-Meyer Assessment ($p = .040$) with median improvement from 27.3 to 31.9 which is just on a lower bound of CID. Spasticity of the wrist measured with Modified Ashworth scale showed to be statistically significant with $p = .050$ and median change from 2.3 to 1.7 points, whereas spasticity of the fingers did not improve significantly, as it did in the other group, with $p = .083$. Median shows that on this parameter one or more patients showed worst spasticity with median raising from 2.5 to 3 points. Gross motoric movement measured with Box and Blocks test improved significantly in this group with $p = .043$, median of 0.5 blocks and 75^{th} percentile from 25.25 to 34.5 blocks. Mean of ability to perform daily activities measured with Barthel Index improved from 87.2 to 89.4 so the improvement shows as MCID. Fine motoric movement improvement measured with Nine-Hole Peg test was noticeable with all off the subjects who were able to perform the assessment in the beginning with 75^{th} percentile going form 6.25 pegs to 9 pegs and $p = .109$, but not with the others.

Based on *Mann-Whitney U test* we used to control the difference between the groups improvements we can see that there is statistically significant difference in 1 out of 6 assessments. This is the Box and Blocks test for gross motoric activity assessment with $p = .038$, where all 5 subjects from the group with potential rehabilitation improving drugs that were able to perform this assessment improved, whereas in the group with drugs with potential detrimental effect only 2 subjects were able to perform it, 1 improved and for 1 the result was lower for 1.5 blocks at post-assessment. All of the other assessments do not show trends of significant difference with $p = .548$ for improvement in physical performance, motor and sensory impairment of upper extremity, measured with Fugl-Meyer Assessment. Assessment of the ability to perform daily activities by Barthel Index had $p = .525$, spasticity for the wrist measured with Modified Ashworth Scale had $p = .864$, spasticity for fingers had $p = .780$, and the assessment to measure the ability to perform fine motoric movements Nine-Hole Peg test had $p = .229$. Unfortunately, the measures could not be compared all together because of the differences in measurements types and based on the results that both groups improved in 3 out of 6 assessments, out of that 1 was significantly different, we cannot confirm or dismiss the hypothesis H3. Based on the literature of the detrimental effect of these drugs on motor recovery (Belagaje, 2017; Cramer, 2005; Goldberg, 1993; Goldberg, 1998; Viale, 2017), we expected a greater difference. We believe that one of the reason why bigger difference was not recorded is due to difference in starting results in all of the assessments of the subjects in this two groups. Group with drugs with potential detrimental effect started on a lower level, especially for Fugl-Meyer Assessment, where median was 15.3 points lower and Barthel Index with 17.5 points lower median, whereas the group with drugs with potential rehabilitation improving effect started with most of the assessments on a quite high level, which could have limited the improvement possibility.

ERD/S and LDA plots show a big difference in ability to differentiate the imagination of left and right hand movement in comparison from the beginning of the BCI based therapy and from the end. With most of the subjects we also noticed a bigger neural activation on the ERD plots from imagination, compatible with LDA plots. As we expected based on the literature survey (Belagaje, 2017; Moresanu et al., 2012; Murphey et al., 2009), that shows that healthy parts of the motoric area take over the activation, a lot more neural activity is obvious on the non-affected hemisphere. In most of the subjects the activation in the end of the therapy sessions did not completely shift on the affected hemisphere. But we can notice that the distribution of activation on the ERD plots form between *Rolandic mu-rhythm* that ranges from 10-12 Hz and *central beta rhythm* in the 14-18 Hz range, that can be seen in resting state and beta rhythm range from 12-30 Hz that is associated with movement and mental task activities, is greater at the end of therapy sessions (He, 2013; Ramadan et al., 2015). High ERD/S activity can be detected after 3.5 seconds, that corresponds to the protocol of each trial, where they get a cue at second 2, and 1 and a half second after the MI feedback activation starts. The statistical difference in the plasticity could not be calculated, so we are not able to say if any of the groups exhibited greater plasticity changes, and the differences from the plots do not represent obvious difference in gain of any of the groups. As seen in the plots, most of the subjects were able to better imagine left and right hand movement at the end of the therapy sessions.

Based on the motoric assessments, ERD/S and LDA plots we cannot say that drugs these subjects were prescribed at stroke had an influence on the recovery with BCI based technology. We can speculate that these drugs do not have a long-lasting effect if they were applied just shortly after the stroke and for a short period of time, based on these results. Studies that combine pharmacological agents like SSRI, dopaminergics or stimulants combined with physical or BCI based therapy show significantly bigger improvements for these subjects, then with the subjects with the same therapy without those pharmacological agents (Cramer, 2005; Hatem et al., 2016; Tran et al., 2016; Viale et al., 2017). Also, we do not have their psychological assessments or doctors' observations if any of the drugs were changed after the first administration. One of the biggest challenges here represents the treatment with SSRIs, since it is known that not all of the antidepressant drugs are effective, and the depression is treated. This would mean that the SSRI treatment could not have been effective, and that could have a bad influence on the results of the group with drugs with potential rehabilitation improving effect. Another factor that could influence the results is the fact if the subjects were taking the drugs, they were prescribed regularly or they did not take them, and the pharmacological modulation was not present in the way we expected it to be from the data we had.

6 CONCLUSIONS

The aim of this study was to investigate the influence of the BCI based therapy with VR avatar and FES feedback on the stroke patients alone and in connection with pharmacotherapy that was prescribed after stroke. We have set 3 hypotheses to guide the present thesis: therapy with this BCI system will have positive effect on subjects' motor function rehabilitation; subjects treated with drugs with potential detrimental effect will have lower motor recovery than subjects treated with drugs with potential rehabilitation improving effect applied before the therapy with BCI based system; subjects treated with drugs with potential detrimental effect will have lower motor recovery, than subjects treated with drugs with potential rehabilitation improving effect applied within the BCI based system therapy. We addressed these hypotheses with corresponding statistical analysis and we can confirm the first hypothesis firmly, the second hypothesis shows a trend to it, but we had to dismiss it, and for the third hypothesis the results are not showing any of the trends so we cannot confirm it or dismiss it.

