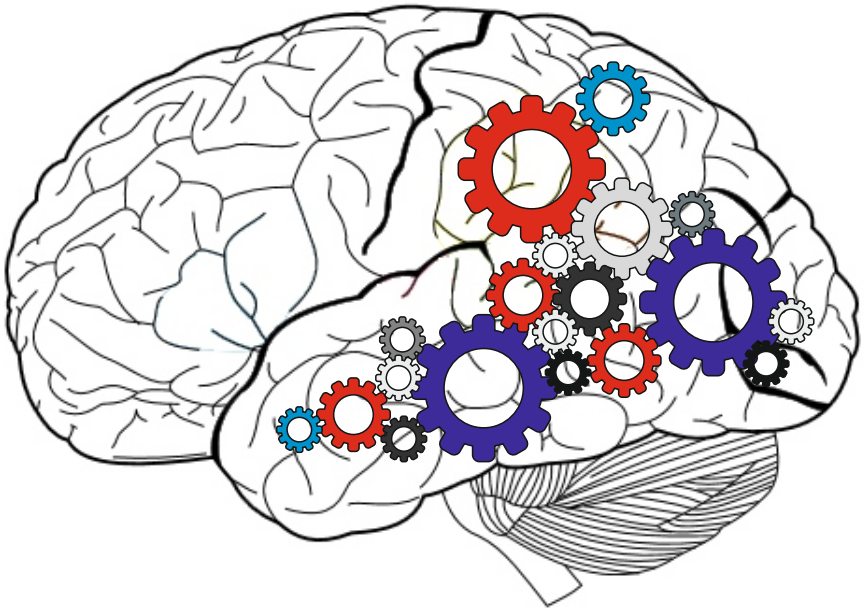
Brain Modulation by Event-Related Desynchronization (ERD) guided Neurofeedback

Toward a New Therapy in Acute Stroke



Chayanin Tangwiriyasakul

BRAIN MODULATION BY EVENT-RELATED DESYNCHRONIZATION (ERD) GUIDED NEUROFEEDBACK

TOWARD A NEW THERAPY IN ACUTE STROKE

CHAYANIN TANGWIRIYASAKUL

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BRAIN MODULATION BY EVENT-RELATED DESYNCHRONIZATION (ERD) GUIDED NEUROFEEDBACK

TOWARD A NEW THERAPY IN ACUTE STROKE

DISSERTATION

to obtain
the degree of doctor at the University of Twente,
on the authority of the rector magnificus,
Prof. dr. H. Brinksma
on account of the decision of the graduation committee,
to be publicly defended on
Thursday, 27th February 2014, at 14:45

by

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Contents

Lists of Abbreviations

AC	Active
ARAT	Action Research Arm Test
ANOVA	Analysis of variance
BCI	Brain-Computer Interface
BL	Baseline
BOLD	Blood Oxygen Level-Dependent
CIMT	Constraint-Induced Movement Therapy
CSP	Common Spatial Pattern
EEG	Electroencephalography
ERD	Event-related desynchronization
FES	Functional electrical stimulation
FM	Fugl-Meyer score
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric acid
IPL	Inferior parietal lobule
LDA	Linear Discriminant Analysis
LTD	Long-term Depression
LTP	Long-term Potentiation
M1	Motor Cortex
ME	Motor Execution
MEG	Magnetoencephalography
MEP	Motor Evoked Potentials
MI	Motor Imagery
MNS	Motor Neuron System
MST	Medisch Spectrum Twente
NF	Neurofeedback
NMDA	N-methyl-D-aspartate
PET	Positron Emission Topography
PFG	Posterior part of the inferior frontal cortex
PDS	Power Density Spectrum
SMR	Sensorimotor rhythm

Chapter 1 Introduction and Scope of the Thesis

1.1 Introduction to stroke

Stroke is one of the major causes of adult motor's disabilities; 800,000 strokes annually occur in the USA [1], in the Netherlands 30,000 stroke patients were reported [2]. Of the two types of stroke hemorrhagic and ischemic, ischemic stroke is found in about 80% of all cases reported [3]. In ischemic stroke, loss of brain function is caused by an occlusion of a blood vessel. Impairment of cerebral blood flow causes a reduction in delivery of important substances (e.g. oxygen, glucose) inducing energy failure at the cellular level, ultimately leading to neuronal death (infarction) [4, 5].

In stroke, three cerebral regions can be defined: the ischemic core, the penumbra and the oligaemic region. The ischemic core is the region with the most severe degree of hypoperfusion. (<5-8 ml$100g^{-1}min^{-1}$ [6, 7]) and all neurons in the ischemic core are beyond therapeutic rescue. Depletion of energy metabolites, the failure of the cell membrane to maintain its physiologic gradients, and water homoeostasis are typical phenomena found inside the ischemic core [6]. Located next to the ischemic core, the penumbra is moderately affected by the hypoperfusion (about 10-20 ml $100g^{-1}min^{-1}$ [6, 7]). In that region, the neuronal damage is potentially reversible [8, 9]. Some parts of the penumbra with perfusion of about 20 ml $100g^{-1}min^{-1}$ are sufficiently large to generate neuronal and electrical activity whereas in the parts, where perfusion is below 15 ml $100g^{-1}min^{-1}$, both neuronal and electrical activity are suppressed [10]. Finally, in the oligaemic tissue, the cerebral blood flow is above the penumbra threshold but below the normal level. Although this region is characterized by a mild degree of hypoperfusion (e.g. high oxygen extraction fraction observed in PET), neurons are not at risk of infarction. Current therapy in the oligaemic tissue is to prevent systematic hypotension and hyperglycaemia [11].

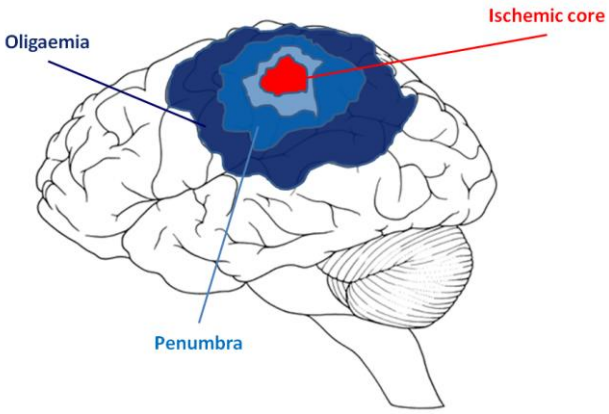

Figure 1: Illustration of the different brain region after stroke. The red area represents the ischemic core, in which the cerebral blood flow (CBF) is less than 10 ml 100g^{-1} min^{-1}. The light-to-middle blue areas represent the penumbra (CBF ≈ 10-20 ml 100g^{-1} min^{-1}). The dark blue part represents the oligaemic part (CBF ≈ 20-50 ml 100g^{-1} min^{-1}). Other non-affected areas are shown in white. This is an original figure drawn based on the idea of Murri et al. [12].

Infarct progression in the core region is divided into three phases. During the acute phase (within a few minutes after the ischemic onset), energy failure and terminal depolarization of cell membranes are observed in the ischemic core [4]. Excitotoxicity (which is normally observed during acute to subacute phases) is the process leading to damage of the nerve cell by excessive stimulation of neurotransmitters, starting shortly after the onset of ischemia [4, 13]. Shortage of energy supply and the release of K^+ and glutamate cause ischemic neurons and glia depolarization.

In the subacute phase (4-6 hours after ischemic onset), expansion of the infarct core into the penumbra (as associated with spreading depressions [14, 15]) is observed [4]. During the subacute phase, a mismatch between the increase of metabolic workload and the low-oxygen supply leads to transient hypoxia and increases in lactate during each depolarization.

Finally, during days or weeks after stroke onset, the delayed phase, further progression of injury causes various secondary phenomena such as edema, inflammation, and programmed cell death [4]. Figure 2 summarizes the sequence of the pathophysiological events during these three phases.

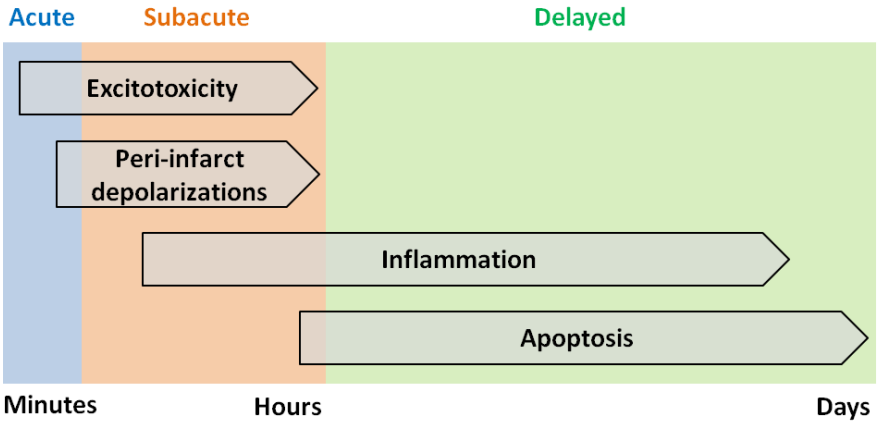

Figure 2: Diagram showing damaging events seen after focal cerebral ischemia. During the acute phase, glia cells and neurons are damaged due to excitotoxicity processes. After that during the subacute phase, expansion of damage to the peri-infarct area is observed. Later, various secondary phenomena (including edema, inflammation) occur (delayed phase).

1.2 Stroke recovery and rehabilitation

Motor recovery from stroke can be divided into true and compensational recovery [16]. Compensational recovery is seen in patients, who cannot use their affected body parts and compensate with other movement strategies [17]. Unlike compensational recovery, true recovery results from changes in the motor neuron systems (MNS) (e.g. axon sprouting, network reorganization) and can be further divided into (i) a short-term recovery and (ii) a long-term recovery [18, 19]. Although parts of the short-term and long-term recovery are overlapping, we classify all changes of the brain within one week after stroke as the short-term recovery. Importance is that the recovery seen in the first few weeks after stroke can be used as a predictor for the long-term recovery [16, 18].

Wieloch and Nikolich [20] suggested a sequence of three processes that occur during stroke recovery. First, surviving cells (especially in the penumbra or peri-infarct sites) are repaired; hence metabolism and neuronal functions recover. Second, axon and dendrite sprouting occurs. Finally, new

neural networks are established and consolidated by optimizing the surviving neurons (known as network re-learning). The first two recovery processes occur spontaneously during the short-term recovery period. After that, during the long-term recovery, parts of the second and the third processes occurs, and most of the available stroke therapies (e.g. constraint induced movement therapy, passive/active training) are aimed to promote these two.

1.2.1 Motor training to assist brain plasticity in stroke

The brain is a plastic organ, which has abilities to change its structures and/or functions in response to internal/external constraints and goals [21]. Dobkin et al. suggested that experience and training induces both physiological and morphological changes after stroke [22]. The physiological changes are axon or dendrite sprouting to (re)establish its corticocortical-or-corticospinal connections [18, 23]. Similar changes can be seen while acquiring a new motor skill in healthy persons; thus, recovery from stroke is considered as learning to acquire new motor skills. This suggestion was later confirmed by Dipietro et al. [24].

During the early phase (hours to days) of acquiring the new motor skill in healthy persons, an increase of spine density is observed in the layer II/III of the pyramidal neurons [25]. The magnitude of spine formation in this phase was correlated with learning efficacy. Next, during the skill maintenance phase (5-16 days), the spine density reduces to baseline level. Later, long-term changes of synaptic efficacy (e.g. LTP, LTD) are found. At cortical level, enlargement and retraction of cortical representations of a trained organ (e.g. hand practice caused changes in the precentral gyrus) during one-to-four weeks after training were reported [26, 27].

During recovery from stroke, changes of cortical micro-circuitry are also observed, especially at the peri-infarct location. The neurons in the peri-infarct sites are more excitable due to the upregulation of NMDA [28] and the downregulation of GABAa [29]. This causes an increase of dendritic tip and axonal sprouting [30]. Apart from the changes at the peri-infarct location, the post-lesion reorganization is also found in the secondary motor cortex area of the ipsilesional hemisphere or in the primary motor cortex of the contralesional hemisphere.

The presumed way motor (re)learning works in stroke recovery is to activate the intact neurons next to the infarct site, or in the secondary motor cortex area through training [18]. Nowak and Hermsdörfer [31] simplified the physiological changes in CNS during motor (re)learning using a diagram (see Figure 3). In this diagram, the central motor drive system is divided into three levels: the upper motor level (primary motor cortex M1 labeled as *A* in the diagram), the lower motor level (spinal motor neurons labeled as *A'*) and the hand-motor axonal level (labeled as *1* in the diagram) [31]. After stroke, part of M1 is affected (shaded in red color); training can induce changes by letting the spared region of M1 (*B* in the diagram) take over the lost function. We can assist this motor (re)learning process through physical practice, but also by mental imagination of the motor action. The latter way is an important aspect of this thesis and will be introduced in the next paragraphs.

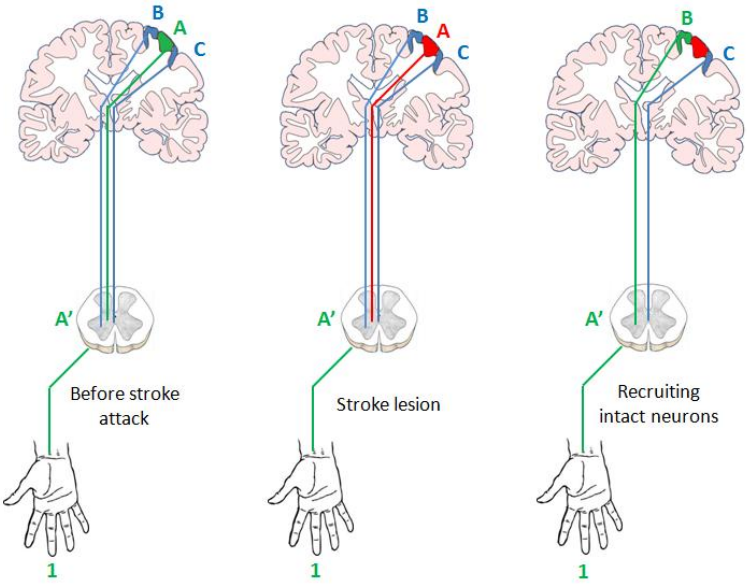

Figure 3: Diagram showing the organization of the central neuron system (CNS) and its post-lesion reorganization. Establishing (new) corticospinal-or-corticocortical connections is a possibility through training. Before stroke insult, the hand (1) is controlled by the motor cortex area (A) through A-to-A'-to-1 connection (green color). After the loss of neurons on the hand motor cortex area (A) due to stroke, the non-affected neurons in area B will take over and strengthen a new corticospinal connection between B-to-A'. This is an original figure constructed based on the idea of Nowak and Hermsdörfer [31].

1.2.2 Mirror neurons, motor observation and motor imagery

Mirror neurons were first discovered by Rizzalatti [32, 33]. They fire either when an individual performs a movement or observes another individual performing the same movement [34].

The mirror neuron system and motor system are largely overlapping. However, the mirror neuron system is more involved in action -preparation/-understanding than the motor neuron system. During motor imagery a stronger activation was seen on the premotor cortex area (which is responsible for movement preparation and movement's goal) than during motor execution; on the other hand, during motor execution stronger motor cortex activation was seen [35].

Mirror neurons are found on the posterior part of the inferior frontal cortex (PFG) and the anterior part of the inferior parietal lobule (IPL) [32, 36]. Anatomical connections between these two areas are found [37], together they form an integrated frontoparietal mirror neuron system (MNS). In experiments in monkey, mirror neurons fired when the monkey grasped for food (motor execution) and also when the monkey observed the experimenter grasping for food (motor observation). Later, Umita et al. showed that mirror neurons also fired during motor imagery [38]. Taken these two together, the motor observation- and motor imagery- system are considered as the subsets of the mirror neuron system. Moreover, the mirror neuron is suggested to play a vital role in motor understanding which is the first step of motor acquisition [34]: after familiarization to a motor act, the mirror neurons fire when hearing an audio cue or during an occluded movement scene of that act [38, 39].

In man, the existence of the mirror neurons was found in TMS studies [40], in which a stimulating single pulse was delivered to the motor cortex while subjects were instructed to just observe an experimenter performing a hand movement. The results showed an increased MEP amplitude recorded from the same muscles normally recruited as the observer performed the similar action by him-/herself. Later, using MEG/EEG as measure, the suppression of the sensorimotor rhythm (SMR) during motor observation/imagery was reported [41, 42].

Although the mirror neurons are activated both during motor imagery and motor observation, there are key differences. Motor imagery originates from an internal stimulus to make recalls from the long-term memory, while motor observation is driven by external stimuli [43, 44]. Therefore motor imagery is a top-down process driven by the subject's memory, while motor observation is a bottom-up process driven by the external stimulus. Several studies suggested that both motor -imagery and -observation training enhance brain plasticity; but it is unclear which one is more effective. In this study, a combination task of both motor imagery and motor observation will be used.

During performing motor imagery/execution/observation, brain circuits are activated. This increases excitability of surviving neurons inducing cortical plasticity [45, 46]. Furthermore, activation also increases excitability of corticospinal pathways [47, 48], which is another essential factor for stroke recovery [49]. Cininelli et al. showed that motor imagery induces enhanced cortical excitability of the affected hemisphere [47]. At the cortical level, changes are also observed using both fMRI and EEG [50-53]. Interestingly, changes at the cortical level are only observed during acquisition of new motor skills, whereas power training of the known skills induces changes at the spinal cord level [54].

Finally, assisting motor (re)learning through imagery training may be exclusive only for patients with intact premotor cortex and (partly) spared motor cortex. This is because these two areas are required to perform motor imagery and play a vital role in motor learning [55, 56].

1.3 EEG and Neurofeedback

1.3.1 Survey of motor imagery therapy

A variety of therapies to enhance recovery from stroke is available such as constraint induced movement therapy, strength training, active/passive movement training, and motor imagery training. Among these, we focused on motor imagery (MI) training. Over the past decade, several research groups have investigated potential benefits of MI training. For example, Page et al. investigated two groups of chronic stroke patients [57]. Subjects

in group 2 received additional motor imagery training, whereas subjects in group 1 received a sham intervention. The patients in group 2 showed an increase of the Fugl-Meyer score (FM), while no change of this score was found in group 1. The positive clinical impact of MI training was also found in other studies [58-67].

In the early MI studies, patients only received an instruction to observe-or-imagine, without feedback indicating their MI performance given. In the later studies, Brain Computer Interface (BCI) technology included feedback of MI performance was used. The use of BCI technology aims to improve-or-maintain (good) MI performance during training. Here, we reviewed thirteen selected studies and classified them into groups according to the type of feedback modality and the patient's condition (acute or chronic), see Figure 4. In Figure 4, we show that most of these studies show gains after receiving motor imagery training except two studies (two red circles, Ietswaart et al. [68] and Cowles et al. [69]). Interestingly, both studies were conducted in acute-to-subacute stroke patients with no-feedback given. Two factors that may hinder the successfulness of MI therapy in these two studies are (i) a reduced of MI ability in acute stroke [70], and (ii) a lack of patients' perseverance to perform effective MI throughout the whole training period [71].

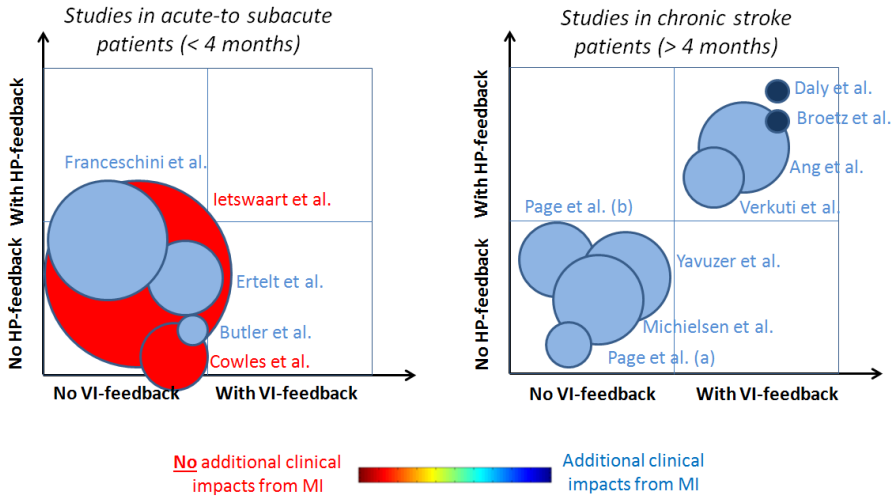

Figure 4: Clinical studies of motor imagery therapy since 2000. Each circle represents a study, the size represents the number of subjects, the color indicates the clinical impact (blue = positive impact; red = no impact). HP and VI stand for haptic and visual feedback, respectively. The diagram is divided into four blocks: without feedback (bottom-left), with visual feedback (bottom-right), with physical feedback (top-left), with combined feedbacks (top-right). Details of each study are given in Table A1 in Appendix-1.

Among the different feedback modalities (e.g. visual, haptic, or a combination of both) implemented in Brain Computer Interface (BCI) systems, there was no clear advantage using any kind of these modalities [72]. Reinkensmeyer suggested that "the benefits of the robotic therapy device (haptic) may be related to providing motivating, quantifiable, and economic delivery of training rather than a specific enhancement of plasticity attributable to robotic forces" [73]. This points to the role of attention and seems to downgrade the necessity of the haptic feedback in stroke therapy, if (and only if) the visual feedback alone can motivate and keep patient's attention to effectively perform motor imagery. In this thesis, a visual feedback based NF-system was chosen because of its cost advantage and ease of implementation for use in a home environment.

1.3.2 Event-Related Desynchronization (ERD)

The electrical activity measured by the EEG represents postsynaptic potentials (local field potentials) from excitatory and inhibitory inputs to

pyramidal neurons [74, 75]. During execution or imagination of a movement suppression of EEG rhythms over the sensorimotor area can be observed, mainly in two frequency bands: alpha (or mu, 8-13 Hz) and beta (15-25 Hz) [42]. Since the alpha rhythm is commonly found over various brain areas during rest, the term mu is used to specify rhythmic activity in this band over the motor cortex area.

Pfurtscheller and Lopes da Silva suggested that ERD is generated by changes of parameters that control oscillations in neuronal networks [42]. These parameters could include intrinsic membrane properties of the neurons, or the strength and extent of interconnections between the network elements formed by either thalamo-cortical or cortico-cortical loops. Decrease of amplitude of SMRs during motor imagery/movement is concurrent with the increase of cellular excitability in the thalamo-cortical loop [76]. It was suggested in Sterade-and-Llinás's study that "the desynchronization of EEG represents the condition when the high amplitude of slow synchronized EEG oscillations are replaced by the low amplitude of fast rhythms" [76]. ERD is suggested to be a biomarker to detect neuronal group activity [77, 78].

1.3.3 ERD in stroke patients

Shortly after stroke, neurons are deprived from oxygen and blood flow causing absence-or-decrease of electrical activity recorded over the ischemic core [45]. Relatively high frequencies of the EEG are suppressed, while the slow frequencies (e.g. delta) remain over the lesion site/hemisphere [79]. During recovery, shift toward the normal EEG spectrum is usually seen [79-82]. In the penumbra area, where the blood-and-oxygen supply is still sufficient in a large portion of neurons to generate synaptic transmission, a normal EEG spectrum is observed [10].

Absent-or-reduced ERD was found on the central M1 electrode (C3 or C4) of the affected hemisphere compared to the healthy hemisphere [83]. This finding was later confirmed by Stępién et al. [84]. Although the reappearance of ERD over the affected hemisphere during recovery is expected, to our knowledge this phenomenon has not yet been reported.

1.4 Conclusions

Stroke is an important cause of adult's disability, and many patients have significant motor deficits. Effective therapies for stroke rehabilitation improve motor function and are considered as a form of motor (re)learning associated with various neuronal processes like axonal or dendrite sprouting and changes in synaptic connectivity [22].

Repetitive physical training is an effective method to promote this process; however, too intense physical training leads to fatigue and demotivates stroke patients. Motor imaginary training is an alternative. Like performing movement, parts of the motor neurons assembly are activated during imagining movement, providing an opportunity to access the motor system and assist in brain plasticity and learning [47, 85]. Apart from receiving effective rehabilitation, timing is another essential factor behind stroke recovery. Because the recovery during the acute phase determines most of the final outcome, early therapy is suggested to maximize outcome after recovery. However, in the acute phase, the ability to perform movements may be limited or absent, even in patients with residual movement ability, as most of them get easily tired. For these patients, a combination of motor imagery and physical training or solely motor imagery training is recommended. In chronic stroke patients clinical gains from MI therapy were reported, but whether MI therapy could assist stroke recovery in acute patients or not is still unclear [71]. A reduced MI ability in acute stroke is assumed to be a major obstacle influencing the efficacy of MI training. Therefore, BCI-feedback technology, in which the patient can observe his/her live performance, may assist to learn to improve MI performance and subsequently assist motor recovery. In this study, the BCI system for stroke rehabilitation is called neurofeedback system.

1.5 Aim and scope of this thesis

In this thesis, we were mainly interested to answer the following questions:

- How can we measure MI performance?
- How do EEG related measures, like ERD, develop in recovering stroke patients?
- How to implement a BCI-neurofeedback system in a user-friendly fashion?
- Does motor training with the MI-neurofeedback system lead to faster motor learning?

To assess MI performance, the ERD measure is a good candidate measure. However, as ERD is a ratio, it depends on baseline power: without a stable and high baseline power its credibility decreases. Baseline power is maximized when a subject is relaxed and does not perform-or-imagine any movement. In chapter 2, we explored the possibility of using different visual stimuli to maximize the baseline power.

Apart from performing good MI throughout training, ERD-based feedback information in a neurofeedback system should guide stroke patients to produce the desired brain activity that could promote stroke recovery [86]. Therefore, in chapter 3, we first investigated the natural evolution of ERD during recovery without feedback, aiming to find its common trend in recovering patients.

For user-friendliness and ease of implementation in a home environment, the number of EEG channels should be minimized. However, classification performance and number of channels are the trade-off parameters. In chapter 4, we studied different classification techniques and different channel configurations to find the most robust classification method, i.e. sufficient performance accuracy with a minimal number of electrodes.

