FEEDBACK EFFICIENCY AND TRAINING EFFECTS DURING ALPHA BAND MODULATION OVER THE HUMAN SENSORIMOTOR CORTEX

DIE WIRKSAMKEIT VON FEEDBACK UND TRAININGSEFFEKTEN WÄHREND DER ALPHABAND MODULATION ÜBER DEM MENSCHLICHEN SENSOMOTORISCHEN CORTEX

Thesis for a doctoral degree

at the Graduate School of Life Sciences,

Julius-Maximilians-Universität Würzburg,

Section Neuroscience

submitted by

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from Würzburg

Würzburg, Germany 2015

Submitted on:

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“It´s all about ants and turtles”

Dedicated to my Friends and Family

CONTENT

Danksagung (Acknowledgement)

Die hier vorliegende Dissertationsarbeit habe ich am Lehrstuhl für Psychologie I der Universität Würzburg angefertigt. Ich möchte mich an dieser Stelle noch einmal bei all jenen bedanken, die mich auf diesem Weg begleitet und unterstützt haben.

Ein herzliches Dankeschön geht an meine Betreuerin Frau Prof. Dr. Andrea Kübler (Institut für Psychologie I) für ihre grenzenlose Geduld und fachliche Unterstützung. Vielen Dank für die Freiheiten die sie mir zur Verwirklichung dieser Arbeit eingeräumt haben. Ich danke allen weiteren Mitgliedern meines Promotionskomitees, Frau Prof. Dr. Brigitte Förster (Biozentrum) und Herrn Prof. Tele Tan (Department of Mechanical Engineering, Perth), für die Begutachtung meiner Arbeit und ihr Interesse an meiner Forschung. Ein besonderer Dank geht des Weiteren an Herrn Prof. Tele Tan, der mir bei der Realisierung meines Forschungsaufenthaltes in Australien tatkräftig zur Seite gestanden hat und mir eine produktive angenehme Zeit in Perth ermöglichte. Ein weiterer Dank geht an Frau Prof. Dr. Brigitte Rockstroh (Institut für Klinische Psychologie, Konstanz), die mich sehr freundlich in ihrer Gruppe aufgenommen und mich bei meiner Arbeit in Reichenau stets unterstützt hat. Ein ganz besonderer Dank geht darüber hinaus an alle Patienten der Psychologischen Klinik Reichenau, die bereitwillig und motiviert an meiner Studie teilnahmen, sowie an alle Studenten, die mich bei der Datenerhebung entlastet haben.

Zudem danke ich all meinen Kolleginnen und Kollegen am Lehrstuhl für Psychologie I, für das stets angenehme Arbeitsklima, den fachlichen Zugewinn sowie die Unterstützung die ich durch euch in unseren gemeinsamen Jahren erfahren habe. Ein besonderer Dank gilt hierbei meinen Kollegen Dr. Helena Erlbeck, Dr. Sebastian Halder und Ivo Käthner für die vielen schönen gemeinsamen Erlebnisse und Erinnerungen.

Des Weiteren gebührt Dank dem Team der Graduate School of Life Science Würzburg für die stets freundliche Unterstützung und Begleitung über die

Promotionszeit hinweg, sowie allen Beteiligten des Graduiertenkolleg Emotion (DFG Research Training Group 1253/2) für ihren Einsatz und die organisatorische Leistung.

Ich bedanke mich ganz herzlich bei meiner Familie, die mir stets das Gefühl gibt stolz auf mich zu sein. Mein ganz besonderes Dankschön geht an meine Freundinnen Luise und Patricia, auf die ich mich immer verlassen kann und ohne die ich nicht so wäre wie ich bin, sowie an meine größte Unterstützung, meinen Freund Frederik, für seine Geduld, Motivation und seinen Rückhalt.

Teresa Sollfrank

Full reference to publications that were a result of this thesis

The following publications were a result of work conducted during the doctoral study and are in part included in this thesis:

Sollfrank, T., Hart, D., Goodsell, R., Foster, J. and Tan, T. (2015). 3D visualization of movements can amplify motor cortex activation during subsequent motor imagery. *Frontiers in Human Neuroscience*, 9, 463. doi: 10.3389/fnhum.2015.00463

Link to publication source: Frontiers in Human Neuroscience, Frontiers Media SA

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Sollfrank, T., Ramsay, A., Perdikis, S., Williamson, J., Murray-Smith, R., Leeb, R., Millán, J.d.R. and Kübler, A. (2015). The effect of multimodal and enriched feedback on SMR BCI performance. *Clinical Neurophysiology*, In Press. doi: 10.1016/j.clinph.2015.06.004

Link to publication source: Clinical Neurophysiology, Elsevier B.V.

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Date of written permission: September 16, 2015.

List of Figures

List of Tables

List of Abbreviations

Abbreviation	Description
ALS	Amyotrophic lateral sclerosis
ASD	Autism spectrum disorder
BBCI	Berlin brain-computer interface
BCI	Brain-computer Interface
CB	Cursor bar feedback
CDSP	Canonical discriminant spatial patterns
ECoG	Electrocorticography
EEG	Electroencephalography
ERD	Event-related desynchronization
ERS	Event-related synchronization
fMRI	Functional magnetic resonance imaging
IAF	Individual alpha frequency
LDA	Linear discriminant analysis
MEG	Magnetoencephalography
MF	Multimodal funnel feedback
MI	Motor imagery
NF	Neurofeedback
PET	Positron emission tomography
SCP	Slow cortical potential
SMR	Sensorimotor rhythms
UF	Unimodal funnel feedback
USD	User-centered design
VR	Virtual reality

1 Graphical abstract

RESEARCH OBJECTIVE

FEEDBACK EFFICIENCY AND TRAINING EFFECTS DURING ALPHA BAND MODULATION OVER THE HUMAN SENSORIMOTOR CORTEX

How one can efficiently be trained to perform alpha band modulation over sensorimotor cortex?
Can training times and feedback exert significant effect of alpha frequency band training over sensorimotor areas?

STUDIES

STUDY I

Is it possbile to amplify motor cortex activation during motor imagery with 3D offline feedback in a single training session?

N=35 healthy participants; **single session**

Two **offline** feedback modalities: 2D and 3D limb movement videos aiming to enhance event-related desynchronisation (ERD) in the alpha band over sensorimotor areas during motor imagery.

- largest alpha band ERD during MI subsequent to the 3D visualization
- support of kinestehtic MI

STUDY II

Can multimodal and enriched online feedback affect performance in motor imagery based BCI control in five training sessions?

N=30 healthy participants; **5 sessions**

Three **online** feedback modalities: conventional uni-modal, enriched unimodal and enriched multimodal feedback in 5 training sessions aiming to activate ERD in the alpha band over sensorimotor areas.

- significant better perfomance after enriched feedback in the initial session
- no significant better perfomance of multimodality

STUDY III

Can patients with schizophrenia learn to regulate their alpha activity over sensorimotor cortex in multiple training sessions?

N=5 patients with schizophrenia, 4 healthy controls; **20 sessions**

Online feedback and 20 training sessions aiming to learn to regulate the alpha band amplitude over sen-sorimotor areas.

- patients learned to regulate alpha amplitude
- effects of enhanced resting alpha amplitude across the training time

OVERALL RESULTS

A realistic feedback can support end-user in motor imagery and enriched visual feedback can support user in control of a BCI. Even patients with schizophrenia can learn to modulate their alpha band activity.