We noticed improvements in the functional motor recovery of these subjects, which is in accordance with previous studies (Cervera et al., 2017). We found improvements in volitional movements, sensorics, spasticity, gross and fine motoric for all of the subjects, whereas the group differences were not as big as expected (Belagaje, 2017; Goldberg, 1993; Goldberg, 1998).

Based on these results we can conclude that the BCI based therapy was effective. Since the difference between the groups did not show as significant, we cannot firmly conclude that the drugs prescribed at the stroke influenced the motor recovery after stroke before this therapy. And since results with BCI-based therapy showed as clinically important, and both groups improved quite equally, in the end we cannot conclude that these drugs had a negative or positive long-lasting effect and they had an influence on the functional motor recovery with this therapy.

6.1 RECOMMENDATIONS FOR FUTURE RESEARCH

As demonstrated by the results in the current thesis the mechanisms and processes that underlie the functional motor recovery with the BCI based technology still need to be explored in detail. Effort must be directed in recruiting more subjects to get firmer results. Based on the limitations, we are aware of the fact that more control over the rehabilitation and pharmacotherapeutic process is needed for the future research on this field, with control on all of the pharmacologic agents' subjects are taking. Also control group with placebo drugs would give us more insight about the influence of pharmacological agent action.

We would also suggest more effort to be directed in including more assessments which are not based just on motor recovery, but also cognitive and psychological assessments, since a lot of subjects reported subjective improvements in cognitive functioning and overall better functioning after the therapy.

Since the trend is showing in this direction, we would also suggest that drugs that could impede the recovery should be avoided in the time period of brain injury and recovery.

7 POVZETEK

Možganska kap predstavlja enega vodilnih vzrokov za možganske okvare z vplivom na motorično, kognitivno delovanje ter duševno zdravje in s tem tudi na samo kvaliteto življenja posameznika (Sisto, Forrest in Glendinning, 2002). Pomemben element okrevanja po možganski kapi so mnogokrat spremljajoče terapije (Cramer, 2015).

Vmesniški sistemi možgani-računalnik (BCI – *brain-computer interface*) so orodja, ki na podlagi motoričnega predstavljanja omogočajo vpogled v zamišljanje motoričnega gibanja posameznika s pomočjo merjenja možganske aktivnosti z EEG (Tran idr., 2016). Povratna informacija, ki jo oseba s to tehnologijo dobi omogoča, da pride do nagrajevalnega učinka v možganih, kar spodbuja pravilno učenje in motivacijo tudi z aktivacijo zrcalnih nevronov v mezolimbičnih strukturah. S tem procesom se sprožajo tudi reorganizacijski procesi nevronskih mrež v možganih, t.i. nevroplastičnost, kar osebam s poškodbami možganov omogoča boljšo rehabilitacijo (Hatem idr., 2016). Povratna zanka z aktivacijo navidezne resničnosti oz. t.i. avatar, in funkcionalno električno stimulacijo (FES) takih sistemov omogoča, da oseba na tarčnem udu prejme tudi taktilno/kinestetično povratno informacijo o želenem gibu v realnem času skladno z motoričnim predstavljanjem in s tem se omogoča aktivacija mišičnih skupin, ki so zaradi posledic kapi postale nefunkcionalne (Langhorne, Coupar in Pollock, 2009).

Pregled literature kaže, da imajo lahko nekatera zdravila, ki se uporabljajo kot standardna terapija po možganski kapi, zaradi drugih indikacij negativen ali pozitiven vpliv na motorično okrevanje. Zaradi mehanizma delovanja lahko vplivajo na proces okrevanja. V študijah so posebej izpostavljena nevroleptična zdravila in GABA agonisti, ki vplivajo na nevroplastičnost in okrevanje po možganski kapi poslabšajo. In zdravila, kot so SSRI, SNRI in dopaminergična zdravila, ki lahko okrevanje izboljšajo (Belagaje, 2017; Conroy idr. 2005; Goldberg, 1993; Goldberg, 1998; Viale idr., 2017).

Namen te študije je bil raziskati vpliv terapije na osnovi BCI tehnologije z avatarjem in povratno informacijo s FES pri pacientih po možganski kapi, in preveriti ali obstaja povezava s farmakoterapijo, ki je bila tem bolnikom predpisana ob kapi. Da bi lahko to preverili smo si postavili 3 hipoteze: terapija s tem BCI sistemom bo pozitivno vplivala na rehabilitacijo motoričnih funkcij udeležencev; udeleženci, ki so prejeli zdravila s potencialnim negativnim učinkom, bodo imeli pred zdravljenjem s sistemom BCI nižjo stopnjo motoričnega funkcioniranja kot udeleženci, ki so imeli predpisana zdravila s potencialnim pozitivnim učinkom; udeleženci, ki so imeli predpisana zdravila s potencialnim negativnim učinkom, bodo imeli slabše motorično okrevanje, kot udeleženci,

ki so imeli predpisana zdravila s potencialnim pozitivnim učinkom po terapiji z BCI sistemom.

Da bi lahko potrdili ali ovrgli postavljene hipoteze smo izvedli ustrezno statistično analizo rezultatov, ki smo jih izmerili pred in po terapiji ter preverili ali bi lahko kateri od dejavnikov kot so starost, ali je prizadeta roka dominantna, kap posledica krvavitve ali zapore žil in čas po kapi ob začetku terapije vplival na izid rezulatov. Rezultati kažejo, da razlike glede na te dejavnike med skupinama niso statistično pomembne. Nadaljna analiza je pokazala, da so se vsi udeleženci skupaj statistično pomembno izboljšali v 4 od 6 motoričnih testov in kažejo klinično pomembno izboljšanje. Sledila je analiza razlik med skupinama in rezultati kažejo, da je bila statistična razlika med skupinama pred začetkom naše terapije statistično nepomembna, vendar trend kaže, da je imela skupina, ki je imela predpisana zdravila s potencialnim negativnim učinkom na vseh testih vidno nižje rezultate. Primerjava med skupinama po naši terapiji je pokazala, da sta se obe skupini izboljšali v 3 od 6 motoričnih testov s statistično pomembno razliko pri testu grobe motorike. Analiza nevroplastičnosti prav tako kaže, da se je pri večini udeležencev sposobnost imaginacije leve in desne roke povečala in s tem sovpada tudi aktivacija možganske aktivnosti, vendar med skupinama ni opaziti pomembne razlike.