Finally, in chapter 5 we investigated whether one could learn to improve his/her MI-and-physical performance upon including neurofeedback in the training. Since similar changes of the brain are observed in stroke patients during recovery as in healthy subjects during acquiring a new motor skill, we

performed an investigation in normal subjects to learn new tasks, to mimic stroke patient's progress in relearning everyday tasks by experiments. For this, healthy control subjects were trained to improve their left (non-dominant, unskilled) hand writing guided by the EEG-ERD-neurofeedback in a BCI system.

Appendix-1

Table A1: A summary of studies that investigated the clinical impacts of motor imagery therapy.

Study	Study population	Type of stroke (time after stroke onset)	Methods	Feedback		Conclusion
				V	H	
Ietswaart [64]	MI=41/Pla=39 /C=41 (Multicenters)	Subcortical (3 months)	4 weeks of training (3 times per week) 3 groups were formed. Group1 (C, control): No addition training Group2 (Pla, Placebo): Additional 45 min of non-motor imagery rehearsal Group3 (MI, motor imagery): Additional 45 mins of motor imagery rehearsal	WO	WO	24% ARAT increase after training in all groups. No additional gain from motor- imagery was observed.
Page et al.(a) [87]	MI=10	Chronic stroke with moderate deficits (36.7 months)	10 weeks of training (3 times per week) 30 minutes of mental practice was done per session.	WO	WO	17% ARAT increased.
Daly et al. [61]	Case study	A chronic stroke patient (10 month after stroke) Isolated digit extension disable	BCI+FES intervention during 3 weeks training (3 times per week) FES : functional electrical stimulation.	W	W	The subject gain volitional isolated finger extension.

Table A1 (continued): A summary of studies that investigated the clinical impacts of motor imagery therapy.

Study	Study population	Type of stroke (time after stroke onset)	Methods	Feedback		Conclusion
				V	H	
Michielsen et al. [59]	MO=20/C=20	Chronic stroke FMA = 38.5 (3.9 years)	6 Weeks training (5 sessions per week, 1hr per session) Group1 (C, control): Only bimanual training Group2 (MO, motor observation): Bimanual training + observing mirror reflection of the unaffected hand	WO	WO	10% increase of FMA was seen only in group2 (MO). No change of FMA in group1 (C) was observed.
Yavuzer et al. [60]	MO=20/C=20	Chronic stroke (5.5 months)	4 weeks of training (5 sessions per day, 2-5 hrs per day) Mirror therapy was done in the MO-group	WO	WO	Higher improvement in Brunnstrom-and-FIM score was seen in the MO-group.
Cowles et al. [69]	OTI=13/C=9	Acute-to-subacute stroke (2.5 weeks) ARAT = 13.8	15 working days (extra 30 mins OTI) Group 1 (C): Only standard physical practice Group 2 (OTI): Standard physical practice + 30 mins of observation to imitate (OTI)	WO	WO	Significant improvement was found in two groups. Same improvement in both groups.

Table A1 (continued): A summary of studies that investigated the clinical impacts of motor imagery therapy.

Study	Study population	Type of stroke (time after stroke onset)	Methods	Feedback		Conclusion
				V	H	
Ang et al. [62]	BCI=8/ Robot=10	Chronic stroke (1 year) FM = 29.7	4 weeks of training (3 session per week) Group 1 (Robot): Passive movement training Group 2 (BCI): Motor imagery training	W	W	Higher gain (20%) was found in group 2 than in group 1 (13.4%), but not significant.
Broetz et al. [63]	Case study	Chronic stroke (1 year) Hemispheric stroke	3 training blocks (2 week training per block) throughout 10 months	W	W	Significant motor improvement was observed.
Page et al. (b) [57]	MI=15/SH=15	Chronic stroke (3.6 years) FM = 33.03 (for MI) FM = 35.75 (for SH)	6 week training (2days per week), 30 mins per session Group 1(MI): physical practice+motor imagery Group 2 (SH): physical practice+sham	WO	WO	Higher gain (20%) was found in group 1 (MI) than in group 2 (3%).
Ertelt et al. [64]	MI=8/C=8	Subacute (3.9 months)	4 week training Group 1 (MI): physical practice + action observation Group 2 (C): physical practice	WO	WO	Positive additional improvement was found in group1.

Table A1 (continued): A summary of studies that investigated the clinical impacts of motor imagery therapy.

Study	Study population	Type of stroke (time after stroke onset)	Methods	Feedback		Conclusion
				V	H	
Verkuti et al. [65]	BCI=6/ Robot=3	Chronic stroke (6.5 months for Robot) (11.67 months for BCI) FM = 17.67 (for BCI), FM= 14.67 (for Robot)	4 week trraining Group 1 (Robot): Passive movement by robot. Group 2 (BCI): Motor imagery based robot.	W	W	FM gain was higher in group 2 (BCI)
Franceschini et al. [66]	MI=40/C=39	Acute-to-subacute stroke (30 days)	4 week training (5 session per week) Group 1 (MI): physical practice + Motor imagery Group 2 (C): physical practice + sham observation	WO	WO	Significantly higher gain was found in group 1 than in group 2.

Table A1 (continued): A summary of studies that investigated the clinical impacts of motor imagery therapy.

Study	Study population	Type of stroke (time after stroke onset)	Methods	Feedback		Conclusion
				V	H	
Butler et al. [67]	Combi=2/MP=1/ PP=1	Moderate upper limb hemi-paresis (3-4 months)	2 weeks of training Group 1 (Combi): Mental practice + CIMT Group 2 (MP): Only mental practice Group 3 (PP): Only CIMT CIMT : Constraint Induced-Movement Therapy.	WO	WO	Combination of mental practice and CIMT resulted in higher motor-improvement than mental or CIMT only.

Note that: V and H denote visual and haptic feedback, respectively. W and WO denote with and without feedback modality (as indicated on the top of each column), respectively.

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Chapter 1

Chapter 2 Importance of Baseline in Event-Related Desynchronization during a Combination Task of Motor Imagery and Motor Observation

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Abstract

Objective: Event Related Desynchronization (ERD) or synchronization (ERS) refers to the modulation of any EEG rhythm in response to a particular event. It is typically quantified as the ratio between a baseline and a task condition ("the event"). Here, we focused on the sensorimotor mu rhythm. We explored the effects of different baselines on mu-power and ERD of the mu rhythm during a motor imagery task.

Methods: Eighteen healthy subjects performed motor imagery tasks while EEGs were recorded. Five different baseline movies were shown. For the imagery task a right hand opening/closing movie was shown. Power and ERD of the mu-rhythm recorded over C3 and C4 for the different baselines were estimated.

Results: 50% of the subjects showed relatively high mu-power for specific baselines only, and ERDs of these subjects were strongly dependent on the baseline used. In 17% of the subjects no preference was found. Contralateral ERD of the mu-rhythm was found in about 67% of the healthy volunteers, with a significant baseline preference in about 75% of that subgroup.

Significance: The sensorimotor ERD quantifies activity of the brain during motor imagery tasks. Selection of the optimal baseline increases ERD.

2.1 Introduction

Event Related Desynchronization (ERD) or synchronization (ERS) refers to the modulation of any EEG rhythm in response to a particular event. ERD was discovered by Gastaut and Bert in 1954, who described the attenuation of the alpha rhythm in adults watching movements (boxing) in films [1]. Pfurtscheller introduced ERD to explain the phenomenon of mu-power decrease, from high mu-power during rest to lower mu-power during movement execution and motor imagery [2, 3, 4]. Motor imagery based ERD may serve as a control signal in Brain Computer Interface (BCI) applications, ranging from communication in locked-in patients to neurofeedback therapy [5, 6]. In 1999, Pfurtscheller and da Silva proposed to quantify ERD/ERS in this context as the percentage change of EEG-mu-band power between the relaxed condition (baseline) and the motor imagery or execution condition [7]. Here, we define "baseline" as a particular condition that maximizes the mu power throughout its duration. ERD/ERS can be observed at particular frequencies, only, e.g. beta or gamma band frequencies. In this study we focus on mu-band-ERD/ERS, which is frequently observed during motor imagery.

Being a ratio, ERD or ERS measures depend on the magnitude and stationarity of the EEG signal in the baseline durations. When baseline power is absent the ERD measure loses its significance. Most previous studies focused on the mu power suppression during motor imagery. For example Manganotti et al. found a suppressive effect of task complexity [8]. Neuper et al. reported the suppressive effect of four different motor imagery tasks (i) kinesthetic motor imagery (MIK), (ii) visual motor imagery (MIV), (iii) motor execution (ME), and (iv) observation of movement (OOM) [9]. Their results showed that BCI classification accuracies were highest for ME and OOM. Orgs et al. [10] and Del Percio et al. [11] described the role of experience on mu attenuation for specific motor imagery tasks between professionals and amateurs. For instance, professional dancers showed larger mu power decreases than non-professional dancers in dance movement, and lower ERD was found for elite karate athletes than for non-athletes.

However, little attention has been paid to the baseline duration. Recently, Blankertz et al. [12] showed the importance of the sensorimotor rhythm

during baseline conditions as a key factor to predict the accuracy of an ERD based BCI. In that study, the power of sensory motor rhythms during the baseline duration (relaxed state, eyes open) was measured in 80 subjects. It was found that the power was directly proportional to the BCI accuracy: strong sensory motor rhythms (high mu-power) yielded high BCI accuracy. Because mu-power reaches its maximum during relaxed and motionless conditions, most of the previous studies suggested and implemented static baseline images, e.g. a static cross or a black screen [10, 12, 13, 14, 15].

In this study, we explored if baseline mu power could be maximized (or even just induced) by using various baseline movies (equivalent to five baseline conditions), ranging from static to dynamic. In addition, we quantified the associated ERD.

2.2 Methods

2.2.1 Subjects

All subjects were healthy young students or faculty members (all right handed subjects with 10 male and 8 female) with no neurological diseases and normal or corrected-to-normal vision (mean age 25.1 years, S.D. = 4.5). Each subject was informed about the experimental procedure and signed a written consent form.

2.2.2 EEG recording

EEGs were recorded using a 60 channel EEG amplifier (TMS-international, The Netherlands) with hardware low-pass cutoff frequency at 1350 Hz and Ag/AgCl electrodes positioned according to the international 5-10 system. The sampling frequency was set to 5000 Hz. All electrode impedances were kept below 5 kOhm. The ground electrode was attached to the nose of each subject. The left and right mastoids (“similar to linked ears”) were used as a reference. All data were stored to disk for further analysis.

2.2.3 Experimental design and procedure

Subjects observed six movies: one showing an opening/closing hand (H; motor imagery state, MI, duration 8 s) and five different baseline movies (relax/reference state, durations 10 s). During the motor imagery condition, subjects were asked to observe and imagine the hand motion with their right hand, and synchronize their imagery with the five hand closing/opening motions presented in this interval. The five hand motions filled up the 8 seconds without static intermissions.

During the five baseline movies, subjects were asked to relax but focus on the visual input. The five different baseline movies were: (1) a single bouncing ball (BB), (2) two moving balls (2B), (3) a slowly moving flower (FL), (4) a static right hand (SH), and (5) white stripes on a black screen (BW). In the BB movie, subjects observed one ball bouncing randomly all over the screen. In the 2B movie, subjects observed two balls hitting each other and moving only in the central part of the screen. In the FL movie, subjects observed slowly moving pink flowers against a panoramic background of sky and mountains. In the SH movie, subjects observed a static right hand on a black screen. In the last baseline movie, BW, subjects observed horizontal and vertical white stripes on a black screen. These five baselines can be classified in terms of movement as: (1) a static group (SH and BW), (2) a mildly- or quasi-static group (FL), and (3) a dynamic group (BB and 2B). ERD and baseline power of all different combinations of baseline and hand movies were studied, i.e. SH-H, BW-H, FL-H, BB-H, and 2B-H.

Each measurement consisted of fifteen runs; at each run, the subject watched five baseline movies and five (identical) opening/closing hand movies. Each time a baseline (or hand) movie was shown, it was counted as one trial. In two subjects (H110, H111), only 14 runs were repeated due to a technical problem. The order of five baselines was randomly presented throughout the experiment. An example is shown in figure 1. Throughout the measurement, subjects sat in a comfortable chair and were asked to sit still and minimize eye blinking. The screen was located 1.2 meter in front. To minimize environmental disturbances, all experiments were carried out in a shielded room. Light was turned off during measurements to keep subjects' attention

to the screen. Six out of eighteen subjects were asked to come back for a second measurement, which consisted of seven runs. The second measurement was carried out between two weeks to six months later depending on the subject's schedules (average 4.33 months (SD=2.07 months)). Statistical analysis was limited to the C3 and C4 electrode position. For illustrative purposes, ERDtopoplots are shown, as well.

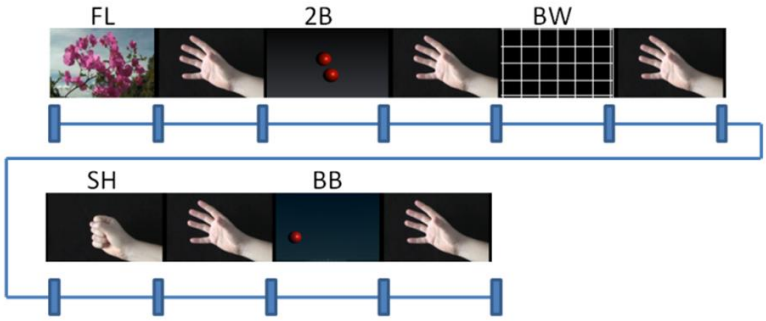

Figure 1: Time course of a typical run showing five different baseline movies (each 10 s in duration) and the five identical hand movies (with a duration of 8 s). Baselines are 'flower', 'two balls', 'white stripes on black screen', 'static right hand', and 'single bouncing ball'. Each baseline movie is regarded as a reference or idle state. Subjects were asked to relax but focus on the visual input. During display of the hand movies subjects were asked to observe and imagine (MI) the opening/closing hand.

2.2.4 Baseline Power and stationarity

All EEG signals were digitally down sampled to 500 Hz and spatially filtered using a large Laplacian reference, which is a modified version of the method proposed by Hjorth [16, 17]. Subsequently, all data were filtered between 0.5 - 30 Hz using a 4^{th} order Butterworth filter. To prevent any transition effects from the previous active trial, every first second of all baseline trials was excluded from analysis. Furthermore, to avoid possible fatigue effects, every last second of all hand moving trials was also excluded. Each baseline (or each hand) duration was partitioned into 9 (or 7) non overlapping one second (500 samples) segments. The mu-power of each segment was estimated using Welch's method with a non-overlapping window length of 500 samples (1 sec), integrating between lower and upper

mu frequencies (8-13Hz) obtained from the power density spectrum (PDS) using

$$Mu_{k,ch}^{i,j} = \int_{f=8\ Hz}^{f=13\ Hz} X(f)\, df, \qquad (1)$$

where $Mu_{k,ch}^{i,j}$ denotes the mu-power of the i^{th} trial at the k^{th} segment in channel *ch* of baseline type j = BB, FL, SH, 2B, and BW, respectively. $X(f)$ denotes the Fourier component at frequency f.

To ensure (weak) stationarity of the recorded EEG signals over fifteen trials of each baseline condition, outlier analysis was performed. To this end, the average mu power, ($\overline{Mu}_{ch}^{i,j}$), was computed from a total of nine mu-power segments for each trial according to

$$\overline{Mu}_{ch}^{i,j} = \frac{\sum_{k=1}^{k=\max(k)} Mu_{k,ch}^{i,j}}{\max(k)} \ . \qquad (2)$$

Note that *"i", "j", "k"* and *"ch"* in Eq.(2) are similar to Eq.(1). Hereafter, the grand averaged mu power and its standard deviation were computed from the fifteen averaged mu powers. We rejected any trial where the average mu power exceeded two times the standard deviation of the grand average mu power. This step was repeated for all five baseline and all hand movies. Note that if any baseline (or hand movie) trial was considered as outlier, we deleted that trial together with its subsequent hand movie trial (or its previous baseline trial).

Several researchers [18, 19] showed that the mu power attenuation was mainly observed on the hemisphere contralateral to the hand of which the movement was imagined. However, some studies [20, 21] also reported bilateral modulations during motor imagery tasks. Therefore, in this study we investigated both C3 and C4.

2.2.5 Computation of ERD/ERS

The mu-ERD/ERS was computed according to [7]

$$ERD\ or\ ERS = \frac{P_{MI} - P_{BL}}{P_{BL}} \times 100, \qquad (3)$$

where P_{MI} denotes the mu-power during the motor imagery (opening/closing hand movie) and P_{BL} denotes mu-power during the baseline. P_{MI} (or P_{BL}) of each channel was the grand averaged mu power (see Equation 1) of the remaining trials.

2.2.6 Statistical analysis

Significance levels were calculated at C3 and C4, only. Welch's ANOVA and Dunnett's T3 post-hoc test were used to test for significant differences among average mu-power of five baselines (or five hand movies) both for single subjects and at group level. Note that the Welch's ANOVA and Dunnett's T3 post-hoc were employed instead of One-Way ANOVA and Tukey post-hoc, since the variances of mu-power in each baseline condition were unequal (see section 2.3.3).

At the single subject level, the 15 trials (or less, depending on how many outlier trials were removed) were divided in one second long segments and assembled as one long 105-135 second long time series. Note that 105 (or 135) seconds resulted from multiplying 7 (or 9) segments with 15 trials. For this series, we computed the mu-power of each segment. First, to classify subjects into groups, we employed a t-test to compare differences between baseline mu-power vs. hand movie mu-power. In any subject, if the mu-power of any baseline was significantly higher than that of the hand movie, we considered that subject as a member of the mu-suppressive group. If not, the average PDS in each baseline was visually inspected; the subject was considered as a member of the non-suppressive group (if a distinctive peak in mu-rhythm was found), or a member of the mu-absent group (otherwise). This resulted in three distinct groups. All members of the mu-absent group were rejected from any further analysis.

Second, to check the distribution of mu-power in each baseline, we first performed a homogeneity test to evaluate if variances for different baselines were similar. Subsequently, we employed Welch's ANOVA and Dunnett's T3 post-hoc test using SPSS to test for significant differences among the average mu-power of five baselines (or five hand movies); each baseline consisted of 105-135 mu-power segments. The significance levels were set at 0.05. Similar procedures were repeated for the analysis of five hand movies.

At the group level, only the non-suppressive and the mu-suppressive group were analyzed. At each group level, mu-powers of similar baseline from all group members were arranged into a single class regardless of their subject origins. Each class consisted of ≈ 1260–1620 segment mu-powers (for the mu-suppressive group or ≈ 210–270 for the non-suppressive group). Note that 1260 (or 1620) resulted from multiplying 105 (or 135) segments with 12 (the number of members in group 3). Similar to the single subject level, Welch's ANOVA and Dunnett's T3 were employed. The same procedures were also repeated for the five hand movies.

2.3 Results

2.3.1 Outlier percentage and stationarity

Outlier analysis resulted in an average of 1.4 (S.D=0.7) rejected trials (9.3%). For the remaining trials, mu-power was (weakly) stationary at the group level in group 1 and group 3 subjects (a total of 14 subjects), using 6 to 7 trials or more, as shown in figures 2 (FL condition). A similar trend was also observed for other baselines and hand movies.

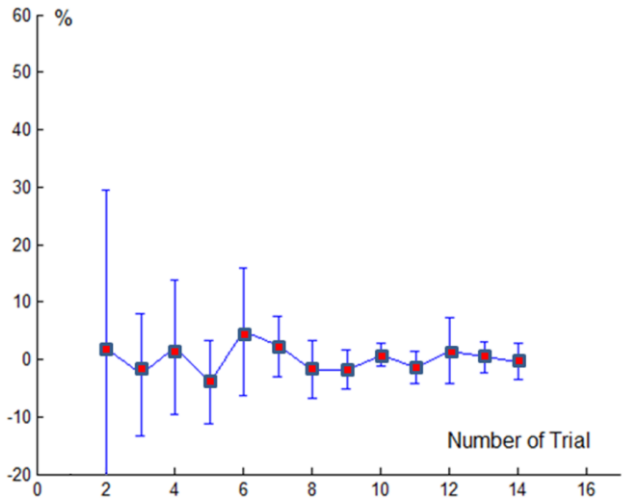

Figure 2: Progressive changes in mu-power as a function of increasing number of trials, averaged over all 14 subjects (all trials were selected randomly). The mu-power becomes (weakly) stationary after 6 to 7 trials. Square symbols indicate the mean, error bars indicate the standard deviation, averaged over 14 subjects. The progressive change in mu-power ($Mu_{avg,k}$) was computed according to: $Mu_{avg,k} = \left(\sum_{i=1}^{14} \frac{|Mu_{i,k} - Mu_{i,k-1}|}{Mu_{i,k}} \times 100\right)/14$ *where* $Mu_{i,k}$ *is the mu-power of subject "i"computed from "k" trials; k is running from 2 to 14.*

2.3.2 Baseline Power

Subjects were classified in three groups according to their baseline power: (1) subjects who could not suppress their mu-rhythm during the motor imagery trials in all five baseline conditions (non-suppressive mu group), (2) subjects who did not show any mu-rhythm for all five baseline conditions (mu-absent group) and (3) subjects with significant mu-suppression in at least one of the five baseline conditions (mu-suppression group). The three groups represent about 11% (2/18), 22% (4/18), and 67% (12/18) of the study population, respectively. Figure 3 shows an example of each group.

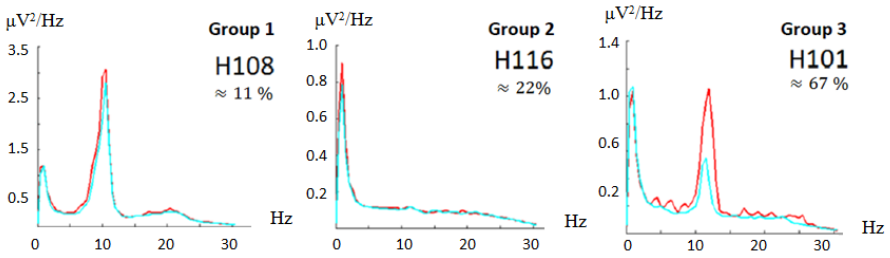

Figure 3: Three representative examples (H108, H116 and H101), of the grand averaged power density spectrum (PDS) of the three groups identified: (1) group I with a non-suppressive mu rhythm during motor imagery, (2) group II with an absent mu-rhythm, (3) group III with a suppressive mu-rhythm during motor imagery. Spectra were calculated from the contralateral mu-rhythm (C3) of 15 trials of hand movies (blue) versus the 15 trials of BB-baseline (red). Percentages denote the percentage of the population sharing a similar response.

2.3.3 Baseline power and ERD

Table A1 presents the ANOVA results for each of 18 subjects for C3 channel (see Appendix-2). Test for homogeneity showed that about 80% (10/12 subjects) of mu-power segments in the five baselines (60% (7/12 subjects) in the hand movies) were not homogeneous. Significant mu power differences were found between the five baseline conditions in 75% (9/12) of group 3.

For each subject, the baselines that show consistently high mu-power are considered as optimal baselines. In figure 4, the group 3 subjects are divided

into two sub-groups: (i) a no preference subgroup, which represents the subjects who show clear contralateral ERDs in almost all baseline conditions (at least 4 out of 5 baselines), which represents ≈ 17% (3/18) of the study population and (ii) a preference subgroup, which represents the subjects who show a clear contralateral ERD in some particular baseline(s) (50% (9/18) of the study population). The inset in figure 4 shows the distribution of the optimal baseline (mu-power is high and a clear and significant contralateral ERD is observed) in the mu suppressive group.

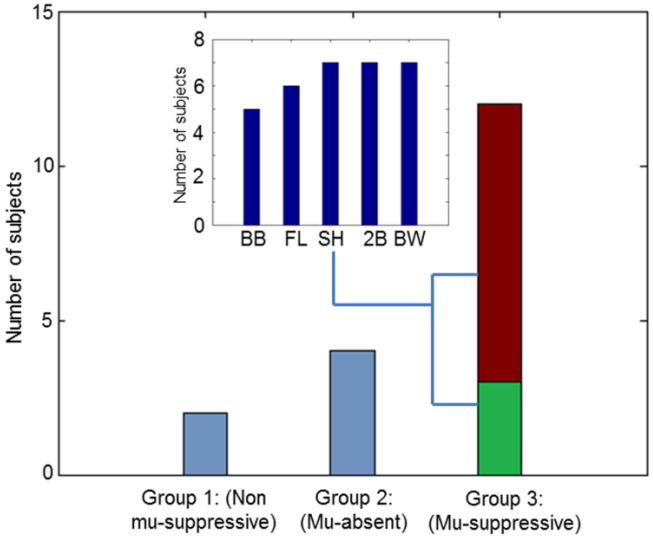

Figure 4: The number of subjects in the three groups (non mu-suppressive, mu-absent and mu-suppressive) using the contralateral mu recorded at C3. The last group is divided into the 'no preference baseline' sub-group (green) and the 'preference baseline' sub-group (brown). The inset represents the distribution of the optimal baseline in the mu-suppressive group.

2.3.4 Group level analysis

Figure 5 shows the mu-power (C3) in each of the 5 hand movies and the 5 baselines from group 3. Significant mu-power differences were only found among the five baselines with $P < 0.01$, but not between the (identical) hand movies. Results are summarized in table 1. No significant mu-power differences between the 5 hand movies or baselines were found in group 1.

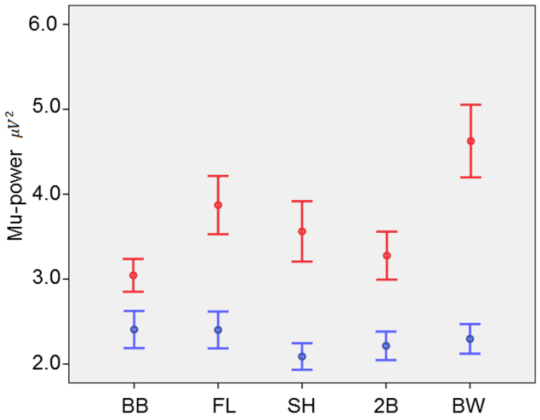

Figure 5: Mu-power (C3) in 5 hand movies (blue) and 5 baselines (red) from group 3. While baselines are all statistically different, hand movies are not.