2 Abstract

Neural oscillations can be measured by electroencephalography (EEG) and these oscillations can be characterized by their frequency, amplitude and phase. The mechanistic properties of neural oscillations and their synchronization are able to explain various aspects of many cognitive functions such as motor control, memory, attention, information transfer across brain regions, segmentation of the sensory input and perception (Arnal and Giraud, 2012). The alpha band frequency is the dominant oscillation in the human brain. This oscillatory activity is found in the scalp EEG at frequencies around 8-13 Hz in all healthy adults (Makeig et al., 2002) and considerable interest has been generated in exploring EEG alpha oscillations with regard to their role in cognitive (Klimesch et al., 1993; Hanselmayr et al., 2005), sensorimotor (Birbaumer, 2006; Sauseng et al., 2009) and physiological (Lehmann, 1971; Niedermeyer, 1997; Kiyatkin, 2010) aspects of human life. The ability to voluntarily regulate the alpha amplitude can be learned with neurofeedback training and offers the possibility to control a brain-computer interface (BCI), a muscle independent interaction channel. BCI research is predominantly focused on the signal processing, the classification and the algorithms necessary to translate brain signals into control commands than on the person interacting with the technical system. The end-user must be properly trained to be able to successfully use the BCI and factors such as task instructions, training, and especially feedback can therefore play an important role in learning to control a BCI (Neumann and Kübler, 2003; Pfurtscheller et al., 2006, 2007; Allison and Neuper, 2010; Friedrich et al., 2012; Kaufmann et al., 2013; Lotte et al., 2013).

The main purpose of this thesis was to investigate how end-users can efficiently be trained to perform alpha band modulation recorded over their sensorimotor cortex. The herein presented work comprises three studies with healthy participants and participants with schizophrenia focusing on the effects of feedback and training time on cortical activation patterns and performance. In the first study, the application of a realistic visual feedback to support end-users in developing a concrete feeling of kinesthetic motor imagery was tested in 2D and 3D visualization modality during a single training session. Participants were able to elicit the typical event-related desynchronisation responses over sensorimotor cortex in both conditions but the most significant decrease in the alpha band power was obtained following the three-dimensional realistic visualization. The second study strengthen the hypothesis that an enriched visual feedback with information about the quality of the input signal supports an easier approach for motor imagery based BCI control and can help to enhance performance. Significantly better performance levels were measurable during five online training sessions in the groups with enriched feedback as compared to a conventional simple visual feedback group, without significant differences in performance between the unimodal (visual) and multimodal (auditory–visual) feedback modality. Furthermore, the last study, in which people with schizophrenia participated in multiple sessions with simple feedback, demonstrated that these patients can learn to voluntarily regulate their alpha band. Compared to the healthy group they required longer training times and could not achieve performance levels as high as the control group. Nonetheless, alpha neurofeedback training lead to a constant increase of the alpha resting power across all 20 training session.

To date only little is known about the effects of feedback and training time on BCI performance and cortical activation patterns. The presented work contributes to the evidence that healthy individuals can benefit from enriched feedback: A realistic presentation can support participants in getting a concrete feeling of motor imagery and enriched feedback, which instructs participants about the quality of their input signal can give support while learning to control the BCI. This thesis demonstrates that people with schizophrenia can learn to gain control of their alpha oscillations recorded over the sensorimotor cortex when participating in sufficient training sessions. In conclusion, this thesis improved current motor imagery BCI feedback protocols and enhanced our understanding of the interplay between feedback and BCI performance.

3 Zusammenfassung (German abstract)

Das Elektroenzephalogramm (EEG) misst neuronale Oszillation, die sich generell auf Basis ihrer Frequenz, Amplitude und Phase charakterisieren lassen. Die physiologischen Eigenschaften neuronaler Oszillation und Synchronisation tragen zur Erläuterung verschiedener Aspekte kognitiver Funktionen bei, wie Motorsteuerung und Gedächtnis, Aufmerksamkeit, Informationsübertragung über Hirnregionen hinweg, Wahrnehmung und die Segmentierung des sensorischen Input (Arnal und Giraud, 2012).

Die dominante Schwingung des menschlichen Gehirns ist die Alphafrequenz. Diese Schwingungsaktivität wird an der Kopfhaut mittels EEG abgeleitet und kann bei allen gesunden Erwachsenen bei Frequenzen um 8-13 Hz gemessen werden (Makeig et al., 2002). Das Alpha Frequenzband spielt eine entscheidende Rolle bei kognitiven (Klimesch et al., 1993; Hanselmayr et al., 2005), sensomotorischen (Birbaumer, 2006; Sauseng et al., 2009) und physiologischen (Lehmann, 1971; Niedermeyer, 1997; Kiyatkin 2010) Prozessen des menschlichen Lebens. Mittels Neurofeedbacktraining erlernen Endnutzer, ihre Hirnströme zu kontrollieren und damit z.B. eine Gehirn-Computer-Schnittstelle (engl: brain-computer interface, BCI), einen muskelunabhängigen Kommunikationskanal zu bedienen. Üblicherweise richtet sich die BCI-Forschung auf die Verbesserung der Signalverarbeitung, die Klassifizierung und technische Weiterentwicklung des BCIs, aber nicht auf die Person, die in Interaktion mit dem technischen System steht. Der Benutzer selbst sollte entsprechend geschult werden, um in der Lage zu sein, das BCI erfolgreich zu nutzen. Wichtige Faktoren sind hierbei die Aufgabenstellung, das Training und insbesondere die Art der Rückmeldung, das sogenannte Feedback (Pfurtscheller kontrollieren et al., 2006, 2007; Allison und Neuper, 2010; Friedrich et al., 2012; Kaufmann et al., 2013; Lotte et al., 2013).

Die hier vorgestellte Arbeit hatte zum Ziel, ein optimiertes Training für Endnutzer zu entwickeln, um eine über den Sensormotorischen Cortex abgeleitete Alphaband-Modulation zu erlernen. Zu diesem Zweck wurden drei Studien durchgeführt, die sich mit den Auswirkungen von Feedback und Trainingsdauer auf kortikale Aktivierungsmuster und BCI-Leistung von gesunden Probanden und Patienten mit einer Schizophrenie Erkrankung befassen.

Die Ergebnisse dreier Studien, in denen Endnutzer erlernten, ihr Alphaband über den sensomotorischen Kortizes zu regulieren, werden im Folgendem detailliert erläutert: Die erste Studie konnte zeigen, dass eine realistische drei dimensionale Visualisierung einer Bewegung eine nachfolgende Bewegungsvorstellung positiv beeinflussen kann. Die Desynchronisation des Alphabandes (10-12 Hz) wurde signifikant erhöht und Endnutzer wurden dabei unterstützt, ein kinesthetisches Gefühl der Bewegungsvorstellung zu erlangen. Eine zweite Studie konnte zeigen, dass ein multidimensionales Feedback, das den Endnutzer über die Qualität der Eingangssignale informiert, zu einer gesteigerten BCI-Kontrolle verhelfen kann. Die Probandengruppe, die ein derartiges informationsreiches Feedback erhielt, zeigte im Vergleich zu einer Gruppe mit einfachem Feedback signifikant höhere Leistungswerte in fünf online Trainingssitzungen. Keine signifikanten Unterschiede in der BCI-Leistung zeigte der Vergleich der unimodalen (visuell) und multimodalen (visuell, akustisch) Feedbackgruppen. In der letzten Studie konnte gezeigt werden, dass auch Patienten mit einer Schizophrenie Erkrankung lernen können, ihr Alphaband in mehreren Sitzungen mit einem einfachen Feedback zu regulieren. Die Patienten zeigten im Gegensatz zu der gesunden Kontrollgruppe ein höheres Pensum an Trainingssitzungen und ein niedrigeres Leistungsniveau. Jedoch führte das Neurofeedbacktraining über die 20 Trainingssitzungen hinweg zu einem kontinuierlichen Anstieg des Alpha-Ruhepeaks.