Opazili smo izboljšavo pri funkcionalni motoriki udeležencev, kar je v skladu s prejšnjimi študijami (Cervera idr., 2017). Za vse udeležence smo lahko opazili izboljšavo hotenega gibanja, senzorike, spastičnosti, grobe in fine motorike, medtem ko razlike med skupinama niso bile tako velike, kot smo glede na literaturo in pretekle študije pričakovali (Belagaje, 2017; Goldberg, 1993; Goldberg, 1998). Glede na dobljene rezultate lahko potrdimo prvo hipotezo, druga hipoteza kaže trend k izboljšanju, vendar smo jo morali ovreči, tretje hipoteze ne moremo ne potrditi in ne ovreči.

Na podlagi teh rezultatov lahko zaključimo, da je bila terapija na podlagi BCI tehnologije uspešna. Ne moremo pa trdno sklepati, da so zdravila, predpisana pri kapi, imela negativen ali pozitiven dolgotrajen učinek in vpliv na funkcionalno motorično okrevanje z BCI tehnologijo.

Za prihodnje raziskave menimo, da je potrebno še podrobneje raziskati mehanizme in procese vključene v funkcionalno motorično okrevanje po možganski kapi s tehnologijo BCI. Potrebno je tudi raziskati vpliv v primerjavi s kontrolno skupino z nevtralnimi zdravili ter večjim številom udeležencev. Glede na omejitve, katerih se zavedamo, bi predlagali, da je za prihodnje raziskave na tem področju potreben večji nadzor nad rehabilitacijo in farmakološko obravnavo oz. predpisovanjem zdravil v času terapije. Prav tako bi predlagali vključitev več testov, ki ne temeljijo samo na motoričnem okrevanju, temveč tudi

kognitivnih in psiholoških ocenah, saj je veliko udeležencev poročalo o subjektivnih izboljšavah kognitivnega delovanja in celostnem boljšem delovanju po terapiji.

Ker se trend kaže v smeri, da imajo lahko nekatera zdravila negativen učinek na motorično okrevanje po možganski kapi, bi prav tako predlagali, da se je potrebno ob možganskih poškodbah izogibati predpisovanju zdravil, ki bi lahko ovirale funkcionalno motorično okrevanje.

8 REFERENCES

Abbott, L. F., and Nelson, S. B. (2000). Synaptic plasticity: taming the beast. *Nature Neuroscience*; 3: 1178-1183.

Alexander, L. D., Black, S. E., Gao, F., Szilgayi, G., Danells, C. J. and McIlroy, W. E. (2010). Correlating lesion size and location to deficits after ischemic stroke: the influence of accounting for altered peri-necrotic tissue and incidental silent infarcts. *Behavioral and Brain Functions*; 6:6.

Alimardani, M., Nishio, S. and Ishiguro, H. (2016). The Importance of Visual Feedback Design in BCIs; from Embodiment to Motor Imagery Learning. *PloS One*;11(9): e0161945.

Andersen, K. K, Olsen, T. S., Dehlendorff, C. and Kammersgaard, L. P. (2009). Hemorrhagic and Ischemic Strokes Compared Stroke Severity, Mortality, and Risk Factors. *Stroke*; 40:2068-2072.

Baggm, S., Pombo, A. P. and Hopman, W. (2002). Effect of age on functional outcomes after stroke rehabilitation. *Stroke;* 33(1):179-85.

Bahannon, R. W. and Smith, M. B. (1987). Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*.; 67(2):206-7.

Bansil, S., Parakash, N., Kaye, J., Wrigley, S., Manatam C., Stevens-hass, C. and Kurlan, R. (2012). Movement Disorders after Stroke in Adults: A Review. *Tremor Other Hyperkinet Mov*; 2: tre-02-42-195-1.

Bajaj, S., Butler, A. J., Drake, D. and Dhamala, M. (2015). Brain effective connectivity during motor-imagery and execution following stroke and rehabilitation. Neuroimage 8, 572–582.

Belagaje, S. (2017). Stroke Rehabilitation. *Continuum*. 23:238-253.

Bliss, T. V. P. and Cooke, S. F. (2011). Long-term potentiation and long-term depression: a clinical perspective. *Clinics (Sao Paulo).* 1: 3–17.

Brewer, L., Horgan, F., Hickey, A. and Williams, D. (2013). Stroke rehabilitation: recent advances and future therapies. *QJM: An International Journal of Medicine*; 106: (1).11–25.

Brown, T. H, Zhao, Y. and Leung, V. (2009). Hebbian Plasticity. *Encyclopedia of neuroscience*. Oxford: Academic Press. p. 1049–1056.

Buch, E., Weber, C., Cohen, L. G., Braun, C. Dimyan, M. A., Ard, T., Mellinger, J., Caria, A., Soekadar, S., Fourkas, A. and Birbaumer, N. (2008). Think to move: a neuromagnetic braincomputer interface (BCI) system for chronic stroke. Stroke; 39(3):910–7.

Bundy, D. T., Souders, L., Baranyai, K., Leonard, L., Schalk, G., Coker, R., Moran, D. W., Huskey, T., Leuthard, E. C. (2017). Contralesional Brain–Computer Interface Control of a Powered Exoskeleton for Motor Recovery in Chronic Stroke Survivors. Stroke: 1: 116.016304.

Calabresi, P., Picconi, B., Tozzi, A. and Filippo, M. (2007). Dopamine-mediated regulation of corticostriatal synaptic plasticity. *Trends Neurosci*.; 30(5):211-9.

Cervera, M. A., Soekadar, S. R., ushiba, J., Millan, J. del R., Liu, M., Birbaumer, N. and Garipelli, G. (2017). Brain-Computer Interfaces for Post-Stroke Motor Rehabilitation: A Meta-Analysis. *Progress in brain research*; 228.