Table 1: Summary of the results from Welch's ANOVA in the group levels.

Channel	Group 1 (Non-suppressive Mu) P-value (Welch-ANOVA)		Group 3 (Suppressive Mu) P-value (Welch-ANOVA)	
	5 Hand movies	5 Baselines	5 Hand movies	5 Baselines
C3	0.53	0.18	0.08	<0.001
C4	0.02	0.05	0.26	<0.001

2.3.5 Analysis of the baseline in subjects H109 and H111

We selected two subjects (H109 and H111) from group 3 as typical examples to show the detailed PDSs in the five baseline conditions and the effect of each baseline on topographical ERDs (TopoERDs).

In figure 6, PDSs during different baselines- vs. motor imagery condition are shown. In subject H109 (top row), the mu-power in the BB and 2B condition is considerably higher than in the other conditions. However, in subject H111 (bottom row), the mu-power in FL, SH, and BW is higher than in the other two conditions. Mu-powers in the different baseline conditions in both H109 and H111 are significantly different (see Table A1 in Appendix-2).

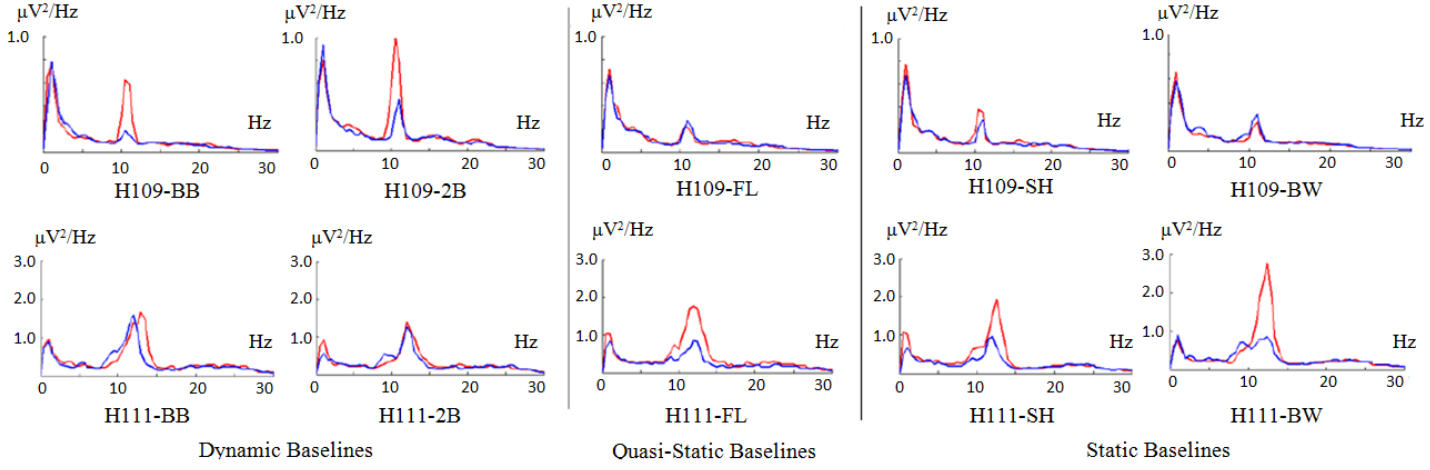

Figure 6: Effects of baseline on PDSs (red) in subjects H109 and H111. PDSs during the MI are shown, as well (blue). All data were from contralateral mu (C3).

2.3.6 Topographical ERDs of five baseline conditions in subjects H109 and H111

TopoERDs of subjects H109 and H111 are presented in figure 7. In subject H109, clear sensorimotor ERDs are observed only in BB- and 2B conditions. This is in line with the PDSs in figure 6, where the baseline mu-power is high in the BB- and 2B conditions. In subject H111, a clear sensorimotor ERD is observed in the TopoERD obtained for the BW condition; besides, smaller sensorimotor ERDs are observed for the FL- and SH conditions. Thus, the BB- and 2B conditions are the optimal baselines for subject H109; whereas the FL-, SH-, and BW conditions are the optimal baselines for subject H111.

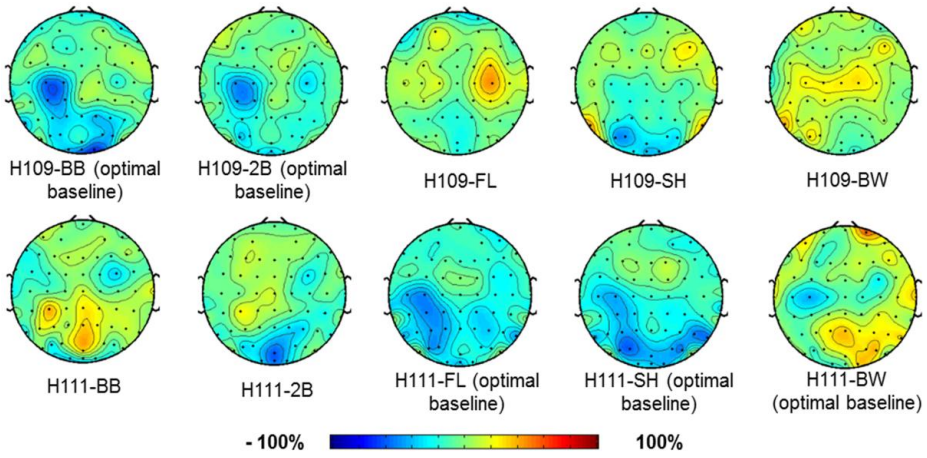

Figure 7: TopoERDs of two subjects H109 and H111. Blue indicates desynchronization of mu-power; red indicates synchronization of mu-power during MI. The BB- and 2B conditions are the optimal baselines for subject H109 while the FL-, SH-, and BW conditions are the optimal baselines for subject H111.

2.3.7 Long term stationarity of ERD

Comparing the TopoERDs from the first and second measurement, the ERDs in four out of six subjects (H101, H106, H107 and H111) are highly reproducible for almost all baselines. The results of the other two subjects show high reproducibility in three out of five baselines. Two examples of

highly stationary TopoERDs are shown in figures 8(a) and 8(b). To compare the first and second measurement of mu-power in all six subjects, we tracked the changes of mu-power rank of each baseline. The results of the six repeated measurement are presented in table 2. In two cases, changes (Up or Down) are significant (bold and italic, see table 2). In table 2, for each baseline condition, the three columns represent the following: 1st column represents the ranking of the mu-power in the 1st and 2nd measurement (1 is highest, 5 is lowest). The 2nd column represents the rank change: e.g. 1Up (1U) or 1Down (1D). Significant changes in ranking are marked red.

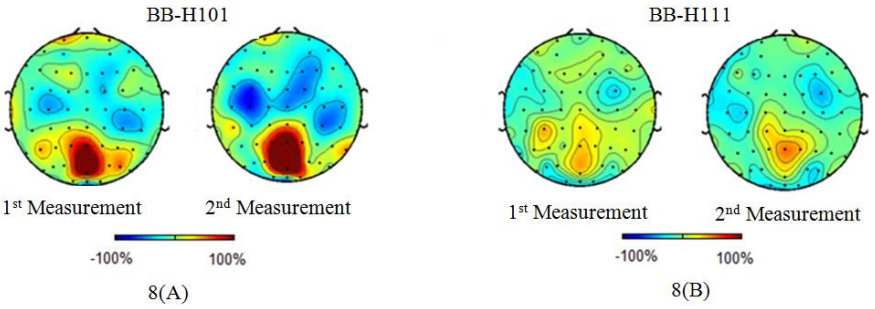

Figure 8: Two examples of topoERDs (subjects H101 and H111, BB baseline movies), showing high similarity between the 1st and 2nd measurement.

Table 2: Summary of mu power ranking among the five baselines in the 1st and 2nd measurement.

Subject	Channel	BB		2B		FL		SH		BW		Time
		Rank 1st/2nd	Changed	Rank 1st/2nd	Changed	Rank 1st/2nd	Changed	Rank 1st/2nd	Changed	Rank 1st/2nd	Changed	delayed (month)
H101	C3	2/2	-	1/1	-	4/3	1U	5/5	-	3/4	1D	5.0
H103	C3	4/5	1D	5/4	1U	2/3	1D	3/1	2U	1/2	1D	5.5
H104	C3	2/2	-	4/3	1U	3/1	2U	5/4	1U	1/5	***4D***	6.5
H106	C3	5/4	1U	4/3	1U	2/2	-	3/5	2D	1/1	-	4.0
H107	C3	5/4	1U	4/3	1U	3/2	1U	2/5	***3D***	1/1	-	4.5
H111	C3	5/5	-	4/4	-	1/3	2D	3/2	1U	2/1	1U	0.5

2.3.8 Analysis of ipsilateral (C4) mu-rhythm

The inter-trial outlier analysis using the ipsilateral mu-rhythm (from C4) showed that 1.2 trials (SD 0.7), were outliers. The three groups, found using analysis of the ipsilateral mu (C4), were similar to those found using the contralateral (C3) modulation of the mu-rhythm: group 1 (≈17% (3/18)), group 2 (≈17% (3/18)), and group 3 (67% (12/18)), see figure A1 in Appendix-2 for more details. In the mu-suppressive group (group 3), 75% (9/12) of the group members were baseline preference subjects (50% of the study population). At group level, significant differences were found among the five baselines ($P < 0.001$) in this group. In sum, no significant differences regarding selection of the optimal baseline were found between using the contralateral (C3) and ipsilateral (C4) mu-rhythm. More details are presented in table A2 (in Appendix-2).

2.4 Discussion

In this study, we explore the relevance of the choice of baseline on the ERD during motor imagery. Without a stable, and preferably strong, baseline mu-rhythm, the suppression of mu rhythm during motor imagery cannot be reliably estimated. Our study shows that maximal mu-power is not always found for a "static baseline'' as in some subjects dynamic or quasi-static baselines showed larger mu powers than static baseline images.

2.4.1 Mu-power can be maximized depending on the baseline used

In about 67% of the study population particular baselines (not necessary static) showed significantly higher mu-power than others. We did not find a common optimal baseline movie in all subjects, rather each subject showed a different optimal baseline. The preference for particular baselines was found to be reproducible, according to the high spatial similarity between the first and second TopoERDs in subjects who participated two times.

Besides the mu-power difference among five baselines, we found that nearly half of the group 3 subjects did show different mu-power in some particular hand movies. However, this difference was less prominent than that between the five baselines in two aspects (1) this difference is found in ≈ 50% of

group 3 subjects compared to ≈ 75% for the five baselines and (2) the absolute mu-power differences between minimum and maximum hand movie mu-power (in ≈ 70% of group3 subjects) was about half (or less) of what was found for the five baseline mu-powers (see table A1 columns 6 and 11). The latter implies that mu-power has a higher variation among the five baseline conditions than among the five hand movies. This high variation among five baselines found in the majority of the study population underlines the stronger effect of baseline on mu-power, and subsequently on ERD than that of hand movie mu-power. This finding implies that it is more difficult to set up the environment to induce maximal baseline mu-power by trying to relax the subjects than to suppress the mu-power by imaging movement.

Group level analysis showed that a significant mu-power difference was only found among five baseline conditions in group 3 while no significant differences were observed among the five hand movies. This confirms the single subject analysis that the difference in ERD was caused by the variation of the baseline rather than that of the hand movie.

As shown in figure 4, two subgroups of mu-suppressive subjects were found and baseline preference subjects represent 50% of the study population (or 75% of group 3 subjects). When a non-optimal baseline is presented to a subject, a clear contralateral ERD will not be observed, as illustrated in figure 7.

All 18 subjects reported mixed responses during the baseline. For instance, many reported that during the BW baseline it was difficult to maintain attention. Some of them started counting the white stripes on the screen. Some of them claimed that it was good to block all movement imagination. During the SH baseline, many subjects reported that it was difficult to block movement imagination. During the FL baseline, most subjects felt most comfortable and most relaxed; sometimes they lost their attention. During the dynamic baselines (BB and 2B), some subjects said that they usually kept their attention to the ball(s). Some claimed that they felt irritation while observing the moving ball(s). It is clear that different visual inputs elicit different responses. In addition, it also shows that even if the same baseline is used, the subject's response is different depending on his or her perspective.

2.4.2 Mu-ERD found in about 67% of the study population

In twelve subjects (≈ 67%), a clear contralateral ERD (mu ERD) was observed. Mu-ERDs could be calculated thanks to high mu-power during baseline. Previous studies reported a percentage of mu-power carrying subjects ranging from 15 to 70% [22, 23, 24]. These values were estimated from baseline where subjects were instructed to be relaxed and keep their eyes open. If a single baseline (e.g. 2B, BW or FL baseline) had been used in our study, mu-ERDs would have been found in approximately 40% of the study population. This emphasizes that selection of the optimal baseline enhances the chance of observing mu-ERD.

In the remaining 33%, mu-ERD was not observed (either non-suppressive mu subjects (group1) or mu-absence subjects (group 2). We hypothesize that the subjects in group 1 may show mu-ERD when (1) more meaningful or more complex hand movements are presented or (2) the kinesthetic imaging strategy is pursued [12, 9]. In group 2 subjects, the reason of mu-rhythm absence is unclear; absence was also reported in many other studies [12, 22, 23, 24].

2.4.3 Independence of mu-power from occipital alpha-power during baseline

Two tests were done to examine possible influence of occipital power on central electrodes (C3 and C4). First, the similar analyses as in tables A1 and A2 were done for O1 and O2. The resulting optimal baselines for O1 and O2 were different from those for C3 and C4, respectively. Second, a correlation analysis was performed to compare mu-power or alpha-power for each baseline movie, between electrode pairs: C3-C4, O1-O2, C3-O1 and C4-O2. Strong correlation was found for C3 vs. C4 ($r = 0.91$, $P < 0.001$) as expected, while the correlation between the mu-power in C3 vs. the alpha power in O1 ($r = 0.25$, $P = 0.056$) was weak. Similarly, strong and weak correlations were found for O1 vs. O2 ($r = 0.79$, $P < 0.001$) and for C4 vs. O2 ($r = 0.49$, $P < 0.001$), respectively.

2.4.4 Functional interpretation of mu-ERD

There exist two types of mu band (lower (8-10Hz) and upper (10-12Hz)), which result in different reactivity patterns during performing a motor task. While lower mu ERD is more widespread, upper mu ERD is more focal [25, 26]. Neuper and Pfurtscheller suggested that the lower and upper mu ERD lead to different functional interpretations: i.e. the wide spread lower mu ERD indicates all cortical areas involving in a motor task but not necessarily indicates the critical area to support a specific movement as the upper mu ERD [18]. Thus selection of narrow mu-band depends on desired interpretation; for a general purpose here we used the broad-band mu (8-13Hz). Specifying an optimal narrow mu-band will not only result in a clearer functional interpretation, it also enhances a chance of observing ERD (since in some subjects only part of the mu-band is suppressed during a motor task).

2.4.5 Limitations and future improvements of the baseline study

In this study, no EMG was recorded. However, potential muscle activity was monitored by visual inspection. Another limitation of our study is the absence of a systematic criterion for the initial selection of the five baselines used. We used both movies and a static image. Of course, we cannot exclude that there may exist a baseline that is optimal for all subjects, for instance a blank or black screen. However, these two conditions would have resulted in very different luminosities that may have an effect on the ERD. In addition, a black screen may have affected the attention of our subjects that were already sitting in a dim room. The screen with the black background and white stripes was regarded as a compromise between a black screen only and a white screen. A third limitation may seem that no real hand movement was included. In our study, however, we focus on the differential sensitivity of mu-rhythm modulation by various external inputs. Finally, although the duration between baseline (10 s.) vs. hand movie (8 s.) was different, the reduction of the baseline length to 8 s. did not change the conclusions from this study. The average baseline mu-power reached a stable level after 5 or 6 seconds (see one example in figure A2 in Appendix-2).

In closing, our study supports the importance of baselines for ERD outcomes. An ideal baseline should block movement imagination, and induce a relaxed state, while maintaining attention. We show that either static- or dynamic baselines can induce or maximize mu-power, with significant inter-individual differences. A common baseline, which maximizes the strength of the mu rhythm, was not found at group level. However, at the individual level, the mu-rhythm can be induced or maximized by choosing a particular baseline movie. Mu rhythms recorded during static baselines were not always stronger than those obtained during dynamic baselines. Therefore, we suggest performing a calibration experiment to determine the optimal baseline at the start of any motor imagery experiment.

Acknowledgements

We would like to thank Cecile de Vos, Erik te Woerd and Fokke van Meulen for their assistance during the experiments. This work was supported by a grant from the Netherlands BrainGain research consortium. We also thank Prof J van de Palen for his assistance with the statistical analysis.

Appendix-2

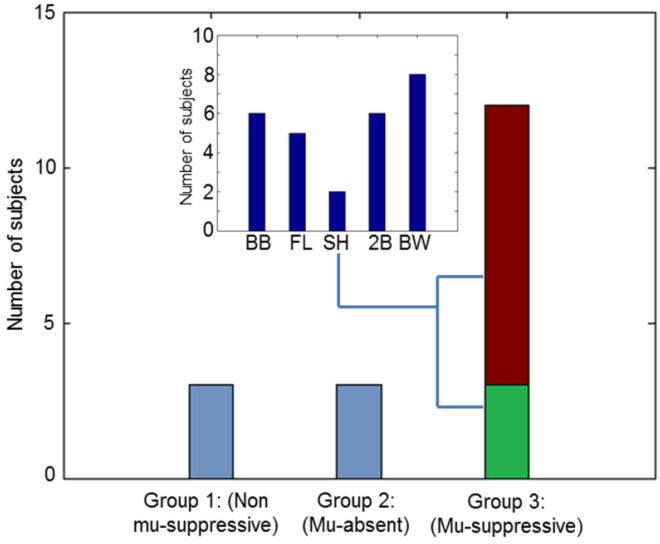

Figure A1: The number of subjects in the three groups (non mu-suppressive, mu-absent and mu-suppressive) using the contralateral mu recorded at C4. The last group is divided into the 'no preference baseline' sub-group (green) and the 'preference baseline' sub-group (brown). The inset represents the distribution of the optimal baseline in the mu-suppressive group.

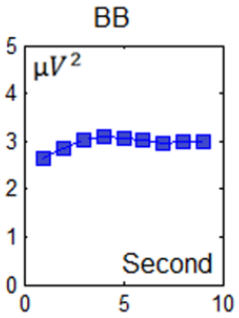

Figure A2: One typical example of average mu-power across 14 subjects (groups 1 and 3) for the BB baseline movie, as a function of its duration.

TableA1: Results obtained from Welch's ANOVA employed to test mu-power differences on five types of grasping hand movies and five baselines in each subject using C3 channel.

Subjects	Group	ANOVA on five hand movies					ANOVA on five baseline movies					Channel	Baseline(s) with contralateral modulation
		P-value	Hand movie(s) with sig. higher mu-power	Significant different from	Abs diff. (μV^2)	Homoge-neous test	P-value	Baseline(s) with sig. higher mu-power	Significant different from	Abs diff. (μV^2)	Homoge-neous test		
H102	1	0.46	None	None	0.82	0.02	0.03	None	None	1.443	<0.01	C3	Not found
H108	1	0.07	None	None	1.99	<0.01	0.42	None	None	1.851	0.1	C3	Not found
H116	2	-	-	-	-		-	-	-	-	-	-	-
H117	2	-	-	-	-		-	-	-	-	-	-	-
H119	2	-	-	-	-		-	-	-	-	-	-	-
H121	2	-	-	-	-		-	-	-	-	-	-	-
H101	3	<0.01	BB-H, FL-H BW-H	> 2B-H	0.58	<0.01	<0.01	BB, 2B, BW	> FL, SH	1.81	<0.01	C3	BB, 2B, BW
H103	3	0.78	None	None	0.58	0.13	<0.01	FL, SH, BW	> 2B	2.91	0.02	C3	BB, FL, BW
H104	3	<0.01	BB-H,FL-H, 2B-H,BW-H	> SH-H	1.04	<0.01	0.58	None	None	0.64	0.63	C3	SH
H106	3	0.15	None	None	2.29	<0.01	<0.01	FL,SH,BW ,2B,BW	> BB > 2B	12.73	<0.01	C3	FL, SH, 2B, BW

TableA1 (Continued): Results obtained from Welch's ANOVA employed to test mu-power differences on five types of grasping hand movies and five baselines in each subject using C3 channel.

Subjects	Group	ANOVA on five hand movies					ANOVA on five baseline movies					Channel	Baseline(s) with contralateral modulation
		P-value	Hand movie(s) with sig. higher mu-power	Significant different from	Abs diff. (μV^2)	Homoge-neous test	P-value	Baseline(s) with sig. higher mu-power	Significant different from	Abs diff. (μV^2)	Homoge-neous test		
H107	3	<0.01	SH-H, BW-H	> 2B-H	0.89	<0.01	0.16	None	None	0.88	<0.01	C3	2B, BW
H109	3	0.55	None	None	0.16	0.37	<0.01	BB 2B	> FL, BW > FL, SH, BW	0.91	<0.01	C3	BB,2B
H110	3	0.35	None	None	0.13	0.18	<0.01	BW SH	> BB, 2B, FL > BB	1.55	<0.01	C3	FL, SH , 2B, BW
H111	3	0.02	BB-H, BW-H	> SH-H	1.18	0.04	<0.01	FL, BW	> BB, SH, 2B	2.72	<0.01	C3	FL, SH, BW
H112	3	0.65	None	None	0.23	0.14	<0.01	SH	> BB* (P = 0.093)	0.38	<0.01	C3	FL, SH
H113	3	0.06	None	None	0.18	<0.01	<0.01	BB, 2B, BW	> FL, SH	1.01	<0.01	C3	All
H115	3	<0.01	FL-H, BW-H	> BB-H	0.64	<0.01	<0.01	BB, FL	> SH	0.73	<0.01	C3	BB, 2B
H120	3	0.29	None	None	0.41	0.01	0.68	None	None	0.22	0.43	C3	SH

See the table caption on the next page.

Table A1 presents the results of 18 subjects. The table has five sections: (i) subject number and its group (columns 1, 2), (ii) statistical analysis of five hand movies (columns 3 - 7), (iii) statistical analysis over five baseline movies (columns 8 – 12), (iv) a selection of an analyzed channel (columns 13), and (v) baseline(s) with clear and significant contralateral modulation (columns 14). For sections (ii) or (iii), p-values to reject or accept the mu-power difference based on Welch's ANOVA is presented in columns 3 or 8. If the null hypothesis is rejected, mu-power is not significantly different (thus, the word "None" will be denoted in columns 4, 5, 9, 10). If the null hypothesis is accepted, the Dunnett's T3 test is employed to reveal any baseline(s) (or hand) movies(s), which have significantly higher mu-power than from other baselines. The > in columns 5 and 10 indicates that the selected baseline in column 4 (or 9) is significantly higher than the baseline(s) in column 5 (or 10) with $P < 0.05$. *One exception was reported in the analysis of five baseline in H112 that mu-powers in SH (see column 9) were higher than that in BB (see column 10) with $P = 0.093$. In columns 7 and 12, P-values from test of homogeneity are presented; mu-powers among five conditions were not homogeneous if $P < 0.01$.

Table A2: Results obtained from Welch's ANOVA employed to test mu-power differences on five types of grasping hand movies and five baselines in each subject using C4 channel.

Subjects	Group	ANOVA on five hand movies					ANOVA on five baseline movies					Channel	Baseline(s) with ipsilateral modulation
		P-value	Hand movie(s) with sig. higher mu-power	Significant different from	Abs diff. (μV^2)	Homoge-neous test	P-value	Baseline(s) with sig. higher mu-power	Significant different from	Abs diff. (μV^2)	Homoge-neous test		
H102	1	0.76	None	None	0.54	0.94	0.04	BW	FL	1.49	0.01	C4	Not found
H108	1	0.02	FL-H	> BB-H	6.43	<0.01	0.36	None	None	2.928	<0.01	C4	Not found
H111	1	0.05	None	None	0.91	0.16	0.06	None	None	0.99	0.02	C4	Not found
H116	2	-	-	-	-		-	-	-	-	-	-	-
H119	2	-	-	-	-		-	-	-	-	-	-	-
H121	2	-	-	-	-		-	-	-	-	-	-	-
H101	3	<0.01	SH-H, BW-H	> 2B-H	1.04	<0.01	<0.01	BB, 2B, BW	> SH	1.33	<0.01	C4	2B
H103	3	0.53	None	None	1.11	0.20	0.02	FL	> 2B	2.84	0.20	C4	FL, BW
H104	3	<0.01	FL-H, BW-H BW-H	> 2B-H > SH-H	1.75	<0.01	<0.01	BW BB	> FL, SH > FL, 2B	3.79	<0.01	C4	BB, BW
H106	3	0.17	None	None	2.50	0.01	<0.01	FL, SH, BW SH, BW	> 2B > BB	9.50	<0.01	C4	SH, BW
H107	3	0.11	None	None	2.29	<0.01	<0.01	2B	> SH	3.11	<0.01	C4	FL, 2B, BW
H109	3	0.01	BW-H	> SH-H, 2B-H	0.35	<0.01	<0.01	BB, 2B, BW	> SH	0.51	<0.01	C4	2B

Table A2 (continued): Results obtained from Welch's ANOVA employed to test mu-power differences on five types of grasping hand movies and five baselines in each subject using C4 channel.