Die hier vorgestellten Arbeiten konnten zeigen, dass ein informationsreiches, realistisches, visuelles Feedback positive Effekte auf die BCI-Leistung und kortikale Aktivierungsmuster ausüben kann. Eine realistische Bewegungsdarstellung kann Menschen dabei helfen eine Bewegungsvorstellung zu erzeugen. Die mehrdimensionale Visualisierung vermittelt dem Nutzer Informationen über die Qualität der Eingangssignale und erleichtert das Erlernen der Bedienung eines BCIs. Zudem konnte gezeigt werden, dass auch Patienten mit einer Schizophrenie Erkrankung in der Lage sind, Kontrolle über ihre Alphafrequenz über dem sensomotorischen Kortizes zu erlangen. Zusammenfassend kann festgehalten werden, dass diese Doktorarbeit bestehende BCI-Protokolle verbessern kann und zu einem besseren Verständnis der Interaktionen von Feedback mit der BCI Leistung und kortikalen Aktivierungsmustern beiträgt.

4 Introduction

The first section introduces the relevant brain structures and mechanisms for the generation of neural signals. Non-invasive recording techniques such as the electroencephalography (EEG) make it possible to detect spontaneous electrical activity of the brain over a period of time recorded from multiple electrodes along the scalp. The second section delves into the spectral content of EEG, with a focus on the neural alpha oscillations recorded over the sensorimotor cortex. A brain-computer interface (BCI) makes it possible to extract and translate specific features of the EEG signals into a computer output. The capabilities of this application and the end-user - BCI interactions are discussed in further details in the last section.

The main purpose of this thesis was to investigate to what extended training time and enriched feedback can influence alpha frequency band modulation with regard to cortical activation and performance. The herein presented studies attempt to answer the question on how one can efficiently be trained to perform alpha band modulation. The goal was to develop an alpha frequency training system that can help individuals to easily gain control of their alpha oscillations recorded over the sensorimotor cortices.

4.1 Relevant structures of the human brain

4.1.1 Electrical activity in neurons

The human nervous system is defined at the cellular level by the presence of neurons - types of cells that are specialized in information processing. A typical neuron consists of a cell body (soma), dendrites, and one or more axons. Neurons and neuroglia cells (cells which support the neurons' activities in various ways) are involved in sending signals rapidly and precisely to other cells. The information processing on a single neuron is possible due to the membrane potential, a voltage difference across the plasma membrane of each cell. This electrical polarization results from a complex interplay between protein structures embedded in the membrane called ion pumps and ion channels (Kandel et al., 2013). These voltage-gated ion channels allow the neuron to generate and transmit an electrical signal called the action potential. The changes in the resulting electric field potentials along the membrane and the magnetic field orientated perpendicular to the electric field can be measured invasively and, if the group of neurons is large enough, also by non-invasive recording techniques such as electroencephalography (EEG) systems.

4.1.2 Sensory and motor areas of the cortex

The cerebral cortex is the outer thin mantle of gray matter covering the surface of each cerebral hemisphere. It is typically 2-3 mm thick and includes sulci (grooves created by folding of the mantle) and gyri (bumps). Certain cortical regions (Fig 1), such as the primary cortices, can be organized by their different functions. These include areas directly receiving sensory input, the so-called motor and sensory cortex, or regions involved in various other cognitive tasks such as language, vision, auditory perception, memory, consciousness, planning, reasoning etc. (Haines, 2012).

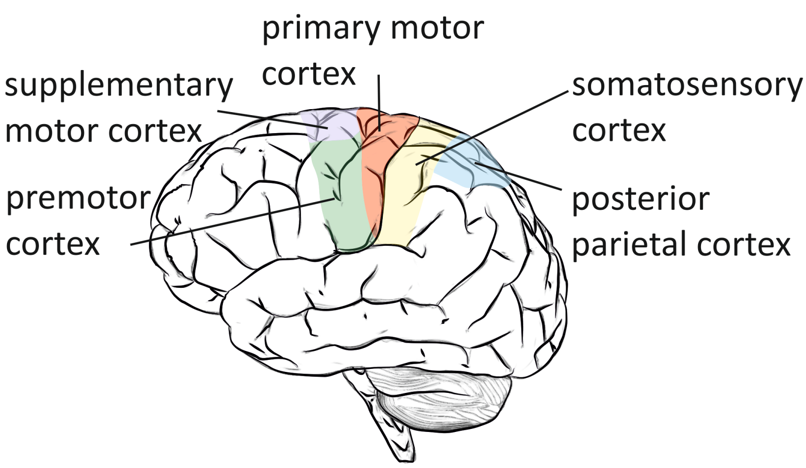

Figure 1: The human sensorimotor cortex: Sensory areas and motor areas of the human cerebral cortex seen from the left side (adapted by Gohlenhofen, 1997).

The primary motor cortex, located on the anterior paracentral lobule of the medial brain surface is the main contributor to generating neural impulses that pass down to the spinal cord. Whereas this area is primarily responsible for the control and the execution of movement, the anteriorly located premotor cortex is involved in the more abstract concepts of movement, such as the preparation for movement, the sensory guidance of movement or the direct control of movements with respect to the spatial position of the body parts. The posterior parietal cortex is thought to be responsible for some aspects of motor planning and for transforming sensory information into motor commands. The primary somatosensory cortex, which lies directly adjacent to the motor cortex, is considered to be a functional part of the motor control loop. The supplementary motor areas are located on the midline surface of the hemisphere anterior to the primary motor cortex. It has many proposed functions such as the internally generated planning of movement and sequences of movements and coordination of both hands (Penfield and Welch, 1951).

In the special case of the sensory and the motor cortex, some of the connections between the body and the respective brain areas controlling voluntary movement are known in detail and offer a map of the proportionate association of the cortex with body members, known as homunculus (Fig 2). While the feet are located close to the vertex, the hand is represented lateralized, following the head area with mouth and tongue (Blankertz et al., 2007). It reflects kinesthetic proprioception, the body as felt in motion, but mappings can vary in details between individuals. The mapping was discovered when electrical stimulation of neurons led to the illusion of a touch (for sensory neurons) or even to the movement (for motor neurons) of the respective body part (Schott, 1993).

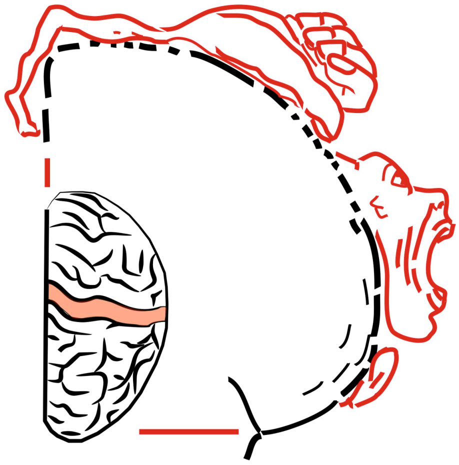

Figure 2: The homunculus. It visualizes the mapping of body muscles to the motor cortex (adapted by Gohlenhofen, 1997). The mapping is not isomorph as important areas as tongue, hands and lips are overly represented.

4.1.3 Neuronal activity in the cerebral cortex

The soma and dendritic trees of the neurons are situated in the cerebral cortex. The cells have an orientation in which the dendritic trees are closer to the surface. If excited, an electric field emerges. The following difficulties can arise with surface, non-invasive recording techniques that capture the electrical activity of the cerebral cortex: 1) the orientation of the field can change outside the skull depending on the position of the neuron in the sulcus or in the gyrus, 2) due to the folds in the sulci. The sulci signal sources are possibly more distant to the electrodes than those located in gyri, resulting in smaller signal amplitudes. Other limiting factors are the volume conduction effects, such as poorly conducting bones or skin, changes in the cerebral blood flow and electromyogenic influences that can attenuate signal amplitudes and act as a low-pass filter. Any increase in distance between the sensor and the signal source has to be overcome by the signal and, therefore, it gets more difficult to determine the exact location of the source (Wolpaw, 2012).