Chen, K. C., Baxter, M. G. and Rodefer, J. S. (2004). Central blockade of muscarinic cholinergic receptors disrupts affective and attentional set-shifting. *Eur. J. Neurosci*.; 20:1081–1088.

Cho, W., Sabathiel, N., Ortner, R., Lechner, A., Irimia, D. I., Allison, B. Z., Edlinger, G. and Guger, C. (2016). Paired Associative Stimulation using Brain-Computer Interfaces for Stroke Rehabilitation: A Pilot study. Eur J Transl Myol; 26:219-22.

Choi, J. W. and Kim, W. K. (2007). Is toprimate a potential therapeutic agent for cerebral hypoxic/ischemic injury? *Exp Neurol*.; 203:5-7.

Clarkson, A. N., Huang, B. S., MacIsaac, S. E., Mody, I. and Carmichael, S. T. (2010). Reducing excessive GABA mediated tonic inhibition promotes functional recovery after stroke. *Nature*; 468:305–309.

Conroy, B., Zorowitz, R., Horn, S. D., Ryser, D. K., Teraoka, J., Smout, R. J. (2005). An exploration of central nervous system medication use and outcomes in stroke rehabilitation. *Archives of physical medicine and rehabilitation*; 86: S73–S81.

Cowen, P. and Sherwood, A. C. (2013). The role of serotonin in cognitive function: Evidence from recent studies and implications for understanding depression. *J Psychopharmacol*.; 27:575–583.

Cramer, S. C. (2015). Drugs to enhance motor recovery after stroke. *Stroke*; 46(10):2998-3005.

Cumberland Consensus Working Group, Cheeran B., Cohen, L., Dobkin, L., Ford, G., Greenwood, R., Howard, D., Husain, M., Macleod, M., Nudo, R., Rothwell, J., Rudd, A., Teo, J., Ward, N., and Wolf, S. (2009). The future of restorative neurosciences in stroke: driving the translational research pipeline from basic science to rehabilitation of people after stroke. *Neurorehabil Neural Repair*; 23(2): 97Y107.

de Vries S. and Mulder, T. (2007). Motor imagery and stroke rehabilitation: a critical discussion. J *Rehabil Med*; 39: 5-13.

Dragovich, A. and Cohen, S. P. (2009). Spinal Analgesia. *Current Therapy in Pain*; 88:640-651.

Engelter, S. T. (2013). Safety in pharmacological enhancement of stroke rehabilitation. *Eur J Phys Rehabil Med.* Apr;49(2):261-7.

Feinberg, M. The problems of anticholinergic adverse effects in older patients. *Drugs Aging*.; 3(4):335-48.

Fleckenstein, A. E., Volz, T. J., Riddle, E. L., Gibb, J. W. and Hanson, G. R. (2007). New insights into the mechanism of action of amphetamines. *Annu Rev Pharmacol Toxicol* 47: 681–698.

Fugl-Meyer, A. R. (1980). Post-stroke hemiplegia assessment of physical properties. *Scand J Rehabil Med*; 7: 85-93.

Fugl-Meyer, A. R, Jaasko, L., Leyman, I., Olsson, S. and Steglind, S. (1975). The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scand J Rehabil Med*; 7:13-31.

García-Laencina, P. J., Rodríguez-Bermudez, G. and Roca-Dorda, J. (2014). Exploring dimensionality reduction of EEG features in motor imagery task classification. *Expert Systems with Applications*; 41(11):5285-5295.

Good, D. C. (1990). Cerebrovascular Disease. *Clinical Methods: The History, Physical, and Laboratory Examinations*; 3rd edition: 288-292.

Good, D. C., Bettermann, K. and Reichwein, R. K. (2011). Stroke Rehabilitation. Continuum Lifelong Learning Neurol.; 17:545–567.

Goldstein, L. B. (1993). Basic and clinical studies of pharmacologic effects on recovery from brain injury. *J Neural Transplant Plast.* Jul-Sep;4(3):175-92.

Goldstein, L. B. (1998). Potential Effect of Common Drugs on Stroke Recovery. *Arch Neurol.*; 55:454-456.

Gotti, C., Zoli, M. and Clementi, F. (2006). Brain nicotinic acetylcholine receptors: native subtypes and their relevance. *Trends Pharmacol. Sci*.; 27:482–491.

Graham, S. H. and Chen, J. (2001). Programmed Cell Death in Cerebral Ischemia. *Journal of Cerebral Blood Flow and Metabolism*; 21:99–109.

Grasselli, G. and Hansel, C. (2014). Cerebellar long-term potentiation: Cellular mechanisms and role in learning. *Int Rev Neurobiol*; 117:39Y51.

Grunder, G., Hippius, H. and Carlsson, A. (2009). The 'Atypicality' of Antipsychotics: A Concept Re-Examined and Re-Defined. *Nat Rev Drug Discov*; 197-202.

Guina, J. and Merrill, B. (2018). Benzodiazepines I: Upping the Care on Downers: The Evidence of Risks, Benefits and Alternatives. *J Clin Med*.; 7(2): 17.

Guina, J., Rossetter, S.R., DeRhodes, B.J., Nahhas, R.W. and Welton, R.S. (2015). Benzodiazepines for PTSD: A systematic review and meta-analysis. *J. Psychiatr. Pract*.; 21:281–303.

Hara, Y. (2015). Brain Plasticity and Rehabilitation after stroke. *J Nippon Med Sch*: 82 (1).
Hatem, S. M., Saussez, G., della Faille, M., Prist, V., Zhang, X., Dispa, D. and Beleyenheuft, Y. (2016). Rehabilitation of motor function after stroke: a multiple systematic review focused on techniques to stimulate upper extremity recovery**.** *Front. Hum. Neurosci*; 10:442.

Harris, J. E. and Janice, J. (2006). Individuals with the Dominant Hand Affected Following Stroke Demonstrate Less Impairment Than Those with the Nondominant Hand Affected. *Neurorehabil Neural Repair*; 20:380–389.

Hasselmo, M. E. (2009). The Role of Acetylcholine in Learning and Memory. *Curr Opin Neurobiol.;* 16(6):710-715.