Subjects	Group	ANOVA on five hand movies					ANOVA on five baseline movies					Channel	Baseline(s) with ipsilateral modulation
		P-value	Hand movie(s) with sig. higher mu-power	Significant different from	Abs diff. (μV^2)	Homoge-neous test	P-value	Baseline(s) with with sig. higher mu-power	Significant different from	Abs diff. (μV^2)	Homoge-neous test		
H110	3	0.43	None	None	0.25	0.07	<0.01	BW	> BB, FL, SH, 2B	6.63	<0.01	C4	All
H112	3	0.22	None	None	0.41	0.00	<0.01	FL, BW	> BB	0.49	<0.01	C4	BW
H113	3	0.03	BW-H	> SH-H** P = 0,63	0.29	<0.01	<0.01	BB, 2B, BW 2B	> SH > BB	1.21	<0.01	C4	BB,FL ,2B,BW
H115	3	0.56	None	None	0.29	0,03	<0.01	FL, BW BW	> SH > 2B	1.44	<0.01	C4	BB, FL ,2B, BW
H117	3	0.02	BW-H	> BB-H, 2B-H	0.26	<0.01	0.03	BB	> SH	0.39	<0.01	C4	BB
H120	3	<0.01	BW-H	> BB-H, SH-H	0.68	<0.01	<0.01	BB, 2B	> SH, BW	0.81	<0.01	C4	BB

See the table caption on the next page.

Table A2 presents the results of 18 subjects. The table has five sections: (i) subject number and its group (columns 1, 2), (ii) statistical analysis of five hand movies (columns 3 - 7), (iii) statistical analysis over five baseline movies (columns 8 – 12), (iv) a selection of an analyzed channel (columns 13), and (v) baseline(s) with clear and significant ipsilateral modulation (columns 14). For sections (ii) or (iii), p-values to reject or accept the mu-power difference is presented in columns 3 or 8. If the null hypothesis is rejected, mu-power is not significantly different (thus, the word "None" will be denoted in columns 4, 5, 9, 10). If the null hypothesis is accepted, the Dunnett's T3 test is employed to reveal any baseline(s) (or hand) movies(s), which have significantly higher mu-power than from other baselines. The > in columns 5 and 10 indicates that the selected baseline in column 4 (or 9) is significantly higher than the baseline(s) in column 5 (or 10) with $P < 0.05$. **One exception was reported in the analysis of five hand movies in H113 that mu-powers in BW-H (column 4) were higher than that in SH-H (column 5) with $P = 0.063$. In columns 7 and 12, P-values from test of homogeneity are presented; mu-powers among five conditions were not homogeneous if $P<0.01$

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Chapter 3 Temporal Evolution of Event-Related Desynchronization in Acute Stroke: A Pilot Study

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Abstract

Objective: Assessment of event-related desynchronization (ERD) may assist in predicting recovery from stroke and rehabilitation, for instance in BCI applications. Here, we explore the temporal evolution of ERD during stroke recovery.

Methods: Ten stroke patients and eleven healthy controls were recruited to participate in a hand movement task while EEG was being recorded. Four measurements were conducted in eight patients within four months. We quantified changes of ERD using a modulation strength measure, S_m, which represents an area and amplitude of ERD.

Results: 7/8 patients showed good recovery. Absence-or-reduction of ipsilesional modulation was initially found in stroke patients but not in the healthy controls. In the patient group, two evolutions were found in 6/8 patients: a significant increase in ipsilesional S_m; and a decreasing trend in contralesional S_m. In the only non-recovery patient, absence of ipsilesional modulation was observed, while his contralesional S_m increased with time after stroke.

Conclusion: The two evolutions presumably reflect the reorganization of brain networks and functional recovery after acute stroke. The significant increase of ipsilesional S_m in patients with a good recovery suggests an important role of this hemisphere during recovery.

Significance: Improved understanding of ERD in acute stroke may assist in prognostication and rehabilitation.

3.1 Introduction

Stroke is one of the leading causes in adults' disabilities. In the US alone, about 800,000 new stroke cases are diagnosed, annually. About half of the adult stroke patients suffer from moderate to severe loss of some motor skills [1, 2]. Various mechanisms are involved in stroke recovery including (i) restitution of non-infarcted penumbral areas; (ii) resolution of diaschisis; (iii) brain plasticity; and (iv) behavioral compensation [3]. Among these, only the first three reflect true recovery from stroke, while behavioral compensation is found in patients who compensate for their loss of function with other movement strategies.

In this study, we focus on brain plasticity, which is one of the key mechanisms in stroke recovery, characterized by a functional and anatomical reorganization of the central nervous system (CNS). These changes occur at various spatial scales. At the microscopic level, dendritic and axonal sprouting are two typical phenomena in the peri-infarct cortex [4, 5] that may partially compensate for neuronal loss in this area [6, 7]. At a larger spatial scale, cortical reorganization has been reported in several studies, too. For instance, using transcranial magnetic stimulation (TMS), shifts in corticomotor representation on the affected hemisphere compared to the non-affected healthy hemisphere were found [8, 9]. In a recent study using magnetoencephalography (MEG), a transient enlargement of motor areas during stroke recovery was observed [10].

Several functional magnetic resonance imaging (fMRI) studies have explored cortical reorganization in stroke patients performing movement tasks. In a study with eight acute stroke patients, increased activation was observed in various areas, including the contralesional (ipsilateral) sensorimotor cortex, contralesional posterior parietal, bilateral prefrontal regions [11]. Similar findings, observed in both the motor and non-motor related brain areas of both hemispheres, were reported by Feydy et al., Ward et al., and Grefkes et al. [12-14]. Lateralized activation towards the ipsilesional hemisphere and a decrease of contralesional activation were two typical evolutions in patients with good recovery [11, 12, 15].

Reorganization of cortical networks can also be studied with the electroencephalography (EEG). In acute cortical stroke, slow activity (1-4 Hz) over the affected hemisphere is typically increased with a reduction of relatively fast activity (8-13 Hz, or 15-25 Hz) [16-20]. During recovery, a shift towards a normal spectral distribution is observed [17, 20-23].

Only a few EEG studies in stroke patients have been performed during active movement. In 1980, Pfurtscheller and Aranibar showed a reduction of Event-Related Desynchronization (ERD) on the affected hemisphere as compared to the unaffected hemisphere in cortical stroke patients with mild hemiparesis, during performance of hand movement [24]. This reduction has also been reported in later studies [25]. A concomitant increase in ERD on the contralesional hemisphere during finger extension was reported by Gerloff et al. [26].

In this study we explore the spatiotemporal dynamics of cortical reorganization in acute hemispheric stroke patients. We will use ERD during active movement of the paretic arm, evaluated over the course of several months after the insult. In particular, we will focus on the role of the ipsi- and contralesional hemisphere in successful recovery of upper extremity function.

3.2 Methods

3.2.1 Subjects

Ten acute hemispheric stroke patients (mean age: 64.9 years, S.D. 13.4, five female, nine left hand motor deficit) and eleven age-matched healthy controls (mean age: 57 years, S.D. 7.8, nine female, ten right handed) were recruited to participate in this study. All patients suffered from a first-time-ever ischemic hemispheric stroke, with no other neurological disorders. The patients were recruited from the stroke unit of the Medisch Spectrum Twente (MST) hospital within 7 – 14 days after stroke onset. The study was approved by the local ethical committee of the MST. Demographic and clinical data of the patients are summarized in Table 1. Magnetic resonance or computed tomography imaging was performed in every stroke patient to

confirm the diagnosis and detect the infarct location (see Figure. A1 in Appendix-3).

TABLE 1: Demographic and clinical data of the stroke patients at inclusion and during follow-up

Subjects	*Gender /Age*	*Affected hand*	*Site/ type of lesion*	*T0*		*T1*		*T2*		*T3*		*Clinical Condition at T0*
				NIHSS	*up-FM*	*NIHSS*	*up-FM*	*NIHSS*	*up-FM*	*NIHSS*	*up-FM*	
S01	F/58	L	R-Sub	1	54	0	66	0	66	0	66	Mild
S03	F/51	L	R-Sub	4	50	3	58	3	62	0	64	Mild
S04	M/68	R	L-Sub	3	48	2	60	0	66	0	66	Moderate
S08	M/58	L	R-Sub	4	52	1	64	1	66	1	66	Mild
S05	M/84	L	R-Sub	10	4	-	-	-	-	-	-	Severe
S02	F/56	L	R-Cor	5	65	1	65	0	66	0	66	Mild
S06	F/81	L	R-Cor	3	49	2	58	1	63	0	65	Moderate
S09	F/62	L	R-Cor	6	24	4	49	2	57	0	64	Severe
S10	F/49	L	R-Cor	7	4	6	4	3	7	-	-	Severe
S07	F/82	L	R-Cor	3	41	-	-	-	-	-	-	Moderate

"Sub" and "Cor" denote subcortical and cortical stroke, respectively. "R" and "L" stand for right and left hemisphere. "M" and "F" indicate male or female. up-FM stands for upper extremity Fugl Meyer scale ranging from 0 to 66 (a healthy subject would have up-FM=66). From the up-FM, we classified the patients into three groups: severe patients (0<up-FM≤25), moderate patients (25<up-FM≤50), mild patients (up-FM>50). T0, T1, T2 and T3 denote the measurement at stroke onset, and after 1, 2 and 4 months respectively. Note that we had switched the left and right hemisphere in S04 (the only left hemispheric stroke) to suit the analysis.

3.2.2 EEG recording

All experiments were conducted in a shielded room. 60-channel EEG recordings (TMS International, The Netherlands) were made using Ag/AgCl electrodes. The sampling frequency was set at 5 kHz. All electrode impedances were kept below 5 kOhm. Two reference electrodes were placed over the left and the right mastoids. All signals were first down-sampled to 500 Hz and spatially filtered using a surface Laplacian estimated from

spherical spline interpolation. All 1st row electrodes (T7, FT7, F7, AF7, FP1, FPz, FP2, AF8, F8, FT8, and T8) and some 2nd row electrodes (F5, AF3, AF4, and F6) were excluded to avoid possible EMG-contaminated signals. All signals were also visually inspected by an experienced neurologist for the presence of muscle or ocular artifacts.

3.2.3 Experimental design

We employed an ERD measure to investigate changes of the patients' brain networks during stroke recovery. ERD is quantified from the percentage change of idle rhythm between the relaxed condition (baseline) and the motor imagery-or-execution condition. ERD can be found either in mu- (8-13 Hz) or beta rhythms (15-25 Hz) depending on subject [27-31]. A selection between these two rhythms was done in the calibration phase, prior to the experiment (see below). During the experiment, two types of movies were shown: (i) a baseline movie (idle) and (ii) a hand movie (active). The two types of movies were used as the cues to either relax-and-perform-no-movement (idle) or imitate/image the movement seen on the screen. Three different baseline movies were: (i) two-moving-balls (2B); (ii) a slowly-moving-flower (FL); and (iii) a grid (GR). The GR was the only static movie of the three, showing white stripes against a black background. Two identical hand moving movies showing either left or right hand opening and closing were shown. Every baseline movie lasted 10 s, every hand movie lasted 10 s. (after the artifact rejection each movie lasted ≈8 s.). Each measurement consisted of two parts: i) calibration and ii) motor execution, which will be explained next.

Calibration: During the calibration phase, we presented three different "baseline movies" and the "hand movie". Being a ratio, ERD depends on the signal power of the sensorimotor rhythm (SMR; mu or beta band) during baseline [32]. By first presenting three different baseline movies, we aimed at finding the baseline movie with maximum SMR power. During the baseline movie, the subject was asked to relax and to neither perform nor image any movement. During presentation of the hand movie the subject was asked to observe the hand movement and synchronously image the movement (the choice of active period during hand movie could be either observe-and-image or observe-and-execute movement [33]; to prevent tiredness we asked to only observe-and-image the movement during the

calibration phase). We showed a dominant hand movie for the healthy subject and a non-paretic hand movie for the stroke patients, in total eight trials of each baseline movie and 24 hand movies. It was proven in a nearly identical experiment (see Tangwiriyaskul et al. [32]) that to reach a stable ERD we need ≈ 7 trials per condition, each of which must last at least 5 seconds. Maximal SMR-power was analyzed at C3 (C4) during the right (left) hand movie. To find the optimal baseline movie, the EEG signals from each trial were first partitioned into periods corresponding to the visual inputs (three baselines or hand movie). Second, we further classified trials of the hand movie into three groups, depending on their previous adjacent baseline movie. Next, at C3 (if the right hand movies was used, otherwise C4) we estimated six power density spectra "PDS" (FL-PDS, 2B-PDS, GR-PDS, HFL-PDS, H2B-PDS, HFL-PDS) using Welch's method (2 sec. window with 1 sec. overlap). Then, we arranged six PSDs into three pairs (e.g. HFL-PSD vs. FL-PSD). From visual inspection of these three pairs, we were able to locate the most suppressive rhythm (mu or beta). This rhythm was considered as SMR. Hereafter, ERD was computed for every channel ($ERD_k = ((AC_k - BL_k)/BL_k) \times 100$, where ERD_k is the ERD value at channel k, AC_k and BL_k are the hand movie and baseline SMR-power at channel k, respectively.). Later, we plotted three topographical ERDs (TopoERDs). Finally, the optimal baseline was chosen from the TopoERD plot that showed the clearest ERD over the contralateral motor cortex (M1). We present one example (see Figure A2 in Appendix-3) of the SMR and the optimal baseline in patient S06. Because the clearest ERD on M1 is observed when the two-ball movie was used, we chose the two-ball movie as the optimal baseline for S06. Table A1 (in Appendix-3) summarizes optimal baseline of each subject.

Motor Execution: During motor execution (ME), we repeated 32 trials of the optimal baseline movie combined with the right hand movie or the left hand movie, 16 trials each, in random order. During the baseline movie, the subject was instructed to relax and not perform/image any movement. During the hand movie, the instruction was to observe the hand movements and synchronously perform or attempt to perform the movement.

3.2.4 Clinical assessment and follow-up

In 8 out of 10 stroke subjects, follow up measurements were made at 1 month (T1), 2 months (T2), and 4 months (T4) after the insult. The optimal baseline found at T0 was used for the subsequent measurements as well. The upper-extremity Fugl-Meyer scale (up-FM) assessed the state of recovery. In controls, five subjects were asked to participate in a second measurement (T1*), with an average time delay of 13 weeks (S.D. = 6 weeks).

3.2.5 Validation of the selected SMR

To ensure that the selected SMR from the calibration phase represented the most discriminable brain activity, we conducted the following steps in ME data. First, C3 (or C4) was selected for a right hemispheric stroke patient or a right handed healthy control (otherwise). Second, at each trial a power spectrum was estimated. Next, we computed the SMR power both in mu and beta bands by integrating the power spectrum between 8-13 Hz for mu and 15-25Hz for beta. Later, we repeated these steps in all trials. Finally, we re-selected the SMR: i.e. the selected SMR was the one with larger (and significant according to the Wilcoxon signed-rank's test) difference between the average SMR power during baseline vs. the average power during ME than the one of another band. This was always true in all but one subject (S08, who was not included in the longitudinal analyses).

3.2.6 Computation of ERD and analysis of modulation strength (S_m)

As a quantitative measure for EEG modulation, we introduce the modulation strength S_m, which reflects the amplitude and the area of significant changes in the ERD over the motor cortex. High S_m indicates that the modulation area is large and/or the ERD-value is strongly negative. Instead of including all 60 channels, we limit our analysis, therefore, to the channels located across the motor cortex (including C3, C4, CP3 and CP4) and use S_m, to quantify significant changes in ERD, as this may be observed from multiple channels.

To compute S_m, first we set a closed boundary, covering the motor cortex area, including electrodes FC5, FC3, FC1, FCz, FC2, FC4, FC6, C5, C3, C1, Cz, C2, C4, C6, CP5, CP3, CP1, CPz, CP2, CP4 and CP6. Second, the motor

cortex area was divided into a left and a right part (Figure. 1(a)). Pixels with absolute ERD-values < 30% were set to zero (green color, see Figure. 1(b)). Subsequently, all pixels were changed from RGB into grayscale, ranging from 0 (black) to 255 (white), see Figure 1(c). Hereafter, we computed an average grayscale-value from all the pixels in the left or right motor cortex, for all repeated measurements. This average grayscale-value was used as the threshold. Then, those pixels with grayscale-values greater than the threshold were considered to be non-significant (Figure. 1(d)). After that, we normalized the grayscale values into a range of [0 1] by dividing every grayscale value by 255. Finally, the modulation strength (S_m) was defined as a summation of the normalized grayscale values of all significant pixels, effectively representing the sum of all significant modulation amplitudes.

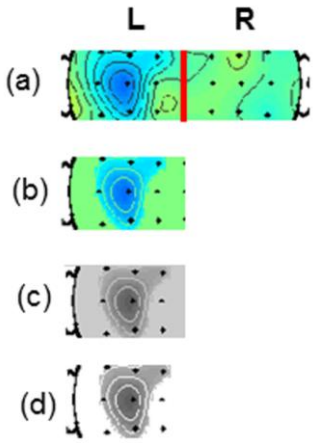

Figure 1: Calculation of modulation strength S_m (data from S10 during his non-paretic hand opening/closing at T1). (a) A closed boundary over motor cortex was defined. (b) All pixels with absolute ERD < 30% were set to zero (seen as green color). (c) RGB figure is changed into grayscale figure. (d) After computing the threshold, all pixels below the threshold were excluded.

3.2.7 Cross hemisphere analysis of modulation strength between stroke and healthy subjects

In each subject, we computed two modulation strengths, one for each hemisphere: (i) ipsilesional normalized modulation strength $\overline{S_m^{IP}}$ during paretic hand movement, and (ii) contralesional normalized modulation strength $\overline{S_m^{CO}}$ during non-paretic hand movement. Both were normalized using: $\overline{S_m^{IP}} = S_m^L / \left(0.5 \times (S_m^L + S_m^R)\right)$, where $\overline{S_m^{IP}}$ denotes the ipsilesional normalized S_m, S_m^L and S_m^R denote the ipsilesional S_m and contralesional S_m during paretic (left) hand and non-paretic (right) hand movements, respectively. A similar procedure was used in the healthy subjects, during left and right hand movement. Group level analysis of $\overline{S_m^{IP}}$ and $\overline{S_m^{CO}}$ of cortical stroke, subcortical stroke and healthy subjects was done using a Wilcoxon signed-rank test. P-values <0.05 were regarded as significant.

3.2.8 Longitudinal analysis of modulation strength in stroke patients during recovery

To evaluate the temporal changes in modulation strengths, we normalized the modulation strength of each hemisphere by dividing each S_m by the average S_m from four measurements.

3.2.9 Statistics

Statistical significance was evaluated using Wilcoxon signed-rank's test.

3.3 Results

Ten patients were initially included. Two stroke patients (S05, S07) dropped out after the first measurement for personal reasons, while the last patient (S10) left the study after his third measurement due to logistic problems. Demographic and clinical data at inclusion and during follow-up are presented in Table 1.

All but one of the remaining eight stroke patients showed significant improvement of the up-FM scores. At T0, in most patients ipsilesional S_m was absent or less than contralesional S_m. At T0 a clear difference between ipsilesional vs. contralesional S_m was present in the stroke patients. In most of the healthy controls (8/11), a bilateral modulation was found during a performance of the motor execution. In six subjects no significant difference between the ipsi- vs. contralateral modulation was seen. Similar to the healthy controls, after good recovery we also observed the bilateral modulation in six patients.

3.3.1 Hemispheric differences

Figure 2(a) illustrates our findings in two stroke patients and two healthy controls while performing hand opening/closing tasks at T0. In the healthy controls (H08 and H10), bilateral modulation is present. In the stroke patients, however, ipsilesional modulation is absent (S06) or strongly reduced (S01).

Among three groups (cortical, subcortical and control), the largest difference between the normalized ipsilesional (during paretic hand movement) and the normalized contralesional (during non-paretic hand movement) S_m was found in the cortical stroke patients with average S_m difference "ΔS_m" $= -1.04$ (p=0.08). A smaller difference was found in the subcortical stroke patients with ΔS_m = -0.25 (p=0.23). In the healthy controls there was (nearly) symmetric activation of both contralateral hemispheres, both during left and right hand movement with ΔS_m = 0.13 (p=0.29). Figure 2(b) summarizes these results. Note that negative ΔS_m reflects smaller ipsilesional S_m than contralesional S_m.

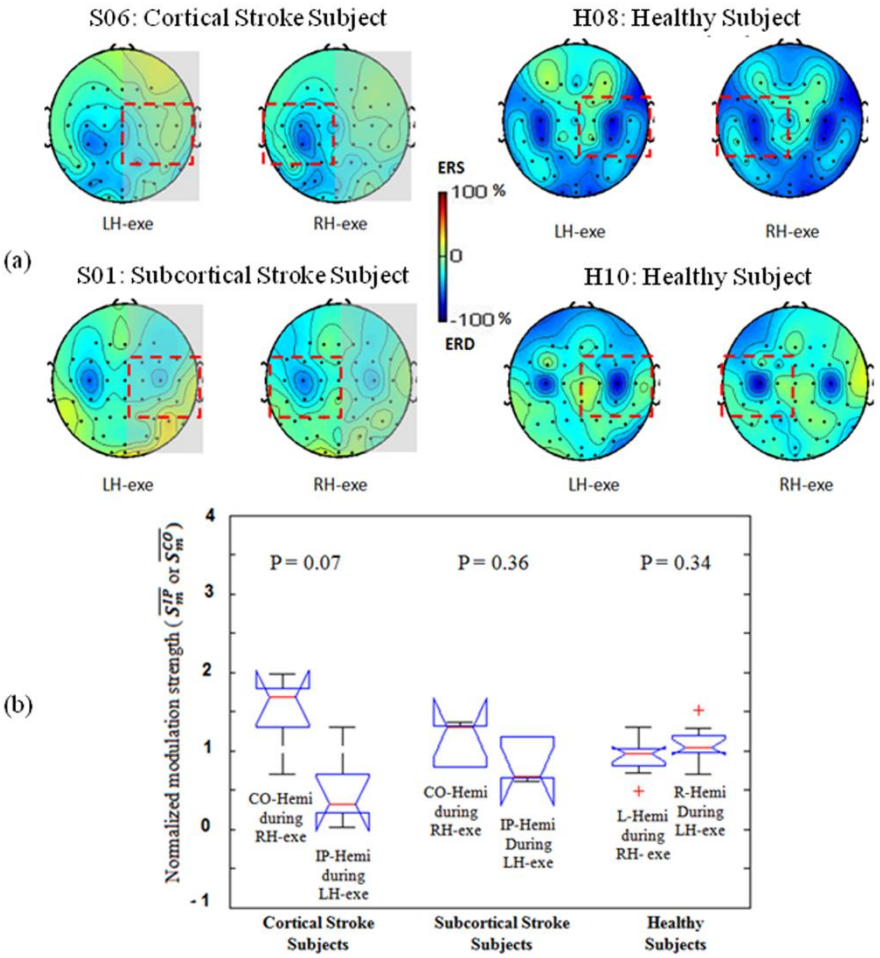

Figure 2: (a: Top) Illustrations of TopoERDs of two stroke subjects (S06, S01) and two healthy subjects (H08, H10) and the stroke-healthy group analysis: All red boxes represent the contralateral motor cortex areas. Absent or less strong modulations were observed in the ipsilesional hemispheres (shaded with gray), while more symmetric modulations were found in both healthy subjects. (b: Bottom): Box-and-whisker plots representing distributions of normalized modulation strength of both ipsilesional (IP) and contralesional hemispheres (CO) in the 5 cortical stroke patients, 5 subcortical stroke patients and both left and right hemispheres in 11 healthy control subjects evaluated at T0. For each box-and-whisker plot, the red bar denotes the median, and the red plus sign denotes the outlier.

3.3.2 Temporal changes of brain patterns during stroke recovery

During recovery, two evolutions of S_m were observed in six stroke subjects (S01, S02, S03, S04, S06, S09): i) a significant increase of ipsilesional S_m and ii) a decreasing trend of contralesional S_m. In the only non-recovery patient (S10), S_m over the contralesional hemisphere increased while S_m over the ipsilesional hemisphere remained absent. This is summarized in Figure 3, both for individual patients as the group average (the pink dash lines in Figure. 3(d), 3(e)). In the healthy controls, no change of S_m between T0 vs. T1* was observed (as illustrated in Figure. 4). At group level, steep changes of S_m in both hemispheres were normally observed during the first month after stroke (T0-to-T1). Hereafter, in the period T1-to-T3, both ipsilesional and contralesional S_m stabilized except for two subcortical stroke patients (S01 and S03, see Figure 3(e)), in whom a steep decline of the ipsilesional S_m occurred after having reached its maximum at T2. Using a Wilcoxon signed-rank's test, the difference between S_m at T0 vs. T1 was significant only on the ipsilesional side ($p<0.05$) but not on the contralesional side ($p=0.46$), see Figure. 5. Although the decrease of contralesional S_m during T0-to-T1 period was not significant at group level, three patients showed a steep decline of contralesional S_m. In three other patients, the contralesional S_m transiently increased and subsequently decreased. In the healthy controls, no significant difference between S_m at T0 vs. T1* was found (with $p=0.50$ and $p=0.89$, for contra- and ipsilateral to the left hand movement, respectively; for the right hand movement, $p=0.50$ and $p=0.23$).

Moreover, a significant increase of up-FM with respect to S_m was found in the ipsilesional hemisphere in the period T0-to-T1. After T1, no significant change of up-FM with respect to S_m was found in either hemisphere (see the details in Table A2 in Appendix-3).