Non-invasive recording techniques can only detect the electric activity of large clustered groups of neurons that have correlated activity and not individual neurons. The sensors record electric or magnetic activity from outside of the neural tissue and are placed either inside the skull (Electrocorticography, ECoG) or outside the skull (EEG and Magnetoencephalography, MEG). Their distance to the signal source ranges from a few millimeters to a few centimeters. In practice, the resulting orders of magnitude for the recording of electric field potentials varies largely between the different recording techniques (EEG=± 30 µV; ECoG=± 200 µV; MEG=± 50 fT). Other imaging techniques, such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET), exist that try to capture the neural activity via indirect effects, such as changes in the blood oxygenation level (Aine, 1994).

4.1.4 Non-invasive recording technique EEG

In 1929, Hans Berger reported remarkable results of experiments in which he showed that it is possible to pick up the electrical activity of the human brain by placing electrodes on the scalp, amplifying the signal and plotting the changes in voltage over time (Berger, 1935). This electrical activity recording is called the EEG. These findings were confirmed by other work groups (Adrian and Matthews, 1934; Jasper and Carmichael, 1935; Gibbs et al., 1936) and led to the acceptance of the EEG as a real phenomenon. Over the past decades, the EEG has proven to be very useful in both scientific and clinical applications (Luck, 2005). This technique allows direct access to the recording of the activity of neural assemblies and makes it possible to detect activity in real-time. EEG signals are picked up by electrodes (varying sizes and materials) that are stuck to the scalp with a contact gel. The EEG signals are the electrical potentials that are determined at each position relative to one or more reference electrodes and are not stationary recorded signals. The signal channels are spread over the scalp whereas the reference electrode is usually placed at the earlobe, mastoids or the tip of the nose (Wolpaw, 2012). EEG recordings provide a high temporal resolution (~0.05 s) and activity changes in the range of milliseconds can be observed but suffer from disadvantages in spatial resolution (~10 mm, Nicolas-Alonso and Gomes-Gil, 2012).

An EEG can measure neural oscillations and, in general, these oscillations can be characterized by their frequency, amplitude and phase. In large-scale oscillations, amplitude changes are considered to result from changes in the synchronization within a neural ensemble, also referred to as local synchronization. The mechanistic properties of neural oscillations and synchronization are computationally interesting for explaining various aspects of many cognitive functions such as motor control and memory, attention and information transfer across brain regions, segmentation of the sensory input and perception (Arnal and Giraud, 2012).

Different names are given to different ranges of the oscillation frequency also called rhythms (see Fig 3). The frequency represents how fast the signal oscillates and is measured by the number of waves per second (Hz). The amplitude represents the magnitude of those oscillations, i.e. how large the oscillation are in microvolts and the power is a measure that estimates the magnitude of oscillatory amplitudes within a defined time window (Klimesch, 2012). Both, the amplitude and the power of an oscillation are dictated by the number of neurons in a population, that fire during a burst (Haken, 1996).

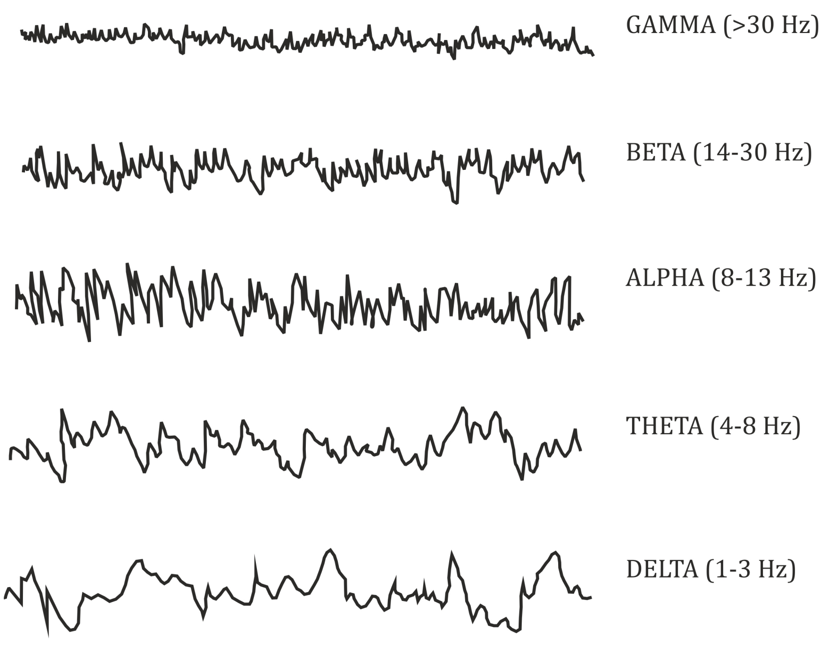

Figure 3: Typical brain oscillations in humans. The oscillations are created by rhythmic synchrony of large coalitions of neurons in the brain. Different behaviors lead specific brain areas to synchronize at different frequencies.

The detected EEG signal sometimes includes signal components that are not caused by neural activity. These artifacts can arise from muscle activity, movements of the eyeball, eye blinks or stray detections from exterior signal sources etc. and can be strong in amplitude. Most of these disturbances can be controlled by proper instruction of the participants, by using additional control electrodes close to possible artifact locations and by proper frequency filtering of the recorded signals (Luck, 2005; Wolpaw, 2012). EEG offers a high temporal resolution with low risk and easy to handle equipment which makes it therefore the optimal technique to record brain signals that can be used as a control input for brain-computer interfaces (BCI) or to provide neurofeedback (NF) to participants (Hwang et al., 2009; Neuper and Pfurtscheller, 2010).

4.1.5 Brain-computer interfaces (BCI)

Non-invasive EEG-based BCIs provide a direct connection between the brain and technical devices by means of EEG signals recorded from outside the brain (Birbaumer et al., 1999; Kübler et al., 2001a; Wolpaw et al., 2002, 2007; Birbaumer, 2006, 2007; Millán et al., 2010). It monitors the end-user's brain activity and translates it into commands while bypassing signals from muscles and peripheral nerves. BCI as a proof-of-concept has already been demonstrated in several contexts and several possible applications: selecting letters from a virtual keyboard (Birbaumer et al., 1999; Nijboer et al., 2008b; Kaufmann et al., 2011a; Halder et al., 2013; Käthner et al., 2013), brain painting (Münßinger et al., 2010; Zickler et al., 2013; Holz et al., 2015), control of computer cursor (Kübler et al., 2005; Trejo et al., 2006; Allison et al., 2012), control of a robot or wheelchair (Leeb et al., 2007a; Carlson et al., 2012; Kaufmann et al., 2014), internet browsing (Bensch et al., 2007; Mugler et al., 2010; Halder et al., 2015), operating prosthetic devices (Pfurtscheller et al., 2000, 2003; Müller-Putz et al., 2005, 2006) or navigating in virtual realities (Bayliss and Ballard, 2000; Leeb et al., 2007b; Lecuyer et al., 2008; Zhao et al., 2009). Such kinds of BCIs are particularly relevant as an aid for disabled people by providing a new interaction link with the outside world. Signals are acquired, processed (digitized, amplified, filtered, features extracted and classified) and translated into a command. The outcome of signal classification is fed back to the end-user, thereby completing the brain-computer interface loop (Fig 4). Thus, EEG-based BCIs can map certain frequencies (i.e. Delta, Theta, Alpha) as well as very fast electrical responses to certain stimuli in real time (i.e. ERP BCIs such as P300). Different features from the EEG can be used to enable the end-user to control an output device. In the herein presented thesis, the focus lies on BCIs driven by the mu rhythm recorded over the sensorimotor cortex, which is why alternative BCI systems are not further explained. For a review please see Wolpaw and colleagues (2002).