He, B. (2013). Neural engineering. *Springer publisher*, New York: 987-1-4614-5226-3.

Huang, Y. Y., Martin, K. C. and Kendel, E. R. (2000). Both protein kinase A and mitogen-activated protein kinase are required in the amygdala for the macromolecular synthesis-dependent late phase of long-term potentiation. *J Neurosci.;* 20(17):6317-25.

Hosp, J. A., Pekanovic, A., Rioult-Pedotti, M. S. and Luft, A. (2011). Dopaminergic Projections from Midbrain to Primary Motor Cortex Mediate Motor Skill Learning. *Journal of Neuroscience;* 31 (7) 2481-2487.

Hsieh, Y. W., Wang, C. H., Wu, S. C., Chen, P. C., Sheu, C. F. and Hsieh, C. L. (2007). Establishing the Minimal Clinically Important Difference of the Barthel Index in Stroke Patients. *Neurorehabilitation and Neural Repair*; 21(3).

Jones, B. E. (2008). Modualtion of cortical and behavioural arousal by cholinergic and orexinergic systems. *Ann. N Y Acad. Sci*.; 1129:26-34.

Kameswara, T., Rajyalakshmi, M., Prasad, T. (2013). An exploration on brain computer interface and its recent trends. *Int. J. Adv. Res. Artif. Intell*.; 1(8), 17–22.

Krakauer, J. W., Carmichael, S. T., Corbett, D., & Wittenberg, G. F. (2012). Getting neurorehabilitation right: what can be learned from animal models? *Neurorehabil Neural Repair*; 26, 923-931.

Kuczemski, R. and Segal, D. S. (1997). Effects of methylphenidate on extra cellular dopamine, serotonin, and norepinephrine: compression with amphetamine. *J Neurochem*, 68:2032–7.

Kreitzer, A. C. and Malenka, R. C. (2005). Dopamine modulation of state-dependent endocannabinoid release and longterm depression in the striatum. *J Neurosci*.; 25:10537Y45.

Irimia, D., Sabathiel, N., Ortner, R., Poboroniuc, M., Coon, W., Allison, B. Z. and Guger, C. (2016). recoveriX: A New BCI-based Technology for Persons with Stroke. *Engineering in Medicine and Biology Society;*1504-1507.

Langhorne, P., Coupar, F. and Pollock, A. (2009). Motor recovery after stroke: a systematic review. *Lancet Neurology* 8 (8): 741–54.

Lee, H. K., Barbarosie, M., Kamevama, K., Bear, M. F. And Huganir, R. L. (2000). Regulation of distinct AMPA receptor phosphorylation sites during bidirectional synaptic plasticity. *Nature.* 405(6789):955-9.

Li, C., Dabrowska, J., Hazra, R., and Rannie, D. G. (2011). Synergistic activation of dopamine D1 and TrkB receptor mediate gain control of synaptic plasticity in the basolateral amygdala. *PLoS One*; 6:e26065.

Licata, S. C., Shinday, N. M., Huizenga, M. N., Darnell, S. B., Sangrey, G. R., Rudolph, U., Rowlett, J. K. and Sadri-Vakili, G. (2013). Alterations in brain-derived neurotrophic factor in the mouse hippocampus following acute but not repeated benzodiazepine treatment. *PLoS One*; 8:e84806.

Logue, S. F. and Gould, T. J. (2014). The neural and genetic basis of executive function: Attention, cognitive flexibility, and response inhibition. *Pharmacol Biochem Behav*.; 123:45–54.

Longo, L. P. and Johnson, B. (2000). Addiction: Part I. benzodiazepines—side effects, abuse risk and alternatives. *Am. Fam. Phys*.; 61:2121–2128.

Mahoney, F. I., Barthel, D. (1965). Functional evaluation: the Barthel Index. *Maryland State Medical Journal*; 14:56-61.

Mathiowetz, V., Weber, K., Kashman, N. and Volland, G. (1985a). Adult norms for the Box and Block Test of manual dexterity. *Am J Occup Ther 39*: 386-391.

Mathiowetz, V., Weber, K., Kashman, N. and Volland, G. (1985b). Adult Norms for the Nine Hole Peg Test of Finger Dexterity. *The Occupational Therapy Journal of Research*; 5:24-33.

McAllister, T. W. (2009). Polymorphisms in genes modulating the dopamine system: do they inf luence outcome and response to medication after traumatic brain injury? *Head Trauma Rehabil*.; 24(1):65-8

Mead, G. E., Hsieh, C. F., Lee, R., Kutlubaev, M. A., Claxton, A., Hankey G. J. and Hackett, M. L. (2012). Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database Syst. Rev.; 11:CD009286.

Merzenich, M. M., Van Vleet, T. M. and Nahum, M. (2014). Brain plasticity-based therapeutics. *Front Hum Neurosci*.; 8:385.

Miller, R. (2009). Mechanisms of Action of Antipsychotic Drugs of Different Classes, Refractoriness to Therapeutic Effects of Classical Neuroleptics, and Individual Variation in Sensitivity to their Actions: PART I. *Curent Neuropharmachology*; 7:302-314.

Mitchell, D. J., McNaughton, N., Flanagan, D. and Kirk, I. J. (2008). Frontal-midline theta from the perspective of hippocampal "theta." *Progress in Neurobiology*; *86*(3), 156–185.

Moresanu, D. F., Buzoianu, A., Florian, S. I. and von Wild, T. (2012). Towards a roadmap in brain protection and recovery. *J Cell Mol Med*.; 16(12): 2861–2871.

Murphy, T. H., Li, P., Betts, K. and Liu, R. (2008). Two-photon imaging of stroke onset *in vivo* reveals that NMDAreceptor independent ischemic depolarization is the major cause of rapid reversible damage to dendrites and spines. *J. Neurosci.* 28, 1756–1772.

Murphy, T. H. and Corbett, D. (2009). Plasticity during stroke recovery: from synapse to behaviour. *Neuroscience;* 10: 861-872.