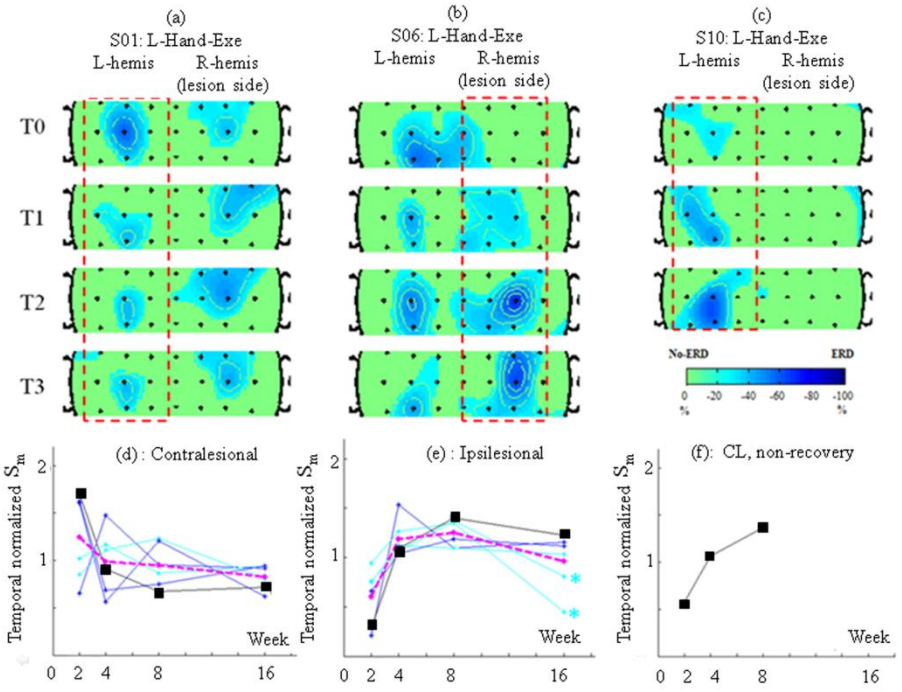

Figure 3: Illustration of evaluation patterns in stroke patients. (a) Spatial decrease of $\boldsymbol{S_m}$ *over the contralesional hemisphere and increase of* $\boldsymbol{S_m}$ *over the lesional hemisphere of patient (S01, good recovery), during paretic hand execution task. (b) Similar pattern in patient S06. (c) Increase of contralesional* $\boldsymbol{S_m}$ *with absence of ipsilesional* $\boldsymbol{S_m}$ *in the single non-recovery patient (S10). Note that the scale underneath Figure 3(c) is also valid for Figures 3(a) and 3(b). (d) Normalized modulation strength of the contralesional hemisphere as a function of time of the six patients with significant recovery, showing a decrease of contralesional* $\boldsymbol{S_m}$*. The black line is the evolution observed in the red box of Figure 3(a); the blue-and-cyan lines show the contralesional evolution observed in the cortical and subcortical stroke subjects, respectively; the pink line represents the average evolution of all six subjects (S01, S02, S03 S04, S06 and S09). (e) Temporal evolution of the normalized modulation strength of the ipsilesional hemisphere for the six patients with significant recovery. The asterisk denotes the temporal evolution with steep decline after having its maximum. (f) Temporal evolution of the contralesional (CL) normalized modulation strength in the single non-recovery patient (S10).*

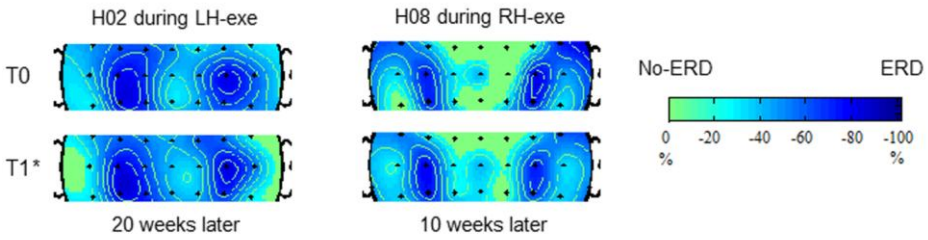

Figure 4: Comparison between T0-TopoERD vs. T1-TopoERD in two healthy controls (H02 and H08) during performance of a left and right hand movement, respectively.*

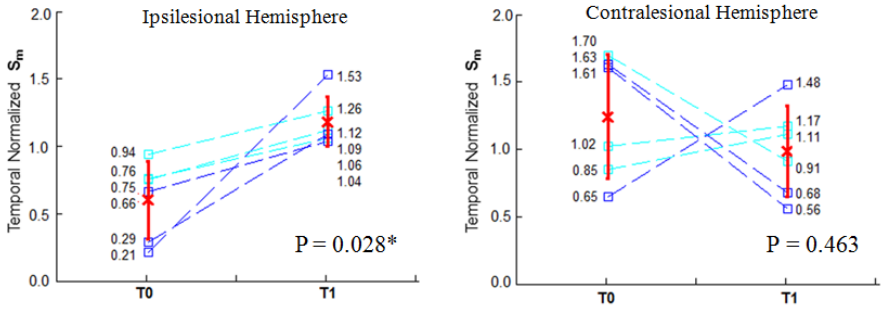

Figure 5: The two subfigures show the changes in $\boldsymbol{S_m}$ at the contralesional and ipsilesional hemisphere at T0 vs.T1 in six stroke patients. Data are the same as in Figures. 3(d) and 3(e) (2 weeks "T0" and 4 weeks "T1"). The blue-and-cyan lines represent the direction of change in the cortical and subcortical subject, respectively. Each red error bar indicates the mean and the standard deviation. The number at the starting/ending of each blue line is the temporal normalized $\boldsymbol{S_m}$ at T0 or T1. The asterisk denotes significance of the p-value (<0.05).

3.4 Discussion

In this pilot study, we quantified the modulation of the sensorimotor rhythm using an optimized ERD measure, during performance of hand movements in acute hemispheric stroke patients and during recovery. We introduced modulation strength "S_m" to assess changes during recovery from acute stroke.

An "asymmetrical brain'' by various measures was generally observed in several hemispheric stroke studies [17, 19, 24]. At baseline, our results are in line with the findings by Stępień et al. [25], showing that a larger hemispheric difference in ERD is present in cortical than in subcortical stroke subjects. This suggests that the two types of stroke differently influence the brain's oscillatory activity (Stępień et al. [25]) and thereby the EEG. The strong reduction-or-absence of the ipsilesional ERD found in the patients with a cortical stroke directly reflects damage to cortical neurons. The slight decrease of ipsilesional ERD in the patients with a subcortical stroke may be caused by disruptions in subcortical-cortical loops [34].

No change of S_m between T0 and T1* was observed in the healthy controls. Conversely, in 85% of the patients with successful recovery, two evolutions of S_m were found: (i) a significant increase of ipsilesional S_m and (ii) a decreasing trend of contralesional S_m. In the single patient without recovery, no significant modulation was observed over the ipsilesional hemisphere, while the contralesional hemisphere showed increase in modulation strength. At group level, steep changes of ipsilesional (significant with both time after stroke and up-FM) and contralesional S_m were observed during the first month (T0-to-T1) after stroke; this finding resembles the recovery that is normally seen during the acute phase rather than the sub-acute or chronic phases [35]. The significant change of ipsilesional S_m suggests a key role of this hemisphere. A number of mechanisms may contribute to these changes of both hemispheres as will be discussed next.

3.4.1 Ipsilesional hemisphere

In the three cortical stroke patients, higher frequency components in the baseline EEG (8-13 Hz or 15-25 Hz) were absent or reduced at T0, which is a typical finding over the affected hemisphere after cortical stroke [17, 19, 22]. Clearly, therefore, ERD, if any, was absent. During recovery, these frequencies gradually re-emerged, and resulted in reappearance of ipsilesional modulation. The re-emergence of higher frequency components may have resulted from axonal sprouting between cortical neurons in the penumbral region, as is normally observed during the initial weeks after stroke. Recently, Kasashima et al. suggested that strengthening of ERD may also reflect an increase in cortical excitability as a higher number of cortical

neurons appears to being activated while performing motor related tasks [36].

In the three subcortical stroke patients, the increase of ipsilesional modulation may reflect the recruitment of the additional secondary motor cortex areas (such as premotor cortex and supplementary motor cortex). Such additional recruitment was also reported in some fMRI and tractography studies [37-39], and direct connections between the non-primary motor cortex and the spinal cord motorneurons were indeed found in an anatomy [40] and tractography study [39]. The initial increase in ipsilesional activation followed by a decrease during stroke recovery was also observed in some fMRI studies in acute subcortical stroke patients [12, 15]. In these studies it was suggested that in the acute phase additional recruitment of the parallel non-primary motor loop was required to generate motor output. After the restitution of the direct corticospinal pathway connecting to M1, however, this additional recruitment was presumably redundant, resulting in a reduction of the ipsilesional activation. In our study, the decrease of the ipsilesional S_m after having reached its maximum was observed in two subcortical stroke subjects but not in the cortical stroke subjects, which may reflect this mechanism.

3.4.2 Contralesional hemisphere

During recovery, the contralesional S_m decreases. This decreasing trend of contralesional S_m suggests a supplementary role of this hemisphere during stroke recovery, which may be different depending on subject's condition-or-recovery strategy. Moreover, in severely affected patients, whose ipsilesional hemisphere cannot be restored, the contralesional hemisphere may play a leading role during recovery [15, 41, 42] such as in our only non-recovery subject (S10): the increase of contralesional S_m could reflect an attempt of the brain to reorganize cortical networks including those from the contralesional hemisphere. In patients with good recovery, enhance-then-decrease of contralesional brain activity was reported in fMRI and PET studies [11, 12, 15, 43]. In the acute phase, larger than physiological contralesional (ipsilateral) brain activity may reflect an enhanced effort to execute movement of the affected hand, similar to the increase in brain activity observed in healthy subjects during difficult movements [44]. As during recovery less effort to execute the movement of the paretic hand is

presumably needed, contralesional activation decreases. Similar findings were reported by [11, 12, 15, 43]: during recovery of the ipsilesional hemisphere less contribution from the contralesional hemisphere to execute hand movement is needed, resulting in a decrease of the contralesional activation. To what extent the recovery process actually depends on or is assisted by the contralesional activity needs further investigation.

In most of the healthy subjects (8/11) and the patients with good recovery (6/7), we observed a bilateral modulation during motor execution. Similar observations were done by Kaiser et al. [33] showing bilateral ERD during a performance of a unilateral hand movement in healthy subjects. In a recent EEG-fMRI study performance of a unilateral hand movement in healthy subjects also showed bilateral alpha-or-beta ERD. Interestingly, however, the BOLD signal was only present on the contralateral hemisphere, and was negatively correlated with the contralateral ERD [45, 46]. In a theoretical study on a relationship between EEG and fMRI by Nunez and Silberstein [47, 48], authors mentioned that "several possible physiological factors cause the mismatches between metabolic and electrical measures of brain function". These EEG/fMRI studies show that changes in (synchronized) activity of pyramidal neurons, which are at the basis of observable ERD signals, are apparently not always accompanied by significant changes in metabolic rates and thus BOLD-fMRI.

Apart from using ERD as a marker for recovery, there is growing interest on using ERD based BCIs to promote motor recovery after stroke. Daly and Wolpaw recently suggested that, guided by BCI, patients can learn to activate certain brain areas to enhance plastic changes in the brain [49]. Although various ERD based BCIs are being developed [33, 50-52], there is no consensus about a classification method and a channel selection. The results from our pilot study suggest that an optimal BCI for stroke rehabilitation should guide stroke patients to learn to (re)activate their ipsilesional hemisphere during training. Because ERD was normally found in both hemispheres in stroke patients, one suggestion is to assign higher weight factors to the EEG channels on the ipsilesional M1 over the channels on the contralesional M1 during training. Furthermore, an optimal classification method should also indicate a focal ERD activation in the motor cortex rather than merely increase classification accuracy.

If the ipsilateral and contralateral evolution of the ERD can be improved or accelerated using BCI guided therapy is presently unclear. We show that functional recovery is accompanied with these ERD modulations, but a causal relationship is not implicated by these findings. Our results do encourage, however, a clinical study using EEG feedback of the ERD during rehabilitation from acute hemispheric stroke.

In conclusion, S_m, which reflects the area and amplitude of the modulation, can be used to detect changes in cortical networks during stroke recovery. During stroke recovery, we found two evolutions: a significant increase of ipsilesional S_m and a decreasing trend of contralesional S_m. The significant increase of ipsilesional S_m may reflect recovery of cortical neurons and neuroplasticity as a key factor during recovery. The decreasing trend of contralesional S_m suggests lesser dependence of this hemisphere in executing the affected hand movement due to the progressive recovery of the ipsilesional hemisphere and may reveal the supplementary role of this hemisphere.

Acknowledgement

We would like to thank all stroke patients and healthy controls for their participation.

Appendix-3

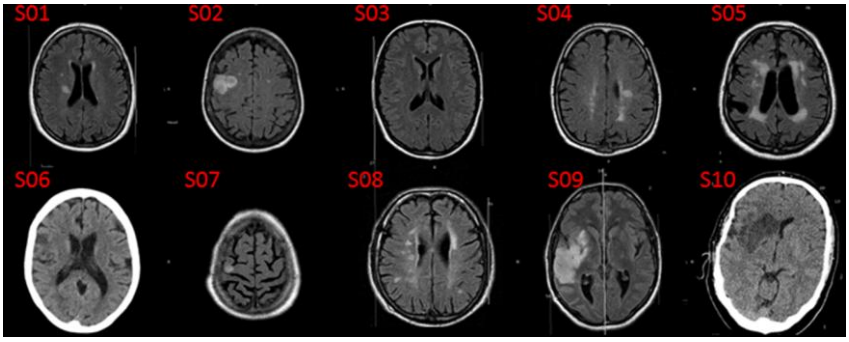

Figure A1: T_1-weighted MRI (S01-S05 and S07-S09) or CT (S06 and S10) images at the level of maximum infarct volume for each stroke subject. S01, S03, S04, S05 and S08 show subcortical infarcts; other scans show cortical infarcts.

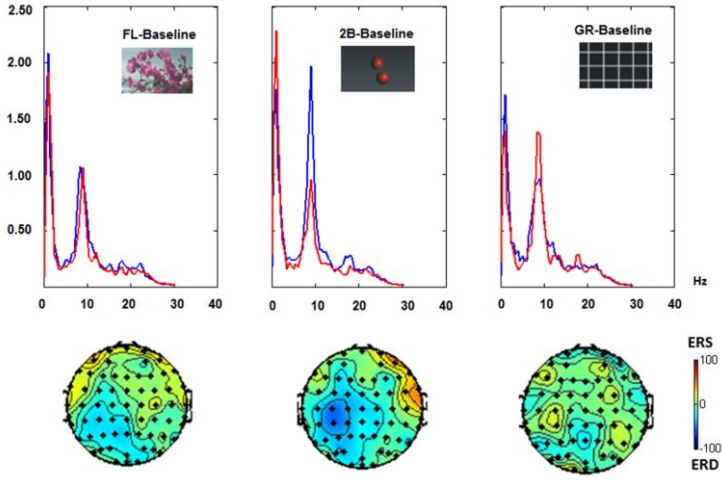

Figure A2: Power density spectrum (PDS) on C3 and its topographical ERD, for the three different baseline movies (FL, 2B and GR) during calibration in S06. Red: hand movie; blue: baseline. TopoERDs for these three baselines are shown below.

Table A1: Experiment conditions in 10 stroke and 11 healthy subjects. Beta denotes beta band frequency range from 15 – 25 Hz; while mu denotes mu band from 8 – 13 Hz. SMR means sensory-motor rhythms. FL, GR, 2B are the three baseline movies used in this study: FL represents the flower movie, GR represents the grid movie, and 2B represents the two balls movie.

Stroke subjects			Healthy subjects		
No.	SMR	*Basedline Used*	*No.*	SMR	*Basedline Used*
S01	Beta	FL	H01	Beta	GR
S02	Beta	GR	H02	Mu	GR
S03	Beta	FL	H03	Beta	GR
S04	Mu	FL	H04	Beta	FL
S05	Beta	FL	H05	Beta	GR
S06	Mu	2B	H06	Mu	FL
S07	Mu	GR	H07	Mu	GR
S08	Beta	FL	H08	Mu	FL
S09	Mu	GR	H09	Beta	FL
S10	Beta	FL	H10	Mu	2B
			H11	Beta	FL

Table A2: Average change of up-FM with respect to S_m across six patients "$slope_{avg}$" and its p-value for each hemisphere in each period. For each subject, the change of up-FM with respect to S_m is defined as a ratio of change of up-FM divided by change of S_m. A Wilcoxon signed-rank's test with $H_0: Median\ of\ slope_{avg} = 0$ was used to test for a significant increase/decrease. Significant p-value was marked with asterisk.

Hemisphere	***T0-to-T1***		***T1-to-T2***		***T2-to-T3***	
	Average slope	p-value	Average slope	p-value	Average slope	p-value
IPSI	0.45 (SD=0.36)	0.04*	-0.36(SD=1.81)	0.69	-0.30(SD=0.64)	0.11
CONTRA	0.13 (SD=0.52)	0.69	0.44(SD=0.83)	0.35	0.15(SD=0.26)	0.29

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Chapter 4 Classification of Motor Imagery Performance in Acute Stroke

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Abstract

Objective: Effective motor imagery performance, seen as strong suppression of the sensorimotor rhythm, is the key element in motor imagery therapy. Therefore, optimization of methods to classify whether the subject is performing the imagery task is a prerequisite. An optimal classification method should have high performance accuracy and use a small number of channels. We investigated the additional benefit of the Common Spatial Pattern filtering (CSP) to a Linear Discriminant Analysis (LDA) classifier, for different channel configurations.

Methods: Ten hemispheric acute stroke patients and eleven healthy subjects were included. EEGs were recorded using 60-channels. The classifier was trained with a motor execution task. For both healthy controls and patients, analysis of recordings was initially limited to 3 and 11 electrodes recording from the motor cortex area, and later repeated using 45 electrodes.

Results: No significant improvement of the addition of CSP to LDA was found (in both cases, the area under the receiving operating characteristic (AU-ROC) ≈ 0.70 (acceptable)). We then repeated the LDA+CSP method on recordings of 45 electrodes, since the use of imagery neuronal circuits may well extend beyond the motor area. AU-ROC rose to 0.90, but no virtual "most responsible" electrode was observed. Finally, in mild-to-moderate stroke patients we could successfully use the EEG data recorded from the healthy hemisphere to train the classifier (AU-ROC≈0.70).

Significance: Including only the channels on the unaffected motor cortex is sufficient to train a classifier.

4.1. Introduction

Stroke is one of the leading causes of adult disability. Physical training is the standard therapy for stroke rehabilitation in patients with motor deficits; however, this requires effort from the patient to activate his/her affected limb, which may result in fatigue or demotivation. Furthermore, in the acute phase, some stroke patients may completely lose their ability to move the affected limb, which restrains participation in standard physical therapy. Recently, therapy based on performing motor imagery (MI) was introduced as an alternative [1]. MI based therapy may not replace the physical training, but it can be included as supplementary to promote or accelerate stroke recovery. It is based on the notion that by imagining a movement, part of the network that is involved in the actual execution of that movement is presumably activated, too [2]. In 2001, Page et al.[3] conducted a feasibility study in thirteen stroke patients showing the positive effects of MI on stroke recovery. In this study, eight out of thirteen patients received a 10-minute MI-session in addition to the standard physical therapy. After six weeks of training, the group of patients with the additional MI-sessions showed an increase of the Fugl-Meyer score, while no changes were observed in the group without MI-sessions. Later, positive effects of MI training on motor improvement were confirmed in other studies [4-7].

Feedback is essential in any rehabilitation strategy [1]. However, while motor execution (ME) in physical therapy is observable, the subject's MI performance is not. MI can be reflected in the modulation of particular EEG rhythms: during imaging of a movement, cortical neurons are activated, resulting in an Event-Related Desynchronization (ERD; decrease of signal power) observed over the sensorimotor cortex. The ERD measure is defined as the relative decrease of the signal power of the sensorimotor rhythm (SMR) between the two conditions, here resting and motor imagery or motor execution [8]. To inform if motor imagery is performed, an EEG based Brain Computer Interface (BCI) system can be used: strong motor imagery is observed when SMR is continuously present during rest, and absent during the active period. An accurate classifier in a BCI system may guide a patient for better control of his/her brain activity during the rest and active period.

Although various EEG based BCI systems for stroke rehabilitation are being developed to classify between rest and active phases, there is no consensus

yet about the optimal classification method. Implementation in a BCI system covers several aspects: (i) selection of SMR frequency band, (ii) choice of a classification technique, and (iii) minimization of the number of channels. Unlike a possible subject-specific SMR band, the classification method and the number of channels are trade-off parameters: most classification methods with high performance accuracy required a large number of channels. Various choices for classification technique and channel selection can be seen in the literature. For example, Kaiser et al [9] used three Laplacian channels (C3, C4, and Cz) to construct the classifier. Gomez-Rodriguez et al. [10] included 35 channels (with common average reference) covering the posterior part of frontal cortex, the motor cortex and the anterior part of parietal cortex. Varkuti et al. [11] included 27 EEG channels with common spatial pattern "CSP" (for the details of CSP, see below) in the MIT-Manus Robot based BCI system, and Ramos-Murguialday et al.[12] included 128 channels, covering parts of frontal, parietal, temporal and motor cortex.

The choice for many channels beyond the motor area was justified by the notion that various other parts of the brain (e.g. the anterior part of inferior frontal cortex, the anterior part of the inferior parietal lobule, and the occipital cortex) were also activated during motor imagery/observation [13-15]. The use of a spatial filter (e.g. Laplacian filtering or Common Spatial Pattern analysis) to reduce volume conduction effects [16] is an alternative approach to enhance classification accuracy. Among these filters, CSP appears to be the most effective [16, 17].

The ideal classification method should require a small number of channels to reduce preparation time/complexity and cost at high accuracy. Patients will feel more comfortable with a BCI system with a reduced number of channels, and this will motivate them to participate in the rehabilitation training. Only a few studies were conducted to find that optimum, and mostly done in healthy subjects [18-20]. Sannelli et al. suggested that the use of 48 channels with CSP gave the best performance; however, upon reducing the number of channels to 32 or 8 they did not find a significantly lower performance [18]. In chronic stroke patients, Bundy et al. [21] suggested using the motor signals in the unaffected hemisphere, as larger than normal brain activity was observed on that side in chronic stroke patients, while Tam et al. suggest using 8-36 channels without hemispheric preference to preserve high classification accuracy [22].

To our knowledge, a study aimed to find the optimal number of channels in acute hemispheric stroke patients, has not yet been done. In hemispheric stroke patients, changes of ipsilesional brain activity toward the activity seen in the normal hemisphere are observed during recovery [23, 24]. This may allow to first train the classifier with data from the non-affected hemisphere, in order to later classify the data recorded from the ipsilateral hemisphere during MI training of the affected area. This may further guide patients attempting to produce similar brain patterns as seen in the healthy hemisphere, thus increasing hemispheric (i.e. EEG) symmetry. EEG symmetry is a typical finding in healthy subjects [25], while EEG asymmetry is correlated with stroke severity [23] and decreases during recovery [26].

In this study, we aim to find the optimal classification method comparing two methods: linear discriminant analysis LDA+CSP vs. LDA alone using different channel numbers/configurations. We take as definition for "optimal" that the classifier has sufficient accuracy (the area under the receiving operating characteristic curve must be at least 0.70), with a minimum number of channels. In addition to evaluations in healthy volunteers, we also train the classifier in hemispheric stroke patients using EEG recordings from the non-affected hemisphere.

4.2. Methods

4.2.1 Subjects

Three groups of subjects were recruited to participate in this study. Group1 (controls) consisted of five relatively young healthy subjects (mean age: 26.4, SD=1.67, three female, four right handed). Group2 (age-matched controls) consisted of eleven elderly healthy subjects (mean age: 57 years, S.D. 7.8, nine female, ten right handed). Group3 consisted of ten first-ever acute hemispheric stroke patients (mean age: 64.9 years, S.D. 13.4, five female, nine left hand motor deficit). Patients participated within a period of 2 weeks after their stroke. Demographic and clinical data of the patients are summarized in the Table 1. Each subject was informed about the

experimental procedure and signed a written consent form. The study was approved by the local ethical committee of Medisch Spectrum Twente hospital. All group2 and group3 subjects participated in an identical experimental paradigm, a slightly different paradigm was used in group1 (see the details in subsection 2.3). The group1 subjects were recruited to find the minimum number of trials needed to estimate a reliable classifier. The comparisons between LDA+CSP versus LDA alone were done only in the group2 and group3 subjects.

Table 1: Demographic and clinical data of the stroke patients (group 3).

Subject	*Gender/Age*	*Affected Hand*	*Site/type of lesion*	*NHISS*	*up-FM*	*Clinical condition*
S301	F/58	Left	R- Subcor	1	54	Mild
S303	F/51	Left	R- Subcor	4	50	Mild
S304	M/68	Right	L-Subcor	3	48	Moderate
S308	M/58	Left	R- Subcor	4	52	Mild
S305	M/84	Left	R- Subcor	10	4	Severe
S302	F/56	Left	R-Cor	5	65	Mild
S306	F/81	Left	R-Cor	3	49	Moderate
S309	F/62	Left	R-Cor	6	24	Severe
S310	F/49	Left	R-Cor	7	4	Severe
S307	F/82	Left	R-Cor	3	41	Moderate

"Subcor" and "Cor" denote subcortical and cortical stroke, respectively. "R" and "L" stand for right and left hemisphere. "M" and "F" indicate male or female. up-FM stands for upper extremity Fugl Meyer scale ranging from 0 to 66 (a healthy subject would have up-FM=66). From the up-FM, we classified the patients into three groups: severely affected patients ($0<\text{up-FM}\leq 25$), moderate ($25<\text{up-FM}\leq 50$), mild ($\text{up-FM}>50$). Note that we had switched the left and right hemisphere in S04 (the only left hemispheric stroke) to suit the analysis.

4.2.2 EEG-recording

All experiments were conducted in a shielded room. 60-channel EEG recordings (TMS International, The Netherlands) were made using Ag/AgCl electrodes positioned according to the international 5-10 system. The left and right mastoids were used as a reference. The sampling frequency was 5 kHz. All electrode impedances were kept below 5 kOhm. All 1st row electrodes

(T7, FT7, F7, AF7, FP1, FPz, FP2, AF8, F8, FT8, and T8) and some 2nd row electrodes (F5, AF3, AF4, and F6) were excluded to avoid possible EMG-contaminated signals.

4.2.3 Experimental Design

Two types of movies were used as the cues to either relax-and-perform-no-movement ("rest") or imitate/image ("action") the movement. Three different relax baseline movies were used: (i) two-moving-balls (2B); (ii) a slowly-moving-flower (FL); and (iii) a grid (GR). The GR was the only static movie, showing white stripes against a black background (for details see figure 1). The "action" movie showed right (or left) hand opening and closing. Every movie lasted 10 seconds. The experiment consisted of three phases: 1) calibration, 2) motor imagery, and 3) motor execution.