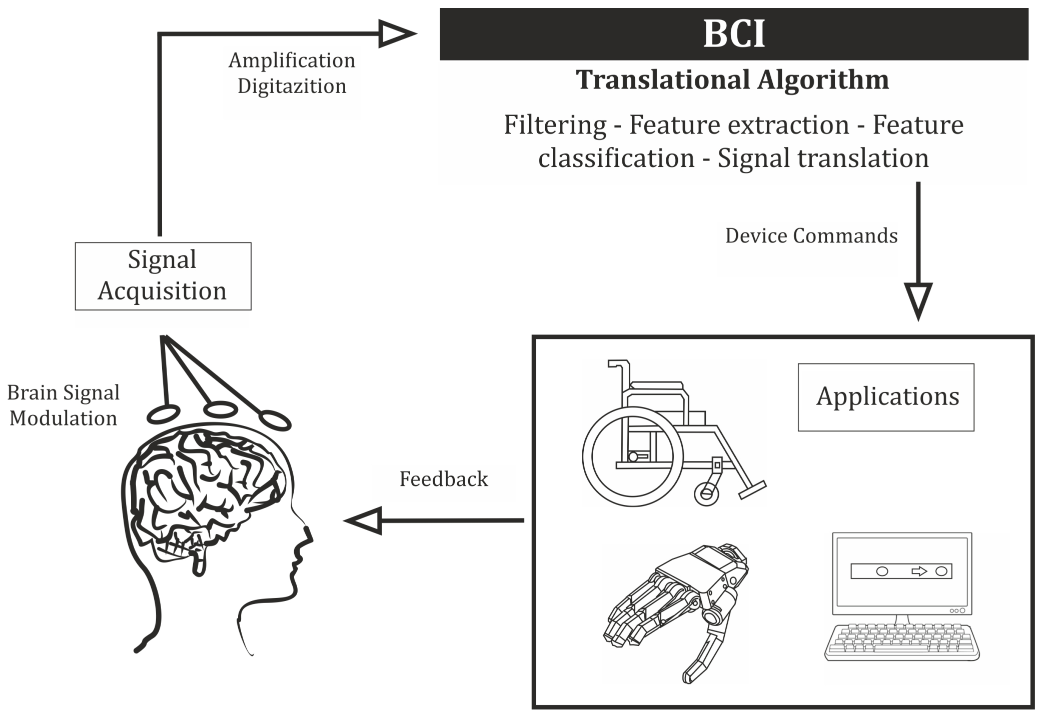

Figure 4: The BCI loop. Electrodes placed on the scalp acquire signals from the brain, which are processed to extract specific signal features that are sent to an output: a device command. Feedback is provided to the end-user and thereby closing the circle.

4.2 Alpha oscillations over sensorimotor cortex

The frequency of brain oscillations depends not only on the membrane properties of single neurons but also on the interconnectivity of networks to which they belong (Pfurtscheller, 2003). Large neuronal pools that are activated coherently can result in high-amplitude, low frequency oscillations, such as the classical alpha band brain rhythm, which is usually identified as oscillations at frequencies, around 8-13 Hz (Neuper and Pfurtscheller, 2001). Although the EEG comprises a range of frequency bands, for the purposes of this thesis the focus will be on the alpha frequency band. Alpha oscillations are sinusoidal, particularly dominant when eyes are closed (Kaiser, 2001). This frequency varies as a result of age, with an increase from childhood to adulthood followed by a decrease in older age (Klimesch, 1999). The exact mechanisms responsible for alpha oscillations generation are still unknown (Bollimunta et al., 2011) but there is evidence that they are generated from communication between thalamocortical and corticocortical structures (Lopes da Silva et al., 1980). This oscillatory activity is found in the scalp EEG in all healthy adults (Makeig et al., 2002) and considerable interest has been generated in exploring EEG alpha oscillations with regard to their role in cognitive (Klimesch et al., 1993; Hanselmayr et al., 2005), sensorimotor (Birbaumer, 2006; Sauseng et al., 2009) and physiological (Lehmann, 1971; Niedermeyer, 1997; Kiyatkin, 2010) aspects of human life. Alpha-band oscillations reflect dynamic and integrative sensory and motor processes and it plays an active role in information processing, which is to link perception and action (Pineda, 2005). An EEG rhythmical component that is described by the same dominant frequency as the alpha rhythm, but with distinct frequency and topographical boundaries, is the mu rhythm. This term is used for a special rhythm that reaches its maximum over the rolandic or central area of the sensorimotor cortex within the alpha range (Kuhlmann, 1978b) and is strongly connected to motor activities and can be modulated by motor imagery.

The dynamic of a neural network can result in phasic changes in the synchrony of cell populations due to externally or internally paced events which lead to characteristic EEG patterns: desynchronized alpha activity (event-related desynchronization, ERD) with small amplitudes in the scalp EEG reflects an activation of a distinct cortical area, whereas synchronized alpha activity (event-related synchronization, ERS), with large amplitudes in the scalp EEG reflects a state of inhibition of neighboring cortical areas with comparatively low excitability (Kuhlman, 1978b; Pfurtscheller and Lopes da Silva, 1999; Neuper and Pfurtscheller, 2001; Pfurtscheller, 2001; Klimesch et al., 2007). The reduction in the signal power may be a result of either the reduction in the magnitude of the source or the reduction in the amplitude recorded over the sensorimotor cortex (Haueisen et al., 2000; Bazanova and Vernon, 2014). A greater level of alpha amplitude reflects the inhibition of non-essential activity, which in turn may facilitate performance in cognitive or motor tasks (Klimesch et al., 2007). The signal-to-noise ratio is increased within the cortex by actively inhibiting non-essential or conflicting processes (von Stein and Sarnthein, 2000; Cooper et al., 2003). Such enhanced alpha oscillations are always time-locked to an event but can be either phase-locked (evoked) or induced (Pfurtscheller, 2003). The generators of this alpha oscillation are not known yet. The question as to whether alpha oscillation is induced by inhibitory activity and/or other factors such as network, resonance or intrinsic properties of certain neuron populations cannot be sufficiently answered yet (Klimesch et al., 2007). Different approaches have been proposed how to measure alpha frequency: the individual alpha peak frequency (Angelakis et al., 2004), the mean peak frequency within a fixed bandwidth (Hooper, 2005) and the individual alpha peak at the center of gravity within the individual alpha frequency range (Klimesch et al., 1993). Inter-individual differences in alpha peak frequency were found to correlate with different aspects such as performance on memory (Dopplmayr et al., 2005), intelligence (Jausovec and Jausovec, 2000) and the efficiency of neurofeedback training (Bazanova et al., 2009).

The characteristics of alpha oscillations and the fact that people can learn to control this particular brain rhythm, makes it possible to use it as a control signal for a brain-computer interface (McFarland and Wolpaw, 2011) or for neurofeedback training (Hwang et al., 2009; Neuper and Pfurtscheller, 2010).