Nour, M., Scalzo, F. and Liebeskind, D. S. (2013). Ischemia-Reperfusion Injury in Stroke. *Intervent Neurol*; 1:185–199.

Nudo, R. J., Wise, B. M., SiFuentes, F. and Milliken, G. W. (1996). Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science;* 272, 1791–1794.

Page, S. J., Fulk, G. D. and Boyne, P. (2012). Clinically Important Differences for the Upper-Extremity Fugl-Meyer Scale in People with Minimal to Moderate Impairment Due to Chronic Stroke. *Physical Therapy;* 92:791-789.

Pamenter, M. E., Hogg, D. W., Ormond, J., Shin, D. M., Woodin, M. A. and Buck, L. T. (2011). Endogenous $GABA_A$ and $GABA_B$ receptor-mediated electrical suppression is critical to neuronal anoxia tolerance. *PNAS*; 108 (27) 11274-11279.

Patel, M. D., McKevitt, C., Lawrence, E., Rudd, A. G. and Wolfe, C. D. (2007). Clinical determinants of long-term quality of life after stroke. *Age and Ageing*; 36: 316–322.

Pfurtscheller, G. and Neuper, C. (2006). Future prospects of ERD/ERS in the context of brain–computer interface (BCI) 35 developments. *Prog Brain Res*.; 159:433–7.

Peckham, P. H., and Knutson, J. S. (2005). Functional Alectrical Stimulation for Neuromuscular Applications. *Annu. Rev. Biomed. Eng.*; 7:327–60.

Perry, R. and Cassagnol, M. (2009). Desvenlafaxine: A new serotonin-norepinephrine reuptake inhibitor for the treatment of adults with major depressive disorder. *Clinical therapeutics*. 31 (1): 1374–404.

Ramadan, R. A., Refat, S., Elshahed, M. A. and Rasha, A. A. (2015). Basics of Brain Computer Interface. *Brain-Computer Interfaces, Intell. Syst. Ref. Libr.*, vol. 74, pp. 31–50.

Remsik, A., Young, B., Vermilyea, R., Kiekhoefer, L., Abrams, J., Elmore, E. S., Schultz, P., Nair, V., Edwards, D., Williams, J. and Prabhakaran, V. (2016). A review of the progression and future implications of brain-computer interface therapies for restoration of distal upper extremity motor function after stroke. *Expert review of medical devices*; 13: 445-454.

Rothman, R.B. and Baumann, M.H. (2003) Monoamine transporters and psychostimulant drugs. *Eur. J. Pharmacol*. 479, 23–40.

Sara, S.J. and Bouret, S., (2012). Orienting and reorienting: the locus coeruleus mediates cognition through arousal. *Neuron*: 76, 130–141.

Scarano, G., La Rocca, D. and Campisi, P. (2012). EEG for Automatic Person Recognition. *Computer*; 45:87-89.

Schallert, T., Jones, T. A., Weaver, M. S., Shapiro, L. E., Crippens, D. and Fulton, R. (1992). Pharmacologic and anatomic considerations in recovery of function. *Physic Med Rehab*; 6: 375-393.

Shin, S. S. and Dixon, C. E. (2015). Alterations in Cholinergic Pathways and Therapeutic Strategies Targeting Cholinergic System after Traumatic Brain Injury. *J Neurotrauma*; 32(19): 1429-1440.

Seidenstein, A. H., Barone, F. C. and Lytton, W. W. (2015). Computer modeling of ischemic stroke. Scholarpedia J.; 10(3): doi:10.4249/scholarpedia.32015.

Siepmann, T., Penzlin, A. I., Kepplinger, J., Illigens B. M., Weidner, K., Reichmann, H. And Barlinn, K. (2015). Selective serotonin reuptake inhibitors to improve outcome in acute ischemic stroke: possible mechanisms and clinical evidence. Brain and Behavior; 5(10), e00373.

Sisto, S. A., Forrest, G. F. and Glendinning, D. (2002). Virtual Reality Applications for Motor Rehabilitation After Stroke. *Top Stroke Rehabil*. 8 (4): 11–23.

Sinischalchi, A., Gallelli, L., Labate, A., Malferrari, G., Palleria, C. and De Sarro, G. (2012). Post-stroke Movement Disorders: Clinical Manifestations and Pharmacological Management. *Curr Neuropharmacol.;* 10(3): 254–262.

Sitaram, R., Ros, T., Stoeckel, L., Haller, S., Scharnowski, F., Lewis-Peacock, J., Weiskoph, N., Blefari, M. L., Rana, M., Oblak, E., Biraumer, N. and Sulzer, J. (2017). Closed-loop brain training: the science of neurofeedback. *Nat Rev Neurosci*.; 18(2):86-100.

Stevens, E. G. V., Emmet, E. S., Wang, Y., McKevitt, C. J. and Wolfe, C. D. A. (2017). The Burden of Stroke in Europe: Overview of stroke burden and care in each EU and SAFE member country. *Stroke Alliance for Europe*.

Taly, A., Corringer, P. J., Guedin, D., Lestage, P. and Changeux, J. P. (2009). Nicotinic receptors: allosteric transitions and therapeutic targets in the nervous system. *Nat. Rev. Drug Discov;* 8:733–750.

Tamara, B., Howard, J. (2013). Privacy by design in brain-computer interfaces. *University of Washington, UWEE*, technical report number UWEETR-2013-0001.

Tamatani, M., Ogawa, S., Nuñez, G., Tohayama, M. (1998). Growth factors prevent changes in Bcl-2 and Bax expression and neuronal apoptosis induced by nitric oxide. *Cell Death Differ;* 5:911–919.

Tran, D. A., Pajaro-Blazquez, M., Daneault, J. F., Gallegos, J. G., Pons, J., Fregni, F., Bonato, P. and Zafonte, R. (2016). Combining dopaminergic facilitation with robot assisted upper limb therapy in stroke survivors: a focused review. *Am J Phys Med Rehabil*; 95:459–74.

Tritsch, N. X., Ding, J. B. And Sabatini, B. L. (2012). Dopaminergic neurons inhibit striatal output through non-canonical release of GABA. *Nature*; 490(7419):262-6.