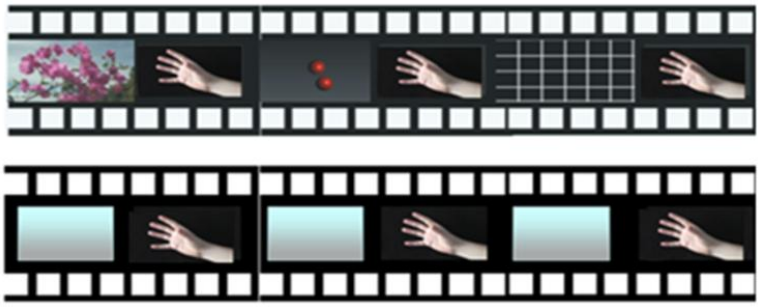

Figure 1: Top: Part of the movie sequences during the calibration condition showing three different baseline movies (flower, balls and grid). Bottom: Part of the movie shown during the classification. The blue/grayish boxes represent the optimal baseline movie for each subject.

1) Calibration: By first presenting three different baseline movies, we aimed at finding the baseline movie that induced maximum SMR-power [27].

2) Motor imagery "MI": During MI, we repeated 16 combinations (trials) of the optimal baseline movie combined with the right hand movie (another 16 trials were repeated for the left hand movie).The subject was asked to relax and not to perform-or-image any movement during the optimal baseline movie, but to image the hand movement seen on the screen.

3) Motor execution "ME": During the ME phase, the same experimental paradigm as in the MI was repeated. However during the action movie, the subject was asked to execute the movement seen on the screen. The patients without residual movement ability were asked to perform-or-attempt moving their affected hand.

Because the aim of recruiting group1 subjects was to reliably classify a minimum number of trials for each of group1 subjects, 40 trials of the flower and the hand movies were repeated both for motor imagery and motor execution. Note that, to prevent any possible tiredness or fatigue, due to the longer experiment, in all group-1 subjects we skipped the calibration phase in that group. The data recorded during the ME-phase of group2 and group3 subjects have been used in a related study [28].

4.2.4 Visual artifact rejection

All EEG signals were digitally down sampled to 500 Hz. Hereafter, all data were filtered between 0.5-30 Hz using a 4^{th} order Butterworth filter. All signals were visually inspected by an experienced clinical neurophysiologist (MvP) for the presence of muscle or ocular artifacts. Any EEG-fragment with an artifact was removed and excluded from the analyses. After artifact rejection, each trial (both the baseline and the hand movies) lasted ≈8 s.

4.2.5 Channel Selection

Different channel selection configurations were formed. For the method without CSP (noCSP), five configurations (conf) were formed: (i) conf-A (a three channel configuration including C3, Cz and C4), (ii) conf-B (an eleven channels configuration, which included the motor cortex channels, i.e. FC5, FC1, FC2, FC6, C3, Cz, C4, CP5, CP1, CP2, and CP6), (iii) conf-C (in this configuration, a Laplacian filter was applied to the EEG signals recorded from the same eleven channels as described in conf-B, later only three channel "C3, Cz, C4" were selected), (iv) conf-D (similar to conf-C, but all eleven channels were selected as the feature dimensions), and (v) conf-E (all signals from 45 EEG channels were spatially filtered using the Laplacian).

For the method with CSP, two CSP configurations were formed: (i) conf-F (which is equivalent to conf-B) and (ii) conf-G (all 45 channels without any spatial filter).

4.2.6 Feature extraction

SMR was limited to the mu-band (7-13 Hz). The mu band power was extracted to classify between rest (baseline) and active (motor imagery/execution). First, EEG signals were selected according to the channels listed in each configuration. We divided the artifact free, concatenated EEG recordings, into smaller epochs (each epoch lasted 2 s. with 1 s. overlap). Subsequently, the mu-power of each epoch was calculated by integrating the power density spectrum (estimated using Welch's method with a window of 2 s. and no overlap) from 7 to 13 Hz. So, for example, the conf-A set resulted in three dimensional feature vectors with integrated mu-power from C3, C4, and Cz, for other configurations see details in table A2 (see Appendix-4).

4.2.7 Classification

In all group1 subjects, we estimated seven classification performances from seven different splitting ratios, i.e. training/testing ratios were 5/95, 10/90, 14/86, 20/80, 25/75, 33/67 and 50/50. In the group2 and group3 subjects, 50% of the features were randomly assigned to train the classifier. Later, we tested the performance of that classifier using the remaining features. The area under the receiving operating characteristic (AU-ROC) was used as performance measure. In this study, we wish to compare classification accuracy between methods with and without CSP. Unlike the noCSP case, for which the power features were directly fed into the LDA-classifier, in the CSP case we first estimated the common spatial filters before proceeding with the feature extraction and classification steps. We will shortly review the fundamental concepts of CSP.

CSP is a technique that maximizes the variance in one class, while minimizing the variance in another class [18, 29]. Let $X_{CSP} \in \mathbb{R}^{CH \times T}$ be a CSP-filtered EEG signal, which is computed according to $X_{CSP} = W^T X$. In this case, $W \in \mathbb{R}^{CH \times CH}$ denotes a CSP-matrix, where CH is the number of

EEG channels. X denotes the bandpass-filtered EEG signals, which is $X \in \mathbb{R}^{CH \times noS}$, where *noS* denotes the number of sampled time points. In this study, we computed the *W*-matrix either from 11 or 45 EEG channels, which resulted in either 11 or 45 CSP filters.

The selected CSP-matrix ($W_{sel} | \, W_{sel} \in \mathbb{R}^{CH \times nFil}$) denotes the spatial matrix consisting of the selected CSP filters (columns in *W*), where *CH* denotes the number of EEG channels (11 or 45), and *nFil* denotes the number of CSP-pairs (*nFil*= 2, 6, 10). If *nFil*=6, the first-and-last three column vectors from the CSP-matrix (*W*) were selected to form W_{sel}. After constructing W_{sel}, the CSP-filtered EEG (or X_{CSP}) was computed according to $X_{CSP} = W_{sel}^{T} X$. Unlike the noCSP methods, we computed a log variance of X_{CSP} as the feature before feeding it into the LDA classifier.

Figure 2 summarizes the scheme of the data analyses. Apart from using the EEG data recorded during a MI task both for training and testing (called MI/MI) two other train/test combinations were used: (i) a condition where we train the classifier using ME data and test the classifier with the MI data (ME/MI) and (ii) a condition where we train the classifier using the EEG data recorded on a single hemisphere during motor execution (half-ME/MI), details will be explained as follow. Note that the CSP method was not used in the half-ME/MI case.

In group3 (stroke), the half-ME/MI based classifier was trained using the data recorded over the unaffected hemisphere (left) while the patient performed his/her unaffected hand movement (RH). To this end, the standard configurations using 3, 11, 45 channels were changed into 1 channel (C3 (for right hemispheric stroke) or C4 (otherwise)), 5 channels (FC5, FC1, C3, CP5, CP1 or their mirrored channels), and 19 channels (F3, FC5, FC1, A1, C3, CP5, CP1, P7, P3, O1, F1, FC3, C5, C1, CP3, P5, P1, PO5, PO3 or their mirrored channels), respectively.

4.2.8 Statistical Analysis

A Kruskal-Wallis Test and a Wilcoxon post-hoc test were employed to test for significant AU-ROC differences among the classification methods.

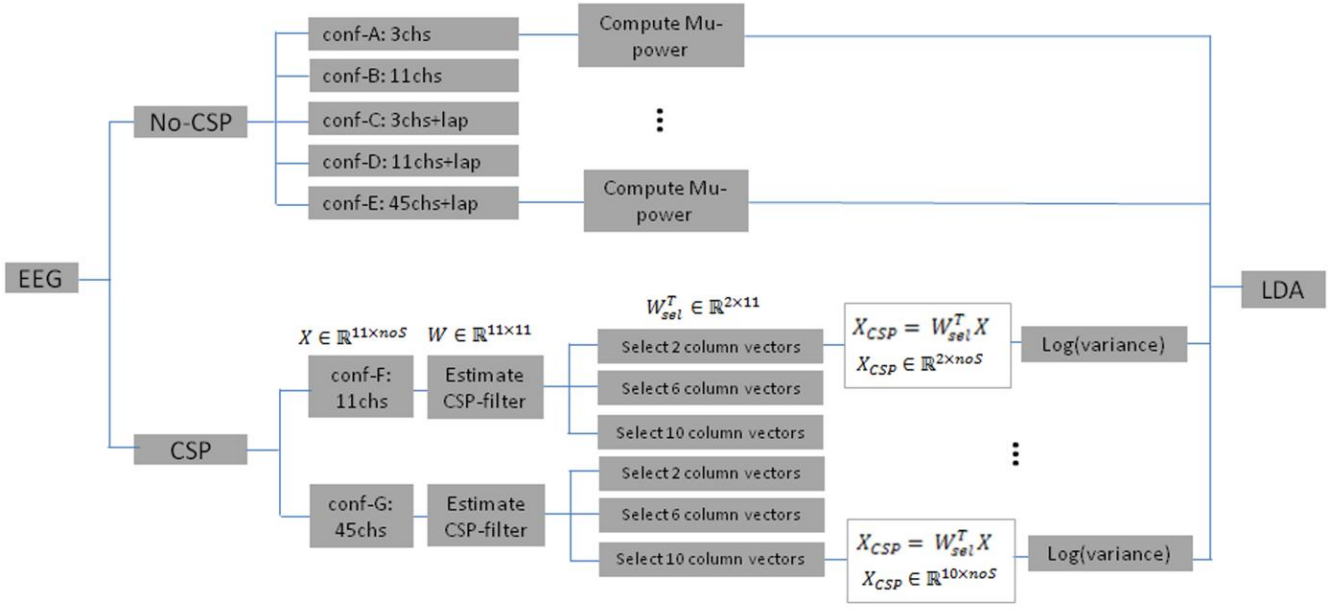

Figure 2: Scheme designed to compare AU-ROC (Area under the ROC curve) among difference classification methods. Lap: Laplace. CSP: Common Spatial Pattern. LDA: Linear Discriminant Analysis. X denotes the bandpass-filtered EEG signal. W and W_{sel}^T denote the CSP and the selected CSP matrices. X_{CSP} is the CSP filtered EEG signal. noS denotes the number of sampled time points.

4.3. Results

Results are divided in three subsections. First, we compared the additional gain of the CSP- over the noCSP based method for different channel configurations. In the following subsection, we present the AU-ROC for using three different data sets (MI/MI, ME/MI and Half-ME/MI); this is mainly to prove whether acceptable high performance accuracy was maintained using ME-based classifier as MI-based classifier or not. Finally, a derivation of the choice of the splitting ratio of the number of trials between testing vs. training will be shown in the last subsection.

4.3.1 Classification performance using CSP versus noCSP

The average AU-ROC was at or above the chance level (AU-ROC=0.7) for all methods at any configuration. The CSP method yielded higher performance accuracy than the noCSP one. In the group-2 subjects during left hand motor imagery (LH-MI), the average AU-ROC increased about 10% using CSP. However, this difference was significant only when we constructed the CSP-filters from the 45 channels EEG (45chCSP), see figure 3. Similar results were also obtained in all group2 and group-3 subjects for both LH/RH-MI. In conclusion, using CSP yields a higher AU-ROC, but this difference was significant only when CSP filters were constructed from 45 channels (45chCSP), see figure 3.

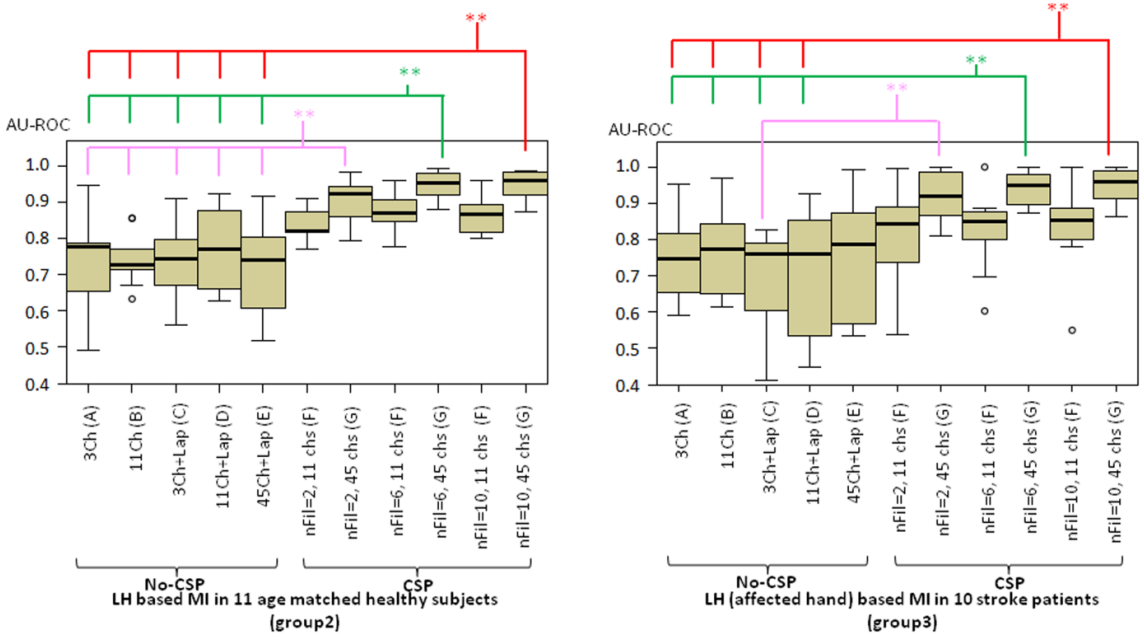

*Figure 3: The left panel shows box plots of AU-ROCs in all configurations (both with and without CSP) from 11 age matched healthy subjects (group2) during left hand motor imagery (LH -MI). ** denotes significantly difference of AU-ROC between each pair (connected with a line) according to the Wilcoxon post-hoc test (with $p<0.05$). The results from the patient group (group3) during LH-MI are presented in the right panel.*

4.3.2 MI/MI vs. ME/MI vs. Half-ME/MI

The average AU-ROC of the ME-based classifier was about 0.70 in both group2 and group3 (or ≈5% drop from the level obtained using MI-based classifier), as seen in figure 4. Among the three cases (MI/MI, ME/MI, and half-ME/MI), the AU-ROC in the MI/MI was the highest, and the AU-ROC in the half-ME/MI was the lowest (except in conf-A and conf-C during LH-MI task of group2, see the right panel of figure 4). Reduction of AU-ROC to chance level (AU-ROC = 0.5) was usually found in the conf-E of the half-ME/MI based classifier (see figure 4 and table A5 in Appendix-4).

In group 2 (age-matched controls), the average AU-ROC (averaged over both LH/RH tasks in all but conf-E) of the half-ME/MI case was 0.68 (SD=0.10). In the conf-E (19 channels), the average AU-ROCs was 0.54 (SD=0.11), see table A5 (in Appendix-4).

In group 3 (patients), the average AU-ROC of the half-ME/MI case across all patients (in all but conf-E) was 0.64 (SD=0.13). For conf-E, the average AU-ROC was 0.63 (SD=0.13). In the non-severe stroke patients, the average AU-ROC (in all but conf-E) was 0.71 (SD=0.08), while the average AU-ROC was 0.49 (SD=0.08) in the three severely affected patients. Summary of AU-ROCs using the half-ME/MI classifier in severe and non-severe patients were shown in table A6 (see Appendix-4).

In conclusion, both the MI/MI and the ME/MI condition yield sufficient performance accuracy. For the Half-ME/MI condition, this is only true for the mild-to-moderate stroke patients.

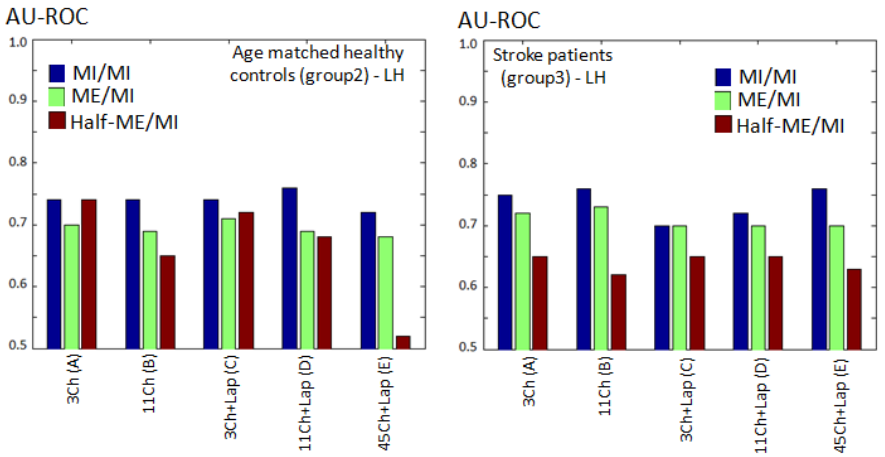

Figure 4: Left panel shows average AU-ROCs of MI/MI (blue), ME/MI (green) and half-ME/MI (brown) in five different channel configurations using the data from 11 age-matched healthy subjects during LH-MI. The average AU-ROCs using the data from 10 stroke patients during LH-MI (affected hand) are presented in the right panel.

4.3.3 AU-ROC at various splitting ratios of the number of trials for training and testing

At group level, the AU-ROC of the conf-A (3 channels) and conf-B (11 channels) reached a stable level using 20% of data (or 8 trials) for training, see figure 5. This was also found in the conf-C and -D (not shown). On the other hand, for conf-E (45 channels) a stable level was not found at the group level, while the optimal splitting ratio varied from 20-35% (mean=27, S.D = 6) for each group1-subject. In conclusion, in all but conf-E (45 channels), AU-ROC reached a stable level using at least 8 trials of EEG data for training.

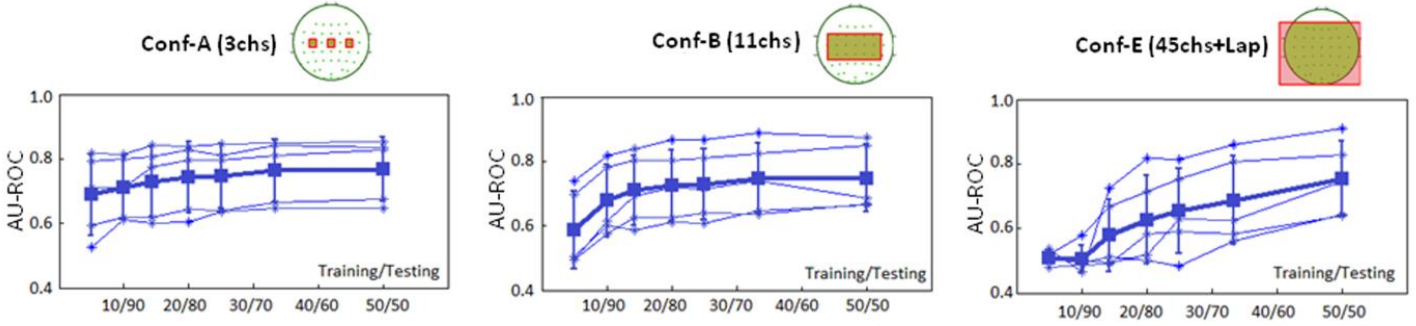

Figure 5: Each thin blue line represents an average AU-ROC (blue square), averaged across all iterations in each k^{th}-fold cross validation (where k = 20,10,7,5,4,3,2 corresponding to the splitting ratio (5/95, 10/90, 14/86, 20/80, 25/75, 33/67, 50/50)), and its standard deviation (error bar) at each splitting ratio (calibration%/test% of number of trials) in each group1 subject during RH-MI (Right Hand –Motor imagery). Each thick blue line represents the group result. Conf means the electrode configuration (number of channels and Laplace operation), as indicated by the red bordered green area on the scalp sketch.

4.4. Discussion

Feedback from an EEG-based BCI system is an essential factor for the success of MI-therapy. An optimal classification method should have high performance accuracy and use a small number of channels (since most of the EEG-based BCI systems are aimed to use in the home environment). In this study, we compared two methods (without and with CSP) using different channel configurations.

4.4.1 Eight trials are sufficient to reliably train the classifier

In the configurations A, B, C and D, the AU-ROC reached a stable level using 20% (8 trials) of the data for training, this suggested that in any electrode located within motor cortex area the SMR-power was weakly stationary using ≈ 8 or more trials; hence, only 8 trials long EEG (or ≈ 60 sec long artifact-free EEG) was sufficient to reliably train the classifier. The minimum training period found here is comparable with the 10 trials (or 50 sec) as suggested by Faller et al.[29].

Although using 8 trials long EEG recordings may not guarantee the stability of SMR power in the case of 45 channels (conf-E), we decided to keep the splitting ratio at 50/50 as in the 3 and 11 channels cases, for better comparison.

4.4.2 CSP versus noCSP

As previously reported [16, 17, 30], high classification performance is normally found in CSP based methods. In our study, classification with CSP was significant higher than noCSP only when the spatial filters were built from 45 channels (45chs-CSP), but no consistent picture of a stable set of electrodes responsible for suppression during imagery. Although the signal-to-noise ratio typically increases using a large number of channels (e.g. 45 channels as in our study) and results in high performance accuracy, imagery sources disperse with the risk of overfitting. This was indeed observed (see examples in figure A1 in Appendix-4). Dispersed weights of CSP filters was also reported by Lotte et al. [31].

The use of 11chs-CSP in this study is equivalent to the RCSP proposed by Lotte et al. [31], using larger weight factors assigned to motor cortex channels

before estimating the CSP matrix. Reducing the number of channels is one way to alleviate from overfitting, but signal-to-noise ratio worsens. As we found no significant advantage using the 11chs-CSP method versus the noCSP one, the method without CSP is recommended to avoid unnecessary computational time.

4.4.3 ME and Half-ME based classifiers in stroke patients

Higher suppression of SMR was normally seen during the ME/MI condition than for the MI/MI, see figure 4. Apparently, repeated motor imagery trials yield less desynchronization than the same number of repeated execution tasks. This suggests that performing successful imagery as such is more difficult than execution, or is more difficult to maintain over trials. Attention and/or fatigue may play their role in that.

Kaiser et al.[9] showed that in elderly healthy subjects the ME-based classifier gave acceptably high performance accuracy similar to the MI-based classifier. Our study shows that the ME based classifier can be used not only in healthy controls but also in stroke patients. Furthermore, we showed that in the healthy controls and the non-severe stroke patients one can train the classifier using only EEG signals recorded on one side of motor cortex area (half-ME based classifier) and still nearly reach an acceptable level.

In the severe stroke patients, the low AU-ROC of the half-ME based classifier is due to the absence of fast activity such as mu or beta [23, 24]. Therefore, there is no difference between mu power in rest vs. motor imagery. So, half-ME based classifier is exclusive only for healthy and non-severe stroke patients.

One key consideration is to train the half-ME based classifier using only the motor cortex-channels to avoid a significant drop of the classification performance as found when all channels in each hemisphere are included.

4.4.4 Channel Selection

Tam et al. [22] and Sannelli et al. [18] suggested that in setting up the right classifier one could reduce the number of EEG channels to eight or five channels, respectively. Indeed, in our MI/MI and ME/MI cases, no significant difference between using three or eleven channels was found. In the half-ME/MI case, we could even train the classifier using C3 or C4 only.

However, the focus of ERD may not be always located on C3 (or C4). Therefore, several studies [10, 12] included a customization step to localize the hot spot. Here, we suggested using five channels on one hemisphere to train the half-ME/MI based classifier. This selection of five channels over motor cortex area will cover all the typical candidates of the hot spot.

4.4.5 Future of BCI systems for rehabilitation of acute stroke patients

Whereas the acute period is the prime interval to receive any therapy [32], clinical gain using MI therapy remained unclear so far in acute stroke [33-37]. In these patients, a reduced MI ability (less perseverance) was found [38] that may limit the effectiveness of MI therapy. Therefore, BCI-feedback was suggested as an effective tool to enhance MI performance [12, 39].

In fMRI studies, a reduction of contralesional activation with increase of ipsilesional activation was found in patients during recovery [40-42]. Similar findings were reported in an EEG study, showing an increase of ERD over the ipsilesional motor cortex in the acute-to-subacute period [28]. Daly and Wolpaw suggested that stroke patients should learn to produce physiological brain activity to restore the normal central neural system, which will consequently improve motor control [43]. Presumably, during the acute-to-subacute period repetitive activation of ipsilesional motor cortex assists in stroke recovery.

For mild-to-moderate acute hemispheric stroke patients, we suggest to use five channels on the healthy motor cortex for training the classifier, and five on the affected cortex for testing. This yields sufficient classification performance, and the ERD over the ipsilesional motor cortex can also be used to monitor stroke recovery [28]. However, this suggestion maybe not applicable for severely affected patients, since in these patients it is still unclear which hemisphere plays the leading role to assist motor recovery. Some studies suggested that to assist recovery the brain's reorganization should mainly occur in the contralesional hemisphere [44, 45]. If true, the channels should be chosen contralesionally to guide the brain (re)activation in that hemisphere. However, we have previously found that in severe stroke patients with good recovery the brain's reorganization was seen in both hemispheres; whereas for patients with reorganization solely in the contralesional hemisphere, successful motor recovery was not observed [28]. So both hemispheres may play a vital role during recovery. Thus, we may

need to select channels on both hemispheres, although further research is still needed to support this claim.

In conclusion, although classification performance significantly improved using the CSP method with a large number of channels (45 channels in this study), this came with risk of overfitting. Furthermore, there was no significant gain in term of accuracy using the CSP method with 11 channels, compared to the noCSP method. Thus, the noCSP method was recommended to classify between rest and active. To promote recovery in acute hemispheric stroke, the noCSP based method using five EEG channels over the healthy motor cortex region recorded during ME is suggested as the classification method for a NF-system based on motor imagery. This contralesional classification was successfully implemented on the ipsilesional side in the non-severe stroke patients and may serve to guide stroke patient to learn to (re)activate ipsilesional ERD similar to the ERD activity over the healthy hemisphere. In the future, an interventional study using the proposed classification method integrated in an online NF-system should be conducted to evaluate its clinical efficacy.

Acknowledgements

We would like to thank all healthy controls and patients for their participation.