4.2.1 Motor imagery (MI)-based brain-computer interfaces

Motor imagery (MI)-based brain-computer interfaces are a special type of BCI, that analyzes and classifies dynamics of single frequency component, such as the mu rhythm or multiple components of sensorimotor rhythms (Wolpaw et al., 1991, 2002; Pfurtscheller et al., 2006a). Mu amplitudes increase in the absence of any movement or sensation, but decrease by sensory stimulation, motor behavior and imagination of movements (Curran and Stokes, 2003). The imagination of movements, or motor imagery, can be defined as a dynamic state during which the representation of a specific motor action is internally reactivated within working memory without any overt motor output (Decety et al., 1989; Sharma et al., 2006). It is a cognitive process in which a subject imagines to perform a movement and it requires the conscious activation of brain regions that are also involved in movement preparation and execution, accompanied by a voluntary inhibition of the actual movement (Lotze, 1999; Mulder, 2007). The execution, observation or motor imagery of limb movement's result in similar somatotopically organized activation patterns (Lotze et al., 1999) and the blocking effects are visible bilaterally but with a clear predominance contralaterally to the moved limb (Blankertz et al., 2007). The discrimination between different limbs motor imagery has shown to be very useful for ERD-based classification (Pfurtscheller et al., 1997; Pfurtscheller and Neuper, 1997; Neuper et al., 2005). For example, one-sided hand motor imagery reveals an ERD of mu rhythm focused over the contralateral hand representation area (Curran and Stokes, 2003; Naeem et al., 2006). Usually, two classes work most reliably, for example, imagination of a grasping movement of one hand against the other hand or one hand against both feet. In some participants, even three classes may lead to successful control (left hand vs. right hand vs. both feet; Pfurtscheller et al., 2006a; Halder et al., 2011; Holz et al., 2013). These features in the EEG can be translated into a computer output in the form of a movement of a cursor on a computer screen and MI-based BCIs can be applied in various ways. It enables communication in healthy end-users (Millán and Mourino, 2003; Birbaumer, 2006; McFarland and Wolpaw, 2011) as well as in patients with severe motor impairment (Neuper et al., 2003; Kübler et al., 2005). The latter is possible due to the fact that conditions affecting the motor system, such as in patients with neurodegenerative diseases, leave the ability to generate motor imagery intact (Neuper et al., 2003; Kübler et al., 2005). Several other terminal devices can be controlled by this kind of BCIs such as prostheses (Pfurtscheller et al., 2000, 2003; Müller-Putz et al., 2005), robots (Millán et al., 2004) or wheelchairs (Galan et al., 2008). In recently published literature MI-based BCIs are used in a therapeutic approach as a training tool for stroke rehabilitation (Grosse-Wentrup et al., 2011; Pichiorri et al., 2011; Ramos-Murguialday et al., 2013). The speed and precision of the MI-based BCIs that can be achieved by healthy participants (Wolpaw and McFarland, 2004; Hammer et al., 2012) equals or exceeds that achieved so far with invasive methods (Kennedy et al., 2000; Daly and Wolpaw, 2008). The operant conditioning process to enable end-users to volitional control their brain signals is called neurofeedback training.

4.2.2 Neurofeedback

The most common type of EEG neurofeedback (NF) is achieved by using either a single or multiple electrodes to alter the amplitude or power of one or two specific frequency bands in a particular area of the brain (Sterman, 1973; Evans and Adarbanel, 1999; Vernon et al., 2003; Weber et al., 2011; de Zambotti et al., 2012). This thesis will concentrate on this form of neurofeedback. Individuals learn to exert a conscious control over some aspect of their brain oscillations in an operant conditioning procedure (Lubar, 1997). Neurofeedback training involves providing the subject in real time with acoustic, visual or combined acoustic-visual information relating to the rhythmic electrical activity of specific cortical areas and functions (Vernon et al., 2003; Masterpasqua and Healey, 2003; Vernon, 2005). The aim is to enable the subject to become aware of particular patterns of cortical activity that are assumed to be associated with a more optimal behavior or state.

Different kind of frequency band NF training has not only been used for treating various neuropsychological impairments such as epilepsy (Rockstroh et al., 1993; Kotchoubey et al., 1999; Sterman and Egner, 2006), attention deficit and hyperactivity disorder (Lubar et al., 1995; Butnik, 2005; Strehl et al., 2006; Arns et al., 2009) and depression and anxiety (Baehr et al., 1997; Hammond, 2005), but also in the treatment of substance use addictions (Scott et al., 2005; Sokhadze et al., 2008; Dehghani-Arani et al., 2013). Neurofeedback in clinical populations is based on the idea that if there is an abnormality in the EEG which has been associated with a particular disorder, for instance, a less well-organized alpha activity in the EEG of patients suffering from schizophrenia (Itil, 1977), neurofeedback can be used to alter a particular brain frequency to what would be expected in healthy individuals to improve the patient's condition.

The effect of alpha neurofeedback training was established especially in the context of cognitive performance. The relation between cognitive performance and EEG alpha activity has been reported by several studies in the previous years (Vernon et al., 2003; Hanslmayr et al., 2005; Gruzelier et al., 2006; Zoefel et al., 2011; Gruzelier, 2014). A large alpha resting power can be a predictor of good cognitive performance; as such, those with higher frequency of resting alpha power may be able to utilize this to actively inhibit irrelevant processes, depending on the needs of the task (Doppelmayr et al., 2002; Herrmann et al., 2004; Hanslmayr et al., 2005; Zoefel et al., 2011; Klimesch, 2012; Wan et al., 2014). Alpha band NF training on different scalp locations has successfully been used to enhance attention and memory performance in healthy younger subjects (Vernon et al., 2003; Escolano et al., 2011; Zoefel et al., 2011; Nan et al., 2012b; Dekker et al., 2014) and in elderly subject groups (Angelakis et al., 2007; Gruzelier, 2014). Those subjects who were able to enhance their frontal alpha power during training performed better on attention, short-term memory and working memory tasks. A greater improvement in cognitive performance was observed in subjects that were able to increase their alpha power following NF training (Hanslmayr et al., 2005).

4.3 The modulation of alpha oscillations

Conventionally, BCI research is focused mostly on the signal processing, classification and algorithms necessary to translate brain signals into control commands. Although a lot of effort was expended to enhance usability and control over BCIs, patients with neurodegenerative or psychological diseases showed a decrease in BCI performance (Kübler et al., 2004, 2008; Piccione et al., 2006; Nijboer et al., 2010) and an increased training effort was required (Kübler et al., 2001a). However, approximately 10-30 % of healthy subjects are not able to gain control over the BCI (Guger et al., 2003; Allison and Neuper, 2010; Blankertz et al., 2010), or cannot achieve accurate control or display large performance variations across sessions and runs (Blankertz et al., 2010; Halder et al., 2011; Hammer et al., 2012; Grosse-Wentrup and Schölkopf, 2013). This non-successful BCI use has often been described with the term ''BCI illiteracy'' (Kübler and Müller, 2007; Blankertz et al., 2010; Vidaurre and Blankertz, 2010), but was replaced in recent publications by "BCI inefficiency" to better stress that the inability may be inherent in the system and not in the end-user (Kübler et al., 2011; Hammer et al., 2012). Several theories exist to try to explain the phenomenon of BCI inefficiency: In some end-users the neuronal systems needed for voluntary control might not produce suitable electrical activity that is detectable on the scalp by EEG, although the necessary neuronal populations are presumably healthy and active in these participants (Kober et al., 2013). Approaches to alleviate this problem have been explored, such as improved signal processing or filter adjustments (Vidaurre and Blankertz, 2010; Vidaurre et al., 2011; Sannelli, 2013). Nevertheless, the end-user and the context in which learning to regulate brain pattern takes place seem to be equally important.

4.3.1 Inter-subject variation

Several factors have been identified which contribute to inter-subject variations in the ability to affect the mu rhythm. Randolph and colleagues (2010) reported that the interaction between age and the amount of time spent daily on hand/arm movements correlates with mu rhythm modulation. Burde and Blankertz (2006) could show that end-users tend to have better BCI performances when they are more comfortable with their ability to deal with technology. A significant positive correlation was found between performance and the extent to which end-users can perceive an imagination task (Vuckovic and Osuagwu, 2013), visuomotor coordination (Hammer et al., 2012) or the ability to concentrate on a particular task (Ahn and Jun, 2015). Besides these factors, mental states and processes might affect the ability to gain control over the EEG signals. This could include concentration, mental strategies, frustration, emotional states, fatigue, distraction and motivation (Curran and Stokes, 2003; Guger et al., 2003; Kleih et al., 2010; Nijboer et al., 2010; Hammer et al., 2012; Kober et al., 2013; Käthner et al., 2014).