Young, B. M., Nigogosayan, Z., Remsik, A., Walton, L. M., Song, J., Nair, V. A., Grogan, S. W., Tyler, M. E., Edwards, D. F., Caldera, K., Sattin, J. A., Williams, J. C. and Prbhakaran, V. (2014). Changes in functional connectivity correlate with behavioral gains in stroke patients after therapy using a brain-computer interface device. *Front Neuroeng.;* 8;7:25.

Viale, L., Catoira, N. P., Di Girolamo, G. and Gonzalez, C. D. (2017). Pharmacotherapy and motor recovery after stroke. *Expert Review of Neurotherapeutics*; 10.1080/14737175.2018.1400910.

Vitrac, C. and Benoit-Marand, M. (2017). Monoaminergic Modulation of Motor Cortex Function. *Front. Neural Circuits*; 11:72.

Walker, F. R. (2013). A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: Do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression? *Neuropharmacology*; 67:304–317.

Wang, Z., Kai, L., Day, M., Yin, H. H., Ding, J., Tkatch, T., Lovinger, D. M. and Surmier, D. J. (2006). Dopaminergic control of corticostriatal long-term synaptic depression in medium spiny neurons is mediated by cholinergic interneurons. *Neuron*; 50:443Y52.

Wolf, W. A., Martin, J. L., Kartje, G. L. and Farrer, R. G. (2014). Evidence for fibroblast growth factor-2 as a mediator of amphetamine-enhanced motor improvement following stroke. *PloS one*.; 9(9):e108031.

World Health Organisation (1978). Cerebrovascular Disorders (Offset Publications). Geneva: *World Health Organization*. NO. 43.

World Health Organization: The top 10 causes of death. Available from: http://who.int/mediacentre/factsheets/fs310/en/.

Volkow, N. D., Wang, G., Fowler, J. S., Logan, J., Gerasimov, M., Maynard, L., Ding, Y., Gatley, S. J., Gifford, A. and Franceschi, D. (2001). Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *J Neurosci*, 21:1–5.

Wolpaw, J. (2003). Brain-Computer interfaces: signals, methods, and goals. *Proceeeding of 1st international IEEE EMBS conference on neural engineering*, vol 1, pp. 584-585.

Wolpaw, J. in Winter Wolpaw, E. (2012). Brain-computer interfaces: principles and practice. *Oxford University Press*.

Xiong, Z. G., Zhu, X. M., Chu, X. P., Minami, M., Hey, J., Wei, W. L., MacDonald, J. F., Wemmie, J. A., Price, M. A., Welsh, M. J. (2004). Neuroprotection in Ischemia: Blocking Calcium-Permeable Acid-Sensing Ion Channels. *Cell*; 118, 687–698.

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IZJAVA O AVTORSTVU MAGISTRSKEGA DELA

Spodaj podpisana Nensi Murovec, z vpisno številko 89142011, vpisana v študijski program Biopsihologija, 2. stopnja, sem avtorica magistrskega dela z naslovom:

Vmesniški sistem možgani – računalnik za funkcionalno motorično okrevanje po možganski kapi v povezavi z zdravili

S svojim podpisom zagotavljam, da je predloženo magistrsko delo izključno rezultat mojega lastnega dela. Prav tako se zavedam, da je predstavljanje tujih del kot mojih lastnih kaznivo po zakonu.

Soglašam z objavo elektronske verzije magistrskega dela v zbirki »Dela FAMNIT« ter zagotavljam, da je elektronska oblika magistrskega dela identična tiskani.

Nensi Murovec

Appendix

Subject information and informed consent to participate in the clinical trial

Stroke rehabilitation through feedback from a brain-computer interface and functional electrical stimulation

Dear participant!

We invite you to participate in this study. You will be informed about it in a detailed conversation.

Your participation in this clinical trial is voluntary. You can leave the study at any time without giving reasons. The refusal of participation or a premature departure from this study will not cause negative consequences for your medical examination.

Clinical trials are needed to provide new medical research results. However, an indispensable prerequisite for conducting a clinical trial is that you can agree in writing to your consent to participate in this clinical trial. Please read the following text as a supplement to briefing with your physiotherapist carefully and do not hesitate to ask questions.

Please sign the consent form only

- if you fully understand the nature and course of the clinical trial,
- if you agree to participate and
- if you are aware of your rights as a participant in this clinical trial.

1. What is the purpose of the clinical trial?

   The study title is "Stroke rehabilitation through feedback from a brain-computer interface and functional electrical stimulation". The system will collect and evaluate the data of your movement intention. For this purpose, standardized tests are carried out at certain time intervals (see below for details). The signal used by the rehabilitation system is the electroencephalogram (EEG), which is recorded by measuring the brain waves.
   Even if the muscles cannot receive nerve impulses during the presentation or attempted motor movement, one can detect activation of the brain area that controls the corresponding body region from the EEG. If, for example, a patient is presented with the task of moving his/her left hand, activation can again be detected in the EEG. Based on this detection, an electrical stimulation of your muscles begins to assist you with the movement. This simultaneous activation of your muscles with the brain areas results in

a better rehabilitation result than doing exercises alone. The purpose of this clinical study is to investigate rehabilitation success over several sessions.

2. How is the clinical trial going?

This clinical trial will be conducted by Guger Technologies OG and will involve approximately 25 people in total with 25 rehabilitation sessions.

The red dots mark each time points at which your sensorimotor and fine motor skills are tested to determine the effect of the therapy. The first assessment takes place today (time point 1), the second at time point 2. In about one month, the first therapy block begins. A therapy block lasts about 3 months and includes 25 sessions (time point 3). We will perform the aforementioned assessments again after five (time point 4) and 10 months (time point 5) to be able to record the long-term effect of the therapy.