Appendix-4

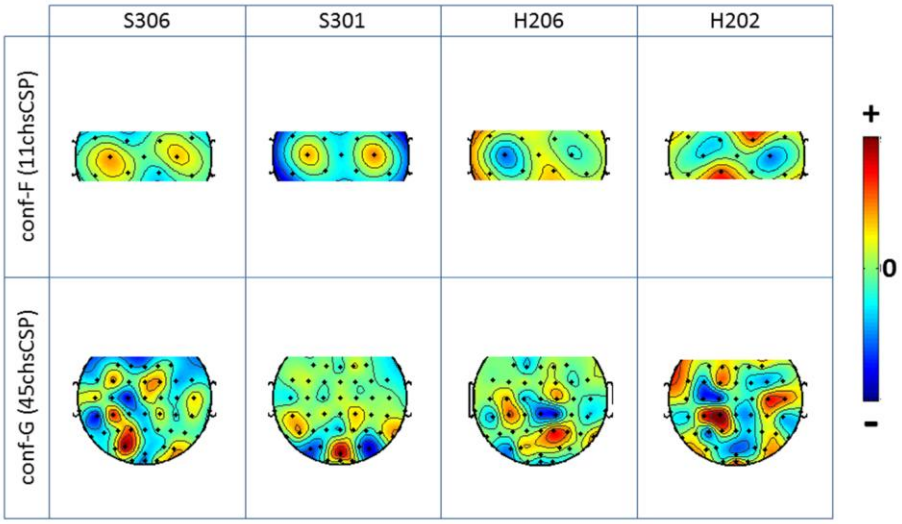

Figure A1: Eight topographical plots showing four CSP filters (built from 11 (top row) and 45 EEG channels (bottom row)) in subjects S306, S301, H206 and H202. Bar denotes the weight factor of the topographical plot. Highly positive/negative weight factor is shown in dark red/blue color. In a channel with a high weight factor, features that discriminate between rest vs. active states show of better.

Table A1: Optimal baselines for age-matched healthy subjects (group 2, top row) and stroke subjects (group3, bottom row).GR= a grid movie, FL= a flower movie, and 2B = a balls moving movie.

Healthy Subjects	H201	H202	H203	H204	H205	H206	H207	H208	H209	H210	H211
Baseline used	GR	GR	GR	FL	GR	FL	GR	FL	FL	2B	FL
Stroke Subjects	S301	S302	S303	S304	S305	S306	S307	S308	S309	S310	
Baseline used	FL	GR	FL	FL	FL	2B	GR	FL	GR	FL	

Table A2: Description of feature vectors for each channel configuration.

Method	Configuration	Feature Vectors		Laplacian
		#No. of vectors	on channels	
NoCSP	Conf-A	3	C3,Cz,C4	No
	Conf-B	11	FC5,FC1,FC2,FC6,C3,Cz C4,CP5,CP1,CP2,CP6	No
	Conf-C	3	C3,Cz,C4	Yes
	Conf-D	11	FC5,FC1,FC2,FC6,C3,Cz C4,CP5,CP1,CP2,CP6	Yes
	Conf-E	45	All 45 channels	Yes
CSP	Conf-F	2	First and last	No
		6	First 3 and last 3	
		10	First 5 and last 5	
	Conf-G	2	First and last	No
		6	First 3 and last 3	
		10	First 5 and last 5	

"First 3 and last 3" means that the first three and last three column vectors were selected to form the selected CSP matrix.

Table A3: Summary of mean and standard deviation for each configuration in the MI/MI based classifiers.

Channel selection (Configuration)	Age-matched healthy control (Group 2)				Stroke patients (Group 3)			
	MI/MI of left hand		MI/MI of right hand		MI/MI of left hand		MI/MI of right hand	
	AU-ROC		AU-ROC		AU-ROC		AU-ROC	
	Avg	SD	Avg	SD	Avg	SD	Avg	SD
3Chs (A)	0.74	0.13	0.73	0.08	0.75	0.11	0.76	0.12
3Chs+Lap (B)	0.74	0.10	0.71	0.11	0.70	0.15	0.73	0.12
11Chs (C)	0.74	0.07	0.69	0.08	0.76	0.11	0.72	0.13
11Chs+Lap (D)	0.76	0.11	0.73	0.09	0.71	0.17	0.72	0.13
nFil2_11Chs (F)	0.84	0.04	0.82	0.09	0.81	0.13	0.83	0.10
nFil6_11Chs (F)	0.87	0.05	0.85	0.08	0.83	0.11	0.84	0.09
nFil10_11Chs(F)	0.86	0.05	0.84	0.07	0.83	0.12	0.84	0.11
45Chs+Lap (E)	0.72	0.13	0.68	0.11	0.76	0.16	0.78	0.12
nFil2_45Chs (G)	0.90	0.06	0.88	0.09	0.92	0.07	0.88	0.12
nFil6_45Chs (G)	0.95	0.04	0.92	0.05	0.94	0.05	0.94	0.06
nFil10_45Chs (G)	0.95	0.04	0.94	0.03	0.95	0.05	0.94	0.06

"nFil2_11Chs" denotes the condition when only two CSP–filters (*nFil*=2) were used and were built from the EEG data recorded from 11 channels. "Lap" means that the Laplacian filter was applied during preprocessing. AU-ROC denotes the area under the receiving operating curve. "*Avg"* and "*SD"* mean the average and standard deviation of AU-ROC across all subjects in each group.

Table A4: Summary of mean and standard deviation for each configuration in the ME/MI based classifiers

Channel selection (Configuration)	Age-matched healthy control (Group 2)				Stroke patients (Group 3)			
	ME/MI of left hand		ME/MI of right hand		ME/MI of left hand		ME/MI of right hand	
	AU-ROC		AU-ROC		AU-ROC		AU-ROC	
	Avg	SD	Avg	SD	Avg	SD	Avg	SD
3Chs (A)	0.70	0.13	0.71	0.06	0.72	0.16	0.74	0.12
3Chs+Lap (B)	0.71	0.10	0.71	0.09	0.70	0.14	0.71	0.13
11Chs (C)	0.69	0.11	0.67	0.08	0.73	0.15	0.72	0.12
11Chs+Lap (D)	0.69	0.14	0.70	0.06	0.70	0.17	0.72	0.14
nFil2_11Chs (F)	0.77	0.07	0.75	0.09	0.75	0.16	0.77	0.12
nFil6_11Chs (F)	0.78	0.09	0.76	0.08	0.77	0.16	0.78	0.12
nFil10_11Chs (F)	0.76	0.09	0.75	0.09	0.76	0.16	0.79	0.10
45Chs+Lap (E)	0.68	0.17	0.61	0.16	0.70	0.17	0.64	0.15
nFil2_45Chs (G)	0.82	0.11	0.78	0.10	0.82	0.15	0.83	0.11
nFil6_45Chs (G)	0.83	0.11	0.80	0.10	0.85	0.15	0.85	0.13
nFil10_45Chs (G)	0.82	0.13	0.80	0.09	0.85	0.16	0.85	0.13

"nFil2_11Chs" denotes a condition when the only two CSP-filters were used and were built from the EEG data recorded from 11 channels. "Lap" means that the Laplacian filter was applied during preprocessing. AU-ROC denotes the area under the receiving operating curve. "*Avg"* and "*SD"* mean the average and standard deviation of AU-ROC across all subjects in each group.

Table A5: Summary of mean and standard deviation for each configuration in the half-ME/MI based classifiers.

Channel selection (Configuration)	**Age-matched healthy control (Group 2)**				**Stroke patients (Group 3)**	
	Half-ME/MI of left hand		**Half-ME/MI of right hand**		**Half-ME/MI of left hand**	
	AU-ROC		**AU-ROC**		**AU-ROC**	
	Avg	**SD**	**Avg**	**SD**	**Avg**	**SD**
1Chs (A)	0.74	0.11	0.67	0.07	0.65	0.14
1Chs+Lap (B)	0.72	0.10	0.67	0.08	0.65	0.12
5Chs (C)	0.65	0.11	0.62	0.11	0.62	0.12
5Chs+Lap (D)	0.68	0.14	0.67	0.11	0.65	0.15
19Chs+Lap (E)	0.52	0.12	0.56	0.10	0.63	0.13

"5Chs" denotes the condition when the classifier was trained using the EEG data recorded over five channels over single-sided M1. "Lap" means that the Laplacian filter was applied during preprocessing. AU-ROC denotes the area under the receiving operating curve. "*Avg"* and "*SD"* mean the average and standard deviation of AU-ROC across all subjects in each group.

Table A6: Summary of mean and standard deviation of AU-ROC for two patients groups (non-severe vs. severe) in the Half-ME/MI based classifier.

Patient group	1Chs (Conf-A)		5Chs (Conf-B)		1Chs+Lap (Conf-C)		5Chs+Lap (Conf-D)		19Chs+Lap (Conf-E)	
	AVG	SD	AVG	SD	AVG	SD	AVG	SD	AVG	SD
Non-severe stroke patients	0.72	0.07	0.68	0.07	0.71	0.06	0.73	0.11	0.67	0.11
Severe stroke patients	0.48	0.11	0.48	0.09	0.51	0.10	0.48	0.06	0.55	0.15

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Chapter 5 Training of an Unskilled Motor Task by Neurofeedback-guided Motor Imagery in Healthy Subjects

Submitted as: Tangwiriyasakul C., Bastiaannet R., Rutten W.L.C., and van Putten M.J.A.M. Training of an Unskilled Motor Task by Neurofeedback guided Motor Imagery in Healthy Subjects.

Abstract

Background: In (sub)-acute stroke patients, a reduced motor imagery (MI) ability and lesser perseverance to maintain good MI performance during rehabilitation protocols may limit the success of MI therapy. To enhance-or-maintain good MI performance, feedback has been implemented in a BCI system. In this study we investigated whether healthy subjects can learn to improve their MI performance by neurofeedback. Since motor relearning during recovery from stroke may be compared to an acquisition of new motor skills in healthy persons, the present study may provide cues for application in stroke patients.

Methods: Fourteen right handed subjects were recruited and randomly assigned into two groups (a combination of BCI and physical training in group 1, and only BCI training in group 2). Both groups were trained to improve their left hand writing guided by BCI feedback during three days. The feedback consisted of online bar wise visualization of the amount of ERD during imagery.

Main Results: At group level, a significant increase of feedback-guided MI performance was found in group 1 only. Therefore, the extra physical training in group 1 suggests its conditioning importance. For the writing, speed increased in both groups, but smoothness of writing remained unchanged.

Significance: Our combined therapy results are of significant importance to improve the efficiency of rehabilitation of (sub-) acute, mild stroke patients.

5.1 Introduction

Stroke is one of the leading causes of adult's disabilities. During rehabilitation, active training of physical movements induces various changes at neuronal level, such as axonal and dendritic sprouting or remapping of cortical function [1, 2].

However, active physical training is not possible in patients with absent or very limited residual movement ability. Since during active and imagined movements partially overlapping neural networks have been shown to be involved [3], imagination of movements (guided by observation) may serve as an alternative or additional approach to access and train the motor system and induce changes in it [4, 5]. Over the past 15 years, several studies reported positive clinical impacts gained from motor imaginary/observation training in chronic stroke patients [6-10]. However, in acute-or-subacute stroke patients potential benefit gained from motor imaginary practice (MI) is still unclear [1, 11, 12]. Possible obstacles are a reduced ability to imagine movements [13], or insufficient perseverance to maintain MI performance throughout the training protocols [12].

Questionnaires [14, 15] are the standard tool to assess MI performance; however, they do not measure the live MI-performance during training in an objective way. During imagining movements, suppression of the sensorimotor rhythm (SMR; mu (8-13 Hz) or beta (15-25 Hz)) can be measured [16], which has motivated to use EEG based Brain Computer Interface (BCI) systems to evaluate MI. The amount of suppression of these EEG rhythms, known as Event-Related Desynchronization (ERD) allows quantification of MI performance.

To enhance MI performance, graded, positive feedback, based on ERD, has been implemented in various BCI systems [17-19]. These studies, in which the subjects were asked to imagine a skilled task (e.g. imaging hand opening/closing), showed increased MI performance; whether the BCI feedback may improve MI performance of an unskilled task is still unclear.

Stroke recovery is considered as a form of motor relearning [20, 21]. Indeed, similar changes in the brain were observed in stroke patients during recovery

as in healthy subjects acquiring a new motor skill [22]. This opens the possibility to mimic stroke patient's progress in relearning everyday tasks by experiments in normal subjects to learn new tasks, like learning to write with the other hand.

In this study, we systematically explore whether BCI-feedback can assist in the learning of an unskilled motor task. We trained right-handed healthy subjects to improve their left hand writing guided by BCI feedback that quantifies MI during the training.

5.2 Methods

5.2.1 Subjects

Fourteen right handed healthy subjects (all naïve to any BCI experiment) were recruited and equally allocated into two groups. Demographical details of all subjects are shown in Table 1. Each subject was informed about the experimental protocol and signed a written informed consent form.

Table 1: Demographic of the subjects and their sensorimotor rhythm (SMR).

Group	Subject	Gender	Age	SMR
1	H11	M	28	Mu
	H12	F	25	Beta
	H13	M	27	Mu
	H14	M	24	Mu
	H15	M	26	Beta
	H16	F	28	Beta
	H17	M	20	Beta
2	H21	F	29	Mu
	H22	F	24	Mu
	H23	M	24	Mu
	H24	F	26	Mu
	H25	M	23	Mu
	H26	M	23	Mu
	H27	M	21	Mu

Note that: M/F denotes male and female, respectively. Mu denotes the mu-band (8-13Hz). Beta denotes the beta-band (15-25Hz).

5.2.2 EEG recording and in-house BCI system

32 channels EEG recordings (TMS International, The Netherlands) were made using Ag/AgCl electrodes positioned according to the international 5-10 system. The left and right mastoids were used as a reference. The sampling frequency was 256 Hz. An in-house BCI system was developed in MATLAB. A FIELDTRIP buffer was used to acquire the data from the amplifier [23].

Although various feedback modalities (e.g. auditory[24], haptic[17], visual [25], or combined features[18]) have been implemented in Brain computer interface (BCI) systems, there is no clear evidence suggesting the advantage of any feedback modality [18]. Here we used a visual bar feedback.

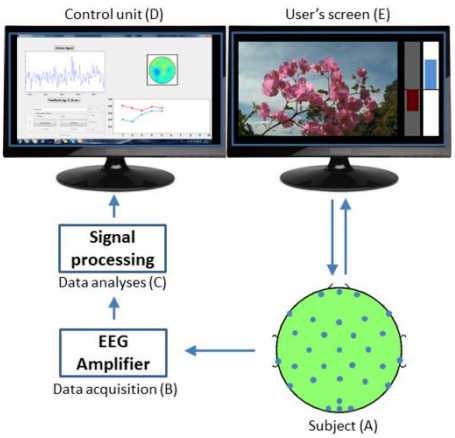

Figure 1: General schematic of our BCI system. Note that this figure represents the system during baseline (relax) condition, while the subject was asked to relax and maximize the blue bar, representing the SMR power in the five channels hyperspace.

5.2.3 Experimental design

Every subject participated in three consecutive day measurements. Two different experimental paradigms were used: (i) a combined prior-motor-practice-and-BCI-training paradigm (MP+BCI) for group1 and (ii) an BCI-

training-only paradigm (BCI-only) for group 2. During BCI training, two types of movies were shown: a baseline movie (showing slowly moving flowers) and a writing movie showing writing action of a person writing the word *Nederland* using his left hand. Note that for the writing movie a naturally left-handed person was recruited and filmed from the writer's perspective. All movies lasted 13 seconds.

A calibration phase (see Figure 2, step-A) was included only on day1 to find a subject defined SMR rhythm (either mu (8-13 Hz) or beta (15-25 Hz)). During calibration, ten combinations of a text movie (showing a static phrase "Move your right arm") and the flower movie were repeated: during the flower movie the subjects were instructed not to image-or-perform any movement but to flex-and-extend the right elbow during the text movie. From inspection of two power density spectra (during baseline and action), estimated from the EEG signals on C3, the most suppressive rhythm was selected as SMR [26]. If there was no clear difference between the PSDs of baseline vs. action in any band, the mu band was selected as default SMR.

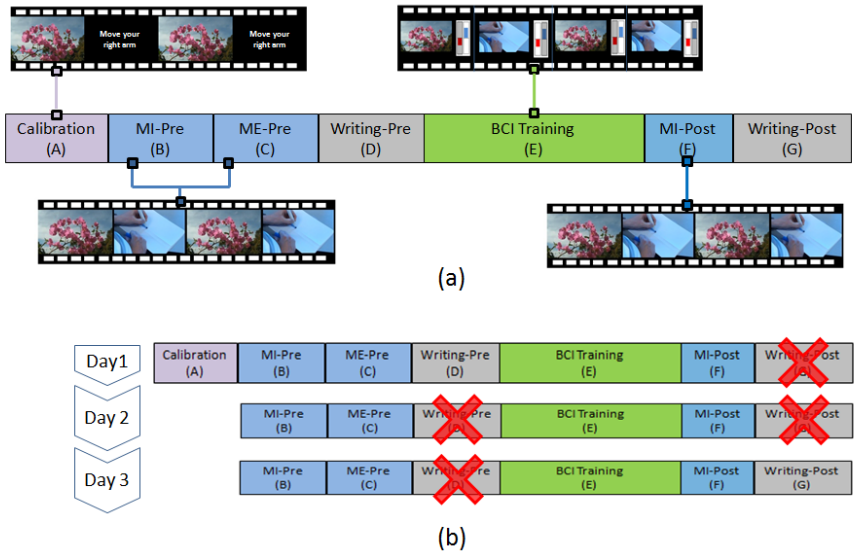

Figure 2: (A) Experimental paradigm used on the 1st day of the measurement protocol in group 1 (MP+BCI). In this group, the same paradigm was used on day 2 and 3, except step A. (B) For group 2 (BCI-only), some MP writing tasks (marked by red crosses) were not included.

Figure 2(A) shows the experimental paradigm used on day 1 of the MP+BCI group (group1). During step B (and C), ten combinations of flower and writing movies were shown to the subject, who was asked to relax-and-not-to-perform any movement during the flower movie but to imagine (or execute for C) the movement seen on screen during the writing movie. To avoid any unintended learning effects in writing skills during step-C, the subject was asked to randomly move his/her hand while holding a pen without precisely writing the word *Nederland*. A LDA (linear Discriminant analysis) classifier was trained using the data recorded from five channels (FC2, FC6, C4, CP2, CP6) during step-C. Later, we asked the subject to write the word *Nederland* with his/her left hand within 30 s. (step D). In each writing template, there were two markers (1.5. cm apart on the vertical axis), between which each subject was instructed to write a 1.5 cm height N-letter.

The BCI training phase (step E) consisted of 8 training blocks (the duration of each block was about five minutes). For each block, ten combinations of the baseline-and-writing movies were repeated. On the right hand side in the user's screen, two feedback bars were displayed. During the flower movie, the subject was asked to maximize the blue bar level (to avoid any confusion, only the blue bar was illuminated and actively moved, while the red one was static and shaded with gray). To maximize the blue bar, the subject was instructed to relax and not to perform/image any movement. During the writing movie the subject was instructed to minimize the red bar level by imaging his/herself writhing with left hand. The feedback bar was updated every 0.5 second using data recorded from two consecutive intervals (1 s. with 0.5 s. overlap). At each interval, SMR-power (of each channel from FC2, FC6, C4, CP2, CP6) was computed by integrating the power density spectrum over the subject's defined SMR. After that, the SMR powers were fed into the LDA classifier; later a distance from the separation line (d-value) in the five channels hyperspace was estimated (a positive d-value indicates resting state, while a negative d-value indicates MI state). Then, we averaged the two d-values obtained from two consecutive intervals. Finally, the height of the feedback-bar was updated according to the average d-value.

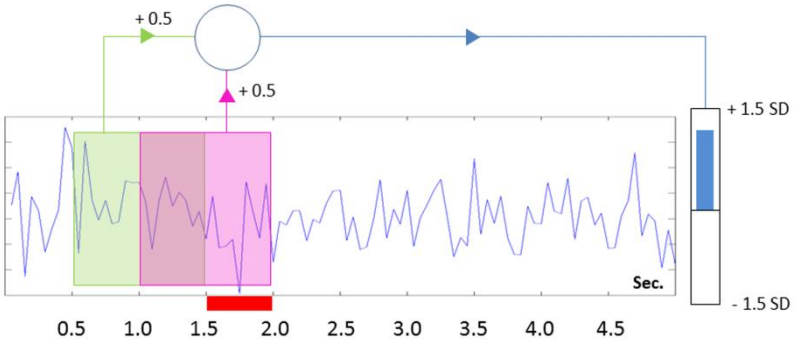

Figure 3: Pink and green boxes show the two EEG intervals (1 s. with 0.5 s. overlap) used to calculate the SMR power of two consecutive intervals. Red bar indicates the current interval.

After the completion of eight blocks, the subject was asked to perform motor imagery without feedback (step F) to investigate changes of MI performance after BCI-training. Finally, the subject was asked to write the word *Nederland* again within 30 s. (step G). For all subjects in group 1, the similar paradigm (excluding the calibration) was repeated in days 2 and 3.

The paradigm for group 2 subjects (BCI-only) differed from that of group 1 in some writing tasks: i.e. no step G on day 1, no steps D and G on day 2, no step D on day 3. After completion of BCI training (step E) on day 3, we asked the subjects in group 2 to complete the writing task (step G) five times. At the end of the experiment on day 3, we asked every subject to write the word *Nederland* one time using the right hand with no time limit.

The use of left hand writing task was to resemble the acute stroke condition (physically paretic with decrease of motor imagery ability): left hand was considered as a quasi paretic hand, while the writing using left hand was an unskilled task. Note that higher MI performance was found in subjects with experience than in the not-trained (or less experienced) one [27].

5.2.4 Performance measures

Two types of performance measures were used: (i) four EEG based performance measures and (ii) two writing based performance measures.

The four EEG based performance measures were: ERD value (using the data recorded on C4), motor imaginary ability (MI-performance), relaxation ability (BL-performance, BL stand for baseline), and overall performance. ERD value was computed by dividing the difference of SMR powers between imagery writing vs. baseline (of the previous adjacent trial) conditions by the SMR power of the baseline condition. The averaged ERD across ten trials was used as a representative. For each block, MI-performance was the number of effective motor imagery trials, (an MI trial which was classified as MI), divided by ten. The BL-performance was computed similarly. Overall performance was the average between BL and MI performances.

Two measures were used to assess improvement in writing skills: (1) the number of letters written within 30 sec, and (2) a sum of squared difference (SDD) of pixel values between a master letter and its corresponding letter. The first measure was used to assess changes in writing speed, and the second measure was used to assess writing consistency in terms of smoothness. The SDD was a sum of differences of all pixel values of each letter with its corresponding master letter (written by the right hand). Before computing the SDD, each letter was morphed into its skeleton format. This measure was sensitive to detect smoothness of each letter (see one example in figure A3 in Appendix-5).

5.3 Results

The results are organized into three sections. We first show the evolution of the EEG based performance during the training course. Then, we compare ERD outcomes before and after training. Finally, we present the improvement of writing performance.

5.3.1 Evolution of MI/BL/overall performance and ERD during the training course.

During three days training, a significant increase of the average overall performance was observed in group 1, but not in group 2. This increase was accompanied by a significant increase of the average ERD with rho = -0.81

and $p<0.05$ (group 1 only). On day 1, a significantly increased overall performance was observed in both groups. In group 2, after reaching a peak of overall performance at the end of day1, a drop in the overall performance was observed (see Figure 4).

At individual level, about 70% of group 1 subjects showed an increasing trend of the overall performance, in group 2 only 30%. In fact, most of the group 2 subjects (60%) showed the decreasing trend of the overall performance, see figure A1 in Appendix-5.

For MI performance alone, during three days training a significant increase of MI performance was seen only in group 1, similar to the overall performance. On day 1, an increasing trend of MI-performance during blocks 4 to 8 was observed in both groups (see two red dash boxes in Figure 4). At the end of day 1, group 2 showed a similar sudden drop of MI performance as the overall performance.

There was no significant increase-or-decrease of BL-performance in any group over all three days. However, on day 1 alone, increase of BL performance was significant in both groups (see Table 2).

Table 2: Pearson's correlation coefficients (rho) and the p-values.

Pearson's Correlation	Group1 (MP+BCI)			Group2 (BCI-only)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
ERD	- 0.88*	-0.08 (p=0.85)	0.22 (p=0.59)	-0.87*	-0.13 (p=0.75)	0.69 (p=0.06)
MI-perf	0.24 (p=0.56)	0.37 (p=0.35)	-0.76*	0.67 (p=0.06)	0.07 (p=0.86)	-0.58 (p=0.43)
BL-perf	0.70*	0.17 (p=0.67)	0.28 (p=0.49)	0.75*	0.49 '(p=0.21)	0.59 (p=0.12)
Overall-perf	0.68*	0.50 (p=0.20)	0.07 (p=0.85)	0.83*	0.28 (p=0.49)	-0.24 (p=0.56)

Note that: "Perf" denotes performance. Significant correlation ($p<0.05$) is marked with an asterisk.

5.3.2 Changes of ERD before and after BCI training

During three-days of training, we observed constant increase of ERD from step-B on the first day to step-F on the last day in group 1, but not in group 2 (see figure A2 in Appendix-5). On a daily basis, the increase of ERD after BCI training was normally found in group 1 (and also on day 1 of group 2).