4.3.2 Performance prediction

In order to understand the phenomenon of BCI inefficiency in more detail a few studies tried to assess predictors of successful performance in order to have a simple and valid predictor to judge whether or not a participant will be able to learn to modulate their brain oscillation. For example, the strength of the resting mu peak in the EEG is an essential indicator of the successful performance with a BCI controlled with motor imagery (Blankertz et al., 2010; Reichert et al., 2015) and makes it possible to explain approximately 28 % of the variance in feedback accuracy. A method for predicting the performance of individual participants before the end of the eleventh training session was introduced by Weber and colleagues (2011). They calculated the amplitude increase from session one to eleven in order to quantify each end-user's performance: participants had to show a clear increase in the EEG amplitudes by the end of their training (> 8 % in the last five training sessions) and this increase should be consistent across all of their training sessions to be categorized as “learner”. Several studies demonstrated that the performance obtained during the initial training phase with patients suffering from Amyotrophic lateral sclerosis (ALS) indicates the duration of training that will be necessary to achieve control over the BCI with more than a 70 % accuracy (Neumann and Birbaumer, 2003; Kübler et al., 2004).

4.3.3 End-user - BCI interaction

There are many variables that degrade BCI performance and a precise categorization may not be a simple issue. Two categories can be defined that are either user-related, such as the individual characteristics and the feedback and instruction that are presented, or system-related, such as the characteristics of the BCI and its application (Kübler et al., 2014, Fig 5). In the machine learning approach, the EEG classifier is optimized on examples of EEG signals that are collected from the end-user while a targeted mental task is performed. With this approach, the training time before the end-users can control the BCI is shortened (Millán et al., 2002; Blankertz et al., 2006). Wolpaw and colleagues (2002) established that “BCI use is a skill” and the end-user may not be able to produce reliable EEG patterns, making it impossible for the BCI to correctly identify the desired mental commands (Allison and Neuper, 2010). Focusing on the person interacting with the technical system, the end-user him/herself must be properly trained to be able to successfully use the BCI.

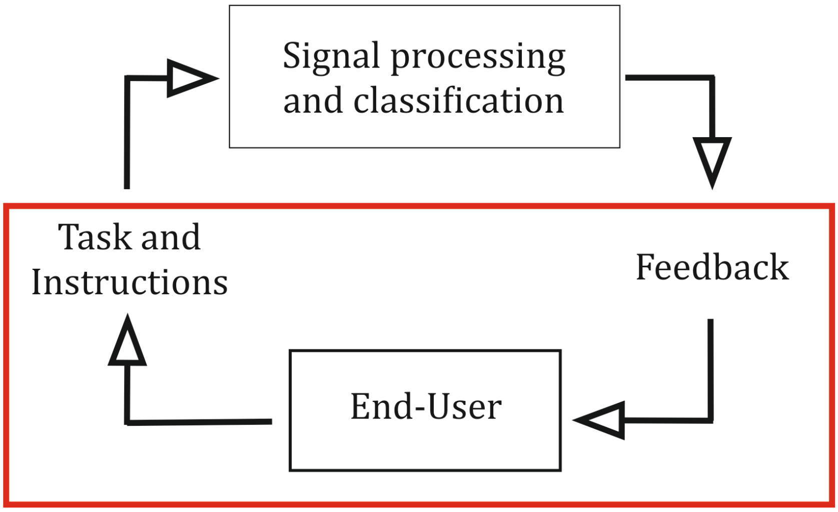

Figure 5: End-user - BCI interaction. BCI research can focus on different aspects to improve performance for example on the signal processing and algorithms necessary to translate mental patterns into control commands but also on the context in which learning takes place which includes the task, given instructions and type of feedback.

Neuper and Pfurtscheller (2010) proposed that NF training is a necessary component to learning the BCI skill, specifically for BCIs based on the recognition of mental imagery tasks, such as motor imagery, the so-called spontaneous BCI, which are the focus of this thesis. The operant conditioning approach is one model to gain control over one's own brain activity (Neuper and Pfurtscheller, 2010). The EEG signal classifier is fixed and unknown to the end-user and one has to find out over several sessions how to control a cursor by modulating the brain activity in a specific way (Wolpaw et al., 1991, 2000; Curran and Stokes, 2003; Birbaumer et al., 2006). Operant learning as in NF studies declares that the occurrence of a positively reinforced behavior will increase, therefore correct or desired brain responses are rewarded by getting points or smiling face (Kübler et al., 1999; Kober et al., 2013). To improve performance the end-user's control strategy has to be optimized and the mental task appropriate to be controlled has to be determined (Curran and Stokes, 2003). Factors, such as task instructions, training time and feedback, can therefore play an important role in learning to control a BCI (Pfurtscheller et al., 2007; Allison and Neuper, 2010; Friedrich et al., 2012; Kaufmann et al., 2013) and are further discussed in the following:

- **Instructions and tasks:** Instructions are inevitable to explain the feedback meaning. It should, therefore, provide the end-user with a clear and specific learning objective and should activate prior experience with the task that the end-user will use to demonstrate correct BCI control. For example, Neuper and colleagues (2005) showed that specifically instructing the end-user to perform kinesthetic imagination of movements rather than the visual imagination of movements substantially improved performances in BCIs based on motor imagery. Additionally the BCI task itself may be improved.

- **Number of training sessions:** A highly discussed variable in the process of learning to use a BCI is the number of sessions necessary to gain control over the brain activity. Existing literature offers a wide spectrum of training times that are proposed for BCI or neurofeedback training. Although some approaches exist that allow providing BCI control already during the very first session (Guger et al., 2000; Blankertz et al., 2007, 2008), by using a preceded calibration and more channels, most of the existing BCI systems require several training sessions (Kübler et al., 2001a; Vidaurre et al., 2006). Healthy end-users are able to learn to significantly increase motor cortical excitability in less than ten sessions (Siniatchkin et al., 2000; Egner et al., 2002; Vernon et al., 2003; Hanslmayr et al., 2005; Friedrich et al., 2009; Pichiorri et al., 2011; Zoefel et al., 2011), or 10-20 sessions (Egner and Gruzelier 2004; Raymond et al. 2005; Dempster and Vernon, 2009; Dekker et al., 2014; Nan et al., 2012b), whereas patients (with some form of psychological or physiological disability) often require more training sessions (Rockstroh et al., 1993; Kotchoubey et al., 1999; Fuchs et al., 2003; Kübler et al., 2005, 2008; Kouijzer et al., 2009; Dehghani-Arani et al., 2013; Escalano et al., 2014).

- **Feedback:** Feedback seems to be an important feature in learning to get in control of the own alpha rhythm activity (Shute, 2008). Feedback is provided during the imagery tasks to enhance participants' performance thereby reinforcing correct behavior. Lotte and colleagues (2013) have suggested that a successful BCI feedback independent of the modality should be non-evaluative and supportive, to give the end-user the feeling of competence. It should be clear, purposeful and meaningful (Hattie and Timperley, 2007). Furthermore, it should not distract the end-user from the task but rather provide enough information about the quality of the performed mental activity. An MI-based BCI or neurofeedback training can use different modalities to meet the demands of the end-user.

4.3.4 User-centered approach

To focus on the end-user – BCI interaction, it is important to take into account the development of the BCI system and to instruct and support the end-user in the most efficient way. This demands for a close investigation of the end-users' needs (e.g. spelling device, motor or cognitive training), requirements (e.g. communication device, motor or cognitive rehabilitation) and restrictions (e.g. limitation in concentration or perception). Valuable work in this direction has been performed in recent years by the BCI community and the potential user of a BCI came more into the focus of BCI development. A user-centered design (USD) involves the individual user, the task and the environment from an early developmental process into implementation and offers appropriate solutions by an iterative process whereby a prototype is designed, tested and modified (Kübler et al., 2014a). The usability was standardized with the International Organization for Standardization (ISO) 9241–210 and was addressed with the three components (Kübler et al., 2014b): effectiveness (i.e., how accurate and complete the task can be mastered by the target group), efficiency (i.e., how much effort and time is needed to be effective), and satisfaction (i.e., how much comfort and acceptability is perceived by the end-user while using the product). Kübler and colleagues (2014b) introduced a USD in end-users with severe motor impairment and in the locked-in state. They could show that the evaluation metrics within the framework of the USD proved to be an applicable and informative approach to evaluate BCI controlled applications.