<u>The following measures are carried out in one session:</u>

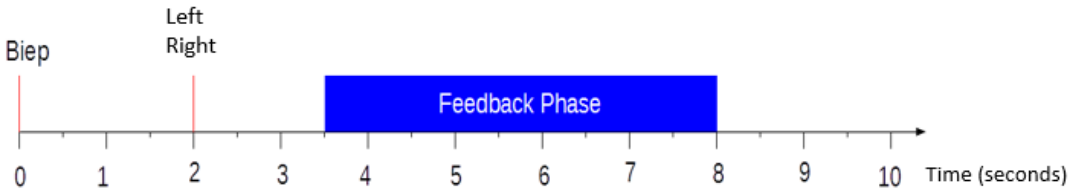
<u>BCI Feedback Training</u>

During each session of this clinical trial, the following experiment is performed over a period of one hour: Electrical stimulation electrodes are placed to both forearms. The therapist then slowly increases the electrical stimulation until your wrist moves up by itself.

The therapist then puts on the EEG cap and fills the EEG electrodes with gel to make contact with the scalp for signal transmission. The system gives feedback on the signal quality of the individual electrodes on the screen. When the training starts, imagine the movement that the system dictates with arrows on a monitor. The auditory instructions are also played via headphones: "left", "right", and "relax". If you hear "left" or "right", please imagine a movement of the corresponding hand, as soon as you hear the word "relax", end the performance. During exercise, the system measures your brain activity and gives two types of feedback when correctly imagined - visual feedback through an avatar and electrical stimulation of movement. The avatar executes the same movement as the stimulation on your hand.

There will be a total of 240 movements, with short breaks in between. The period per movement is 8 seconds. There is a break of 1 second between each movement. At the

end of a run, the system saves and evaluates the results. You are free to cancel the experiment at any time.



3. What is the benefit of participating in the clinical trial?

It has already been shown in previous studies that stroke rehabilitation with motor imagery alone can bring success. An improved effect through the addition of a brain-computer interface is being investigated among other things with the help of this study. An improvement in your condition may therefore be hoped, but never guaranteed, as always in medical studies. However, for medical science, this study provides insight into the power of this approach. This allows us to further improve our systems and thus contribute in the future to improving the quality of life of stroke patients.

4. Are there risks, complaints and side effects?

As far as known, there are no risks for the patients. The EEG acquisition is carried out with a certified biosignal amplifier, and the stimulation of the muscles also with a certified electrostimulator as medical device.
However, the following patients must be excluded from the study:
• Patients with existing or occurring pregnancy during the study period.
• Patients with active or passive implanted medical devices that counteract the use of functional electrical stimulation.
• Patients with implanted metallic fragments in the upper extremities.
• Patients with untreated epilepsy.
• Patients with increased intracranial pressure.
• Patients with pronounced hemi-neglect.
• Patients with a history of cerebral aneurysm.
• Patients under the influence of anesthetics or similar medication.
• Patients with cognitive impairment, so that the task is not understood.
• Patients who do not sufficiently understand the English instructions and patient information.
• Patients with fractures or upper limb lesions.
• Patients with severe lung disease, infections, kidney disease, liver damage and heart damage.

Patients with severe pusher syndrome.
• Patients with significant upper limb circulatory disorders.
• Patients who are unable to sit upright for at least 60 minutes without help.
• Patients with reduced sensitivity who are unable to perceive pain.
• Patients with peripheral nervous system disorders of the upper extremities.
• Individuals receiving botulinum toxin therapy during the active study period in the upper extremities for the treatment of spasms.

5. Additional intake of medicines?

NO

6. Does participation in the clinical trial have any other impact on lifestyle and what are the obligations?

NO

7. What to do if symptoms, side effects and / or injuries occur?

If any symptoms, side effects or injuries occur during the clinical trial, you must report them to a physician. In emergancy cases, the emergency service is notified.

8. When will the clinical trial be terminated prematurely?

You can revoke your willingness to participate at any time without stating any reasons and terminate an experiment prematurely at any time.

9. How are the data collected in this clinical trial used?

Unless otherwise stated by law, only employees have access to the confidential information that identifies you by identification number. These people are subject to confidentiality.

The transfer of data is solely for statistical purposes and you are invariably not mentioned by name. Also, you will not be named in any publications of the data of this clinical study.

To analyze your rehabilitation progress sometimes videos of your movements are made. However, on these recordings, you will be made unrecognizable, in order to prevent any association to you.

10. Are costs incurred for the participants? Is there a reimbursement or compensation?

By participating in this clinical trial, you will not incur any additional costs.

Participation in the study is voluntary. You will not receive any compensation for this reason.

11. Possibility to discuss further questions

For further questions related to this clinical trial, please contact your physical therapists or their colleagues. Questions that affect your rights as a patient and participant in this clinical trial will be answered.

Name of the contact person: _____
Always available at: _____ Email: _____@gtecus.com

Name of the contact person: _____
Always available at: _____ Email: _____@gtecus.com

Name of the contact person: _____
Always available at: _____ Email: _____@gtecus.com

12. Should other treating physicians be informed of participation in the clinical trial?

Participation in the study will not affect in any way ongoing treatment by a physician. It is therefore not mandatory that the doctor be informed about the study.

13. Consent

Name of patient in capital letters: ....
Date: ..... Code: ....

I declare my willingness to participate in the clinical trial "Stroke Rehabilitation via Feedback from a Brain-Computer Interface and Functional Electrical Stimulation".

I have been informed by Mr. XXXX or Mr. XXXX in detail and understood possible burdens and risks, as well as the nature, significance and scope of the clinical study, as well as the resulting requirements for me. I have also read the text of this test subject information and consent form, which comprises a total of 5 pages. Questions that were answered were understandable and sufficiently answered. I had plenty of time to decide. I have no further questions at the moment.

I will comply with the instructions required to conduct the clinical trial, but I reserve the right to terminate my voluntary participation at any time, without incurring any disadvantages for my further medical care.
At the same time, I agree to record my data collected during this clinical trial. In order to verify the accuracy of the data recording, authorized representatives of the contracting authority and the competent authorities may inspect the examiner's personal medical data.
When dealing with the data, the provisions of the Data Protection Act are observed.
I have received a copy of this patient information and consent form. The original remains with the examiner.

.....

(Date and signature of the patient)

.....

(Date, name and signature of the responsible examiner)

(The patient receives a signed copy of the patient information and consent form, the original remains in the study folder of the examiner / in.)