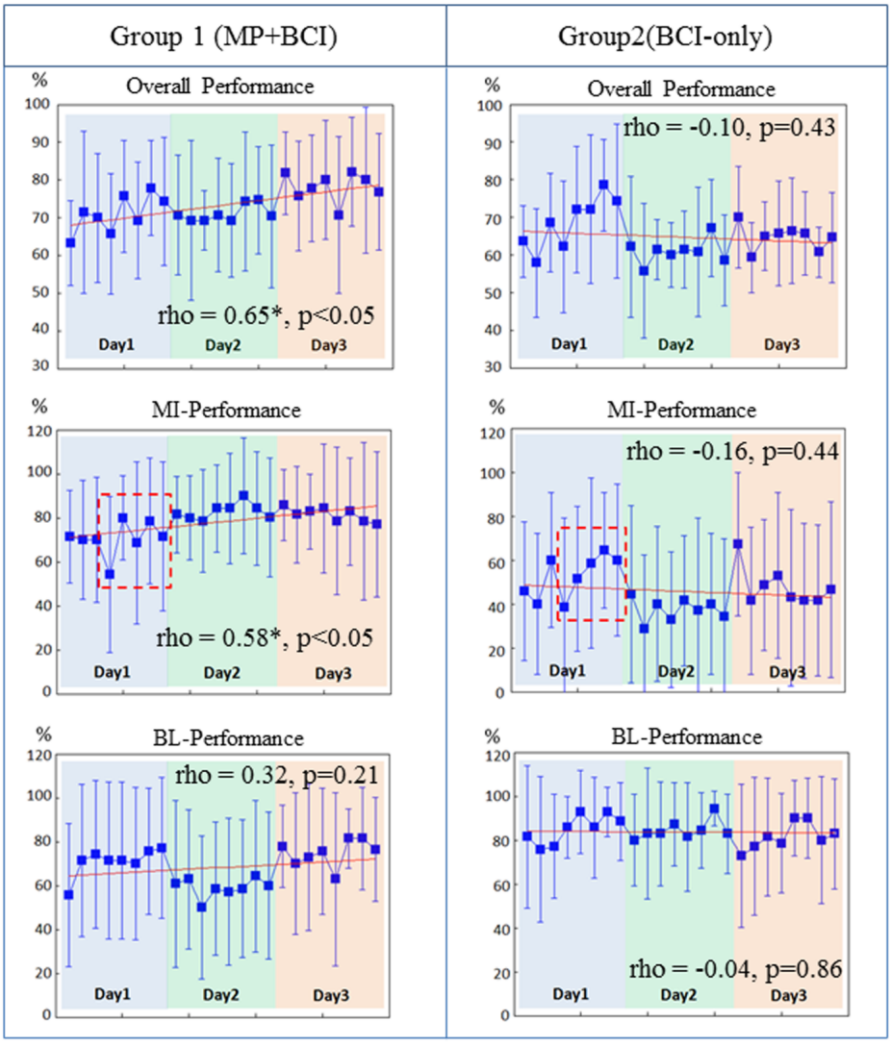

Figure 4: Six evolutions of overall (in the top rows), MI (in the middle rows), and BL (in the bottom rows) performances in groups 1 and 2. The blue squares denote the mean performance averaged across subjects in each block. The error bars denote one standard deviation. Linear trend line is shown in red. Pearson's rho and its p-values are inserted in each subfigure.

5.3.3 Left-hand writing speed and smoothness during three days training.

At group level, an increase of writing speed during the course of three days was seen in both groups especially during Pre1-to-Post1 period (see Figure 5). Increased smoothness was observed in a few subjects (one example is shown in figure A4 in Appendix-5), but not at group level, see Figure 6.

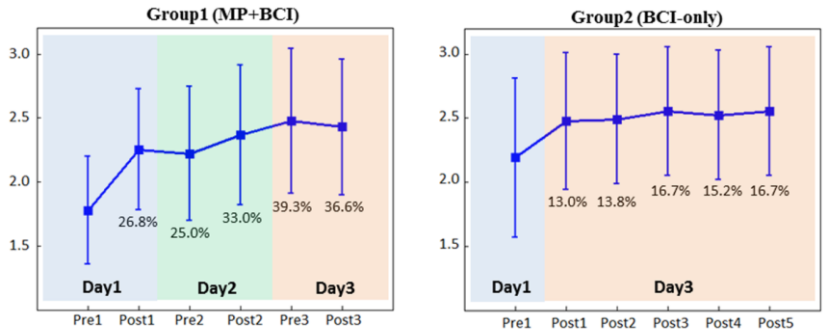

Figure 5: Average number of words completed within 30 sec in groups 1 and 2. The blue squares denote the average of number of words across all subjects within each group. The error bars denote one standard deviation. The percentage increase of a number of words relative to the Pre-1 is shown underneath each error bar.

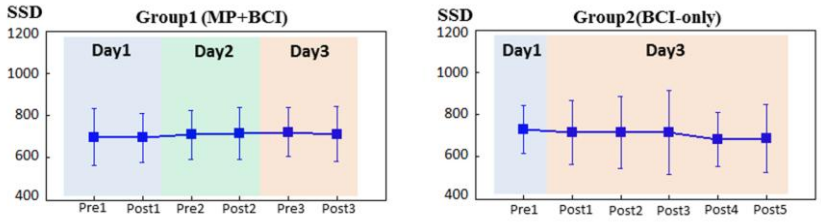

Figure 6: Evolution of SSD of letter-N during a course of training in groups 1 (left) and 2 (right). The blue squares and error bars denote the average SDD and one standard deviation across all subjects in each group. SSD stand for the sum of squared difference.

5.4 Discussion

In this study, we explored if BCI feedback based on MI may assist in the learning of an unskilled motor task in healthy volunteers. It is argued that motor relearning after stroke bears similarities to motor learning in healthy individuals [22], and our results may, therefore, be relevant for the use of BCI feedback in stroke patients.

5.4.1 Changes of EEG based performances during training

Among the four EEG based performances (ERD, Overall, MI, and BL) used in this study, the first three features were correlated with one another. During three days training, increase of ERD/overall/MI was found only in group 1. The increase of MI performance in this group indicates the importance of performing motor practice prior to the BCI training. Performing motor practice was proven to enhance the action understanding and assist a subject to perform kinesthetic motor imagery effectively [12, 27, 28]. Unlike the MI-performance, a significant change of BL performance was not observed in any group throughout three-days of training, but only on day 1, in both groups. We hypothesize that the significant increase of BL performance on day 1 just indicates a short tuning period, to adapt the subject to the system.

5.4.2 Leaning effects in other BCI systems

Learning to increase MI-performance guided by feedback has been investigated in both healthy subjects and stroke patients. In healthy subjects, our system was equivalent to the one of Ono et al. [29]. In that study, subjects were asked to imagine closing/opening of their right hand. About 48% decrease of ERD (together with about 17% increase of overall performance) was found after three days of training. These results were comparable to the 50% reduction of ERD and 10% increase of overall performance in group 1 of our study. Since no prior motor practice was done in Ono's study, this suggests that the prior motor practice was only required to assist imagery of the unskilled task.

In chronic stroke patients, increased BCI performance was found in two studies (Soekadar et al. [17] and Buch et al. [30]). A MEG based BCI with haptic feedback was used in both studies while the patients were instructed

to imagine closing/opening of their plegic hand. Increased MI performance was reported in both studies. To our knowledge, learning to improve MI-performance guided by BCI system has not yet been investigated in (sub)-acute stroke patients. Whereas the (sub)-acute phase is considered as a prime period to enhance recovery [31], the limited motor imagery ability in this phase [13] may hinder the successfulness of BCI based therapy in the (sub-) acute state. For these patients, we may be able to improve their MI performance by adding motor practice prior to BCI training, similar to what we did in this study.

5.4.3 Improvement of writing skills

Fitts and Posner [32] described three stages of motor learning consisting of (i) a cognitive phase, in which a cognitive map of the movements required to accomplish the task is established, (ii) an associative stage, in which coordinates of the movements in time and space are set, and (iii) a autonomous stage, in which less and less conscious attention is required to complete the task. In athlete training, slow and inconsistent movement was seen during the cognitive phase, while more fluid and more consistent movement developed in the associative phase [33]. Since in our study all subjects were able to write the word *Nederland* correctly right after the first writing task (pre1), a cognitive movement map was presumably made within Pre1. Faster writing speed as observed in both two groups indicates that all subjects were in the associative stage.

Although increase of writing speed was higher in group 1 (36.6% at Post-3) than that in group 2 (13% at Post-1), the high increase in group 1 is mainly caused by the lower initial writing speed in group 1. Interestingly, both groups shared the similar trend of writing speed throughout three days training, starting with a steep rise in the Pre1-to-Post1 period then leveling off. This may reflect the nature of writing development: first the subjects intend to write as fast as possible without making mistakes. After reaching a plateau of writing speed, the subjects would shift their intention to improve their writing consistency.

Several factors may hinder the success of improving smoothness of writing in this study. First, the training duration may have been too short: even in group 1, an extra one minute long motor practice per day may not be

sufficient to induce any additional physical gain. Second, improvement of smoothness of writing will go along with increase of muscle strength, which cannot be realized by imagery training [1].

5.4.4 Changes in brain activity in BCI training and their relevance to motor learning.

The motor cortex area is an important area to encode motor memory and plays an essential role in motor learning [34]. Changes of the brain activity in this area accompany motor learning [35]. Using TMS, Pascual-Leone et al. showed an initial increased activity in the motor cortex area; hereafter explicit knowledge of that trained motor skill was acquired, and subsequent decrease of the brain activity was observed [36]. Similar results were found using ERD on the contralateral motor cortex as measure [37]. Explicit knowledge of a motor task is reached, when that task can be done subconsciously [38]. Picard et al. suggested that after long-term training the brain motor cortex becomes more efficient, resulting in a reduced metabolic activity in this area [39]. This explains the decrease of brain activity when the motor task is over-learned. Since the left hand writing was a complex task (in which proprioceptive and visual information were always required to complete the task), we hypothesize that all subjects in this study did not yet (or will never) reach the phase of explicit knowledge.

In this study, the increase of ERD after 8 blocks training was found only in combination with physical training. This suggests that BCI training alone is not adequate to induce changes in the brain. This inadequacy may result from an inability to effectively imagine left hand writing, which could not be improved by feedback guidance alone. Rather, the additional motor practice as in group 1 is required to enhance the action understanding to effectively imagine left hand writing.

Although the increase of brain activity (ERD) was found in this study, explicit motor acquisition was not reached, unlike in the studies of Zhaung et al. and Pascual-Leone et al [36, 37]. This may be due to the discrepancy of motor tasks used. Here, we used a left hand writing task, while motor sequencing tasks (e.g. the remembrance of finger movement series) were used in all other studies. The improvement of a writing skill is more complex, covering both movement dynamics and movement kinematics.

In conclusion, we showed that feedback information based on ERD alone was not sufficient to improve MI-or-actual performance of an unskilled writing task. Since motor acquisition in healthy persons is comparable to motor relearning in stroke patients, the results in this study may be translated to stroke patients [22]. Especially for acute stroke patients with reduced MI ability, performing motor practice before the BCI training may be a key to enhance action understanding, thereby leading to good MI performance during BCI training.

Acknowledgements

We would like to thank all healthy subjects for their participation.

Appendix-5

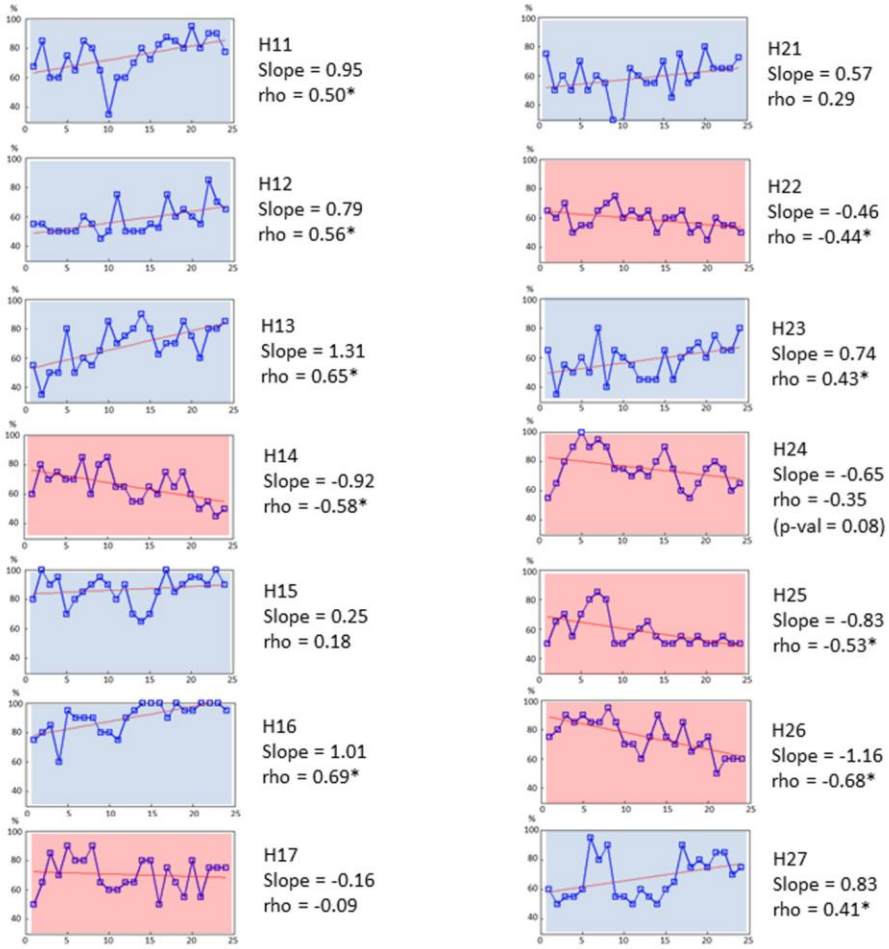

Figure A1: Evolution of the overall performance (blue squares) for each subject during the training courses. The red lines show the linear regression line. Subject's label, slope of the linear regression line and the spearman's correlation coefficient "rho" are noted on the right hand side of each subfigure. Significant spearman's correlation ($p<0.05$) is marked with an asterisk. Increasing or decreasing trend is shaded with light blue and red color, respectively.

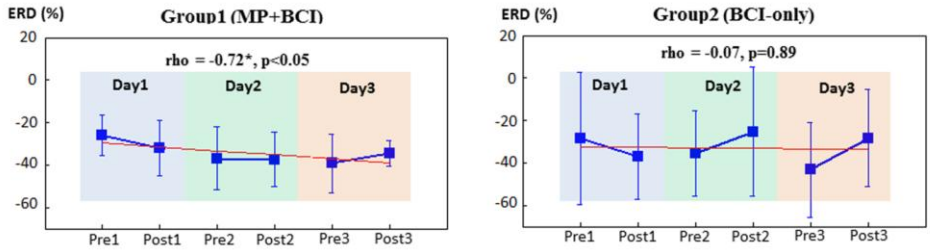

Figure A2: Mean ERD value of C4 averaged across subjects in each group during the pre/post BCI-training. The blue squares denote the mean performance averaged across subjects in each block. The error bars denote one standard deviation. Linear trend line is shown in red. Pearson's rho and its p-values are inserted at the top of each subfigure.

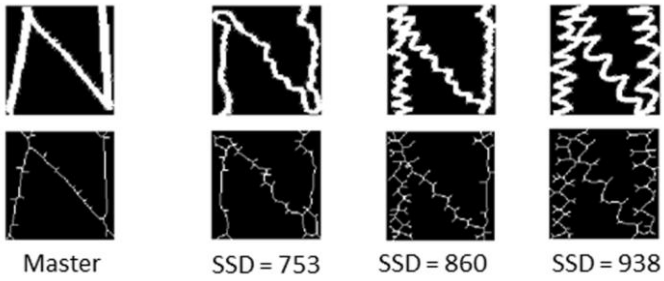

Figure A3: Example of a sum of squared difference (SSD) in three difference letters (different level of smoothness) with respect to the master letter.

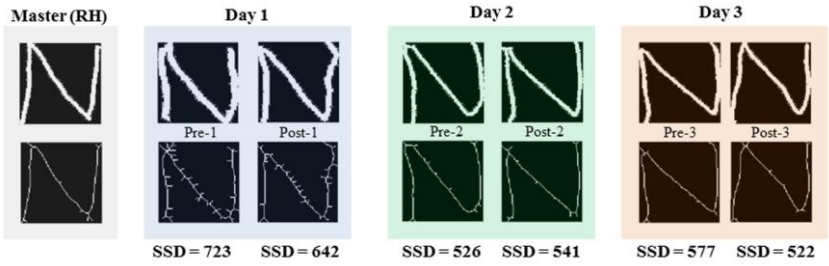

Figure A4: Example of letter-N evolution showing an increased smoothness during three days of training in H12. Top row figures show real letters; whereas the bottom row figures show their corresponding morphed letters. SSD denotes the sum of squared difference between each letter and its master letter, written by the right hand.

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Chapter 6 Summary and General Discussion

Motor imagery (MI) therapy is suggested to assist motor (re)learning during stroke rehabilitation. During MI training, part of motor neurons is being recruited similar to motor execution. Repetitive recruitment of motor neurons through mental training leads to enhancement and/or restoration of connections among neurons (brain's plasticity). Clinical gain in restoring motor dysfunction by MI therapy was proven in various chronic stroke patients, but not yet in patients at acute-or-subacute phase, which is considered as a prime period to determine the final outcome after stroke. In acute stroke patients, motor imagery has been shown to be less strong, so it is important to improve MI performance. One way to do that is to incorporate feedback about the MI effort in an EEG based BCI training system.

In this thesis, we focused on four main questions that would lead to optimal design of the neurofeedback system and answer whether this system would assist motor (re)learning or not. The four questions were:

1) How can we reliably measure MI performance?
2) How do EEG related measures, like ERD, develop in recovering stroke patients?
3) How to implement a neurofeedback system in an effective and user-friendly fashion?
4) Does motor training with the MI-neurofeedback system lead to faster motor learning?

To answer these fours questions, four studies were conducted as presented in the four previous chapters. Here we will summarize the results and conclusions from those chapters, discuss the overall outcome and suggest future work.

6.1 Summary

6.1.1 Importance of baseline to Event-Related Desynchronization (ERD)

Suppression of EEG sensorimotor rhythm (SMR), causing an Event-Related Desynchronization, is one candidate to measure MI performance. Good MI performance is seen as highly negative ERD, which indicates high cortical activity. Since ERD is the ratio between the SMR power of the active and the relaxed (baseline) states, one cannot neglect the importance of (variability of) the SMR power during baseline (baseline power) to ERD. To increase ERD reliability, the baseline power should be maximal and stable. Visual inputs (either a movie or static picture) is a standard cue used in any motor imagery paradigm. The SMR power reaches its peak level when the subject is relaxed, not performing or imagining any movement. In this study, we started with a search for the condition of maximal and stable baseline power using five different types of movies (baseline movies). The five movies were a two ball moving movie, a bouncing ball movie, a slowly waving flower movie, a static hand movie, and a white-strips-on-a-black-screen movie. An optimal baseline movie with a high and stable baseline power was not found at group level, rather the optimal baseline movie was subject dependent. From this study, we concluded that finding the individual optimal baseline movie is required to increase the reliability of the ERD.

6.1.2 Evolution of ERD during stroke recovery

To assist recovery from stroke by neurofeedback, the feedback should guide patients to produce/enhance the brain's reorganization that accompanies recovery. In this study, we tried to answer that question by exploring the "natural" evolution, so without feedback, of the brain using ERD during recovery. We found a significant increase of ipsilesional ERD in patients with good recovery. Thus, this increase of ipsilesional ERD could serve as predictor for recovery. And, to enhance recovery, the neurofeedback system should be designed to detect and promote activation over the ipsilesional hemisphere.

6.1.3 Suitable classification methods for acute stroke patients

Patient's compliance is an essential prerequisite for any stroke rehabilitation therapy. However during MI training, we cannot directly quantify MI performance, like we can easily classify performing physical performance by direct observation. As previously stated, ERD is our indicator of MI performance. Although many research groups have worked on a neurofeedback system for stroke recovery, there is no consensus about the optimal classification of ERD. The optimal classification method should give acceptably high classification performance using the smallest number of channels. In general, classification accuracy increases with the number of EEG channels involved. One processing technique in that respect is the common spatial pattern analysis method (CSP). It improves the signal-to-noise ratio and thereby classification performance. In this study we conducted a benchmark study by comparing LDA classification with and without CSP, for different channel configurations.

We found that performance accuracy was maximal using the CSP method and 45 EEG channels. However, use of CSP on 45 channels has a risk of overfitting. Since the performance accuracy for eleven and five channels without CSP was at or above the acceptable level (i.e. area under the ROC-curve = 0.70), we concluded that LDA classification can do without CSP, and that 5 channels per hemisphere is enough (which also reduces computational effort).

In hemispheric mild-to-moderate acute stroke patients, we showed that one could train the classifier using the data recorded on the unaffected motor cortex during healthy hand motor execution. We subsequently used it to classify the data recorded in the affected motor cortex during imagining affected hand movements. The use of this classifier ensures the activation of motor neurons during classifier training, and guides patients to learn to produce "healthy" brain patterns.

6.1.4 Importance of physical training prior to neurofeedback training to improve MI performance of the unskilled task

The goal of neurofeedback-guided MI training is to assist motor (re)learning in stroke patients. Since similar changes of the brain are observed during

motor acquisition in healthy persons as during motor (re)learning in stroke patients, we started the study by training fourteen right handed healthy subjects to improve their left hand writing. These healthy subjects were allocated into two groups. All subjects received the same amount of neurofeedback training, but group 1 received additional physical training. At group level, the progress of MI performance was seen in group 1 only. This indicated that feedback of MI-performance alone was not enough.

6.2 General discussion

In this thesis, we investigated EEG changes during recovery from stroke and developed a prototype of an EEG-imagery-neurofeedback system. Since ERD is a good indicator of MI performance and was shown to correlate with recovery, ERD was chosen as the parameter for feedback to guide patients to improve-or-maintain MI performance during training. However, the results from the pilot test in fourteen healthy subjects suggested limited importance of neurofeedback training to enhance MI performance of an unskilled task. This suggests also a limited usefulness for patient-relearning, although this should still be proven by experiment.

6.2.1 Does a resting state of the brain exist and what is its relevance to motor learning?

The ERD measure was our major tool in this thesis. As being a ratio, ERD is largely dependent on the SMR power measured on the motor cortex area at rest (baseline power), i.e. a stable and high baseline power is required to ensure the reliability of ERD. Indeed, the baseline power is a predictor for BCI performance [1, 2]: i.e. a high BCI performance is often found in subjects with high baseline power [1]. We showed that baseline power varied for different movies, in the same subject. High baseline power is known to be maximized during the brain's resting state. While there is no clear definition of this state, some claim that a resting condition may not exist: "*the resting state is merely an active event in the absence of specific stimuli*" [3]. Furthermore, attention appears to affect the level of SMR power at rest as well, since a reduced SMR power is found in ADHD patients [4]. Therefore, the ideal resting condition may be a condition that blocks all

movement imagination, while maintaining attention. We hypothesize that different movies elicit a subject's mental response differently. This may explain why a common baseline movie was not found.

Although a resting state is usually included in mental practice, the role of this state in mental practice is unclear [5]. Some suggested that the resting state is always required to remove all distractions and unnecessary mental activity to increase MI performance [6-8]. However, some suggested that the resting state is redundant, and in some case it even downgrades the benefits of MI to motor learning [9,10]. At present, the resting state is required to set up a classifier, but whether it should be included-or-excluded during the MI training paradigm still needs to be answered.

6.2.2 Motor imagery training for stroke rehabilitation: what is missing?

There is a problem when looking at good outcome measures for MI training [11]. A number of measures are used to represent progress of stroke recovery, but these measures are mostly qualitative/subjective. Also, the few quantitative measures that do exist are usually employed for performance of small- and simple- movement (e.g. grip strength), while measures of meaningful-and-complex movements in daily life activities are mostly subjective (e.g. Barthel score).

To systematically investigate the effects of MI therapy, we need a quantitative measure of daily life activity, to compare with. For example, if one would quantify a coffee drinking task, several aspects should be included such as ability to adjust force to hold the coffee cup at different movement stages and ability to coordinate body parts (synergy). Motor control researches usually make distinction between these two: where the former is defined as the movement dynamics, by synergy is meant the movement kinematics [11].

Physical disability after stroke is caused by the loss of strength and dexterity [12]. Loss of dexterity is a direct effect of the damaged tissue in the brain, whereas the loss of strength is caused by an intrinsic change of muscle fibers as a consequence of the interruption of corticospinal tract due to stroke (direct) and by immobility and inactivity of patients (indirect) [13, 14]. How MI training affects the dynamics and kinematics is presently unclear. Current

evidences limit the effects of MI training to induce changes only in the brain [15-17], but recovery from stroke requires improvement from all aspects including establishing cognitive maps of the movements in the brain as well as strength-and-endurance. Since the effects from training with motor imagery training are primarily located in the brain, this suggests the limitation of MI training to induce changes of the spinal circuits. The latter may result more from strength/endurance training [18]. Recently, Patten et al. showed that a combination of skill-and-strength training led to higher functional improvement than skill training alone [19].

A preserved motor learning ability is another important aspect in stroke rehabilitation. Studies in chronic stroke patients showed that the motor learning ability of the affected side is reduced but not totally lost [20-24]. This reduced motor learning ability is mainly caused by an impaired anticipatory scaling to adapt to external forces. To our knowledge, there is no evidence about the motor learning ability in (sub-) acute patients. For these patients, we suggest to use MI training only in patients with intact premotor cortex and (partly) spared motor cortex area, being the most important for motor imagery and motor acquisition.

Last but not least, the most effective dose of MI training is unknown [5, 25]. The does used at present may not always lead to successful motor acquisition/relearning [26].

6.2.3 Motor versus mental practice (motor imagery)

Although mental training along with physical training leads to higher clinical gain than physical training alone, increasing the amount of physical training leads to more improvement than increasing mental training [5]. Therefore, in any case physical training is the first to be chosen, when possible. The amount of physical training should be carefully limited to avoid unintended fatigue and tiredness in stroke patients, but large enough to induce physical gain.

6.3 Epilogue/Outlook

In the final stage of this study, we investigated how to improve imagery. For this, we developed an EEG-ERD based MI-neurofeedback system, in which the feedback information showed live MI performance. However, the result from our pilot study showed limited effect of neurofeedback. As such this may be a "*warning*", when proceeding to test the method in patients.

"Shall we discard the motor imagery training?" The answer is no. Although motor imagery training may not play a leading role in motor (re)learning, its supportive role is undeniable [27, 28]. We suggest to use the combination of motor- and mental practice as the most promising approach to assist recovery from stroke.

In the future, the next logical step is to find the optimal ratio between motor and mental training that would optimize motor acquisition in healthy subjects. Once that ratio of mental/motor practice is found, a pilot study in stroke patients can be started.

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