5 Studies of this dissertation

The main purpose of this thesis was to investigate to what extent training time and enriched feedback can influence alpha frequency band modulation recorded over the sensorimotor cortex.

To address this issue, the first study investigated the role of a three-dimensional offline feedback in healthy participants in a single motor imagery training session, by measuring the effects on the event-related desynchronization of the mu rhythm (10-12 Hz). Subsequently, participants were trained in several online MI-based BCI sessions with enriched and multimodal feedback, to compare their BCI performance and user satisfaction with respect to the different feedback types. The last study focused on the trainability of the alpha rhythm (10-12 Hz) in patients with schizophrenia, questioning the effects on activation patterns and cognitive performance. All studies refer to the modulation of the alpha rhythm over the sensorimotor cortex and represent practical applications such as a communication technique or motor and cognitive rehabilitation.

The herein presented studies follow a user-centered design, supporting the interplay of the end-user with the BCI system with respect to the end-users' needs, requirements and restrictions. Variables like instruction, feedback types and training time are reported by the measurements of cortical activation, BCI performance and user satisfaction in healthy participants and in patients with schizophrenia and are based on the following hypothesis:

- Healthy participants, as well as patients with the reduced ability to concentrate, can learn to modulate the alpha power (study 1, 2 and 3).
- Feedback has significant effects on cortical activation patterns, BCI performance, and user satisfaction. An informative online feedback that is distinct and comprehensible can support end-user in getting in control of the alpha modulation (study 1 and 2).
- Training time is an individual feature in the process of learning to modulate specific frequency band (study 2 and 3).

The following studies incorporate the interplay of these variables to answer the question as to how one can efficiently be trained to perform alpha band modulation. The goal of this thesis was to develop guidelines for an user centered design for alpha frequency training that can help individuals to easily gain control over their alpha oscillations recorded over the sensorimotor cortex.

6 Study I - 3D visualization of movements and motor cortex activation during subsequent motor imagery

The following study has been published elsewhere (Sollfrank et al., 2015a). The methodological approach and the results were adopted.

6.1 Introduction

As already described earlier, the mental imagery of motor actions can produce replicable EEG patterns over primary sensory motor cortex areas that are very similar to the EEG patterns following the planning, the execution and the observation of real movements (Beisteiner et al., 1995; Lang et al., 1996; Pfurtscheller and Neuper, 1997). The mental process during motor imagery refers to an active procedure during which a specific action is reproduced within working memory without any actual movements (Decety and Grèzes, 1999; Jackson et al., 2001); function, behavior, and performance are rehearsed mentally as if the person is actually performing them (Zimmermann-Schlatter et al., 2008). Imagining movements of upper or lower limbs result in a desynchronization of the mu rhythm (8–12 Hz) over specific areas of the sensorimotor cortex.

These EEG signal features can be translated into a BCI command to support motor rehabilitation: by affecting motor learning, this approach could help to guide brain plasticity by demanding close attention to a specific motor task (for Review see Zimmermann-Schlatter et al., 2008) and it has recently been suggested that motor imagery-based BCI training can restore motor control in persons with hemiplegia due to stroke (Daly and Wolpaw, 2008; Broetz et al., 2010; Caria et al., 2011; Pichiorri et al., 2014).

“The activation of cortical networks through repetitive motor imagery practice can be supported with suitable feedback and training approaches. First time end-users cannot be expected to perform the required mental tasks perfectly and the poor performance during the calibration task can result in the feedback being wrong (Lotte et al., 2013). The feedback and the feedback environment should be inherently motivating and a rich visual representation of the signal, in the form of a three-dimensional video game or virtual reality environment, may enhance the end user`s control over a MI-based BCI (Pineda et al., 2003). Subjects learned to control levels of sensorimotor rhythm activity and were able to control a BCI during a motivationally engaging and a realistic, interactive task (Pfurtscheller et al., 2007; Friedmann et al., 2007). On the basis of these findings, some researchers have proposed that realistic feedback is a powerful medium to improve BCI-presentation by creating immersive and motivating environments (Leeb et al., 2007a, b; Friedmann et al., 2007; Ron-Angevin and Diaz-Estrella, 2009). This may also be expected to help the end-user adapting to richer and more complex environments; thus, lowering the mismatch between the provided feedback during training and during the real-world use. For example, one could expect that observing a realistic moving hand should have a greater effect on the sensorimotor rhythms than watching an abstract feedback (Pfurtscheller et al., 2007)" (Sollfrank et al., 2015a).

Some people report having difficulties in performing motor imagery. Neuper and colleagues (2005) argued that subjects should imagine a self-performed action with an interior view, such as a kinesthetic experience of movement, while avoiding muscle tension. To improve motor imagery based BCI control, user training should emphasize kinesthetic experiences instead of visual representations of actions. These different types of motor imagery are very likely associated with dissimilar electrophysiological activation patterns on the sensorimotor cortex in terms of time, frequency and spatial domains. Instructions are crucial for explaining the task to the end-user and to support motor imagery and visual cues can help to acquire the feeling of a kinesthetic experience.

6.2 Study aims

Interventions that optimally involve the most effective kind of feedback visualization must be properly identified in order to enhance standard care approaches for the rehabilitation of motor function (Daly and Wolpaw, 2008;

Mulder, 2007). Thus, a study was conducted to assess the effects of visual offline feedback on the process of learning kinesthetic motor imagery.

Firstly, it is investigated, if offline feedback during a single session can influence event-related activation patterns over the sensorimotor cortex. Secondly, the patterns of event-related desynchronization of the mu rhythm (10-12 Hz) during motor imagery are compared with respect to the three-dimensional and two-dimensional visualization of five different upper and lower limb movements. Thirdly, it shall be clarified, if there is an advantage associated with the use of enriched three-dimensional movement visualizations that can thereby give prospective support for the use of an MI-based BCI.

It is assumed that offline feedback can support end-users in controlling their brain oscillation (McFarland et al., 1998). Further, event-related desynchronization is expected to be more pronounced after the three-dimensional compared to the two-dimensional condition (Pfurtscheller et al., 2007). In addition, it is predicted that the three-dimensional visualization of the limb movements supports end-users in getting a kinesthetic feeling during subsequent motor imagery (Neuper et al., 2005).

6.3 Methods

6.3.1 Participants

"In total, 39 healthy MI-based BCI novices took part in the study which was approved by the Human Research Ethics Committee of the Office of Research and Development at Curtin University. Each participant was informed about the purpose of the study and signed informed consent prior to participation. Four of the participants were excluded from analysis due to noise in the data: Three of them were moving too much during the experiment and for one it was not possible to attain impedances lower than 20 kΩ. Of the 35 participants whose data were included in the final analysis, 18 were women and the mean age of the sample was 26.56 years (SD 5.33, range 18-54). Two participants were left-handed. All participants had normal or corrected-to-normal vision" (Sollfrank et al., 2015a).

6.3.2 Experimental set-up

“Participants were seated in a comfortable chair directly in front of a True3Di 24" SDM-240M Stereoscopic 3D Monitor wearing stereoscopic glasses. Each participant’s chin lay on a pre-assembled chin holder. Participants were instructed to sit in a relaxed posture with their eyes open and avoiding any eye and body movements. Using a within-subjects design, all participants were instructed to watch attentively 18 randomized videos of different limb movements for the left and right body part that were presented on a stereoscopic screen. Videos were displayed in 2D and 3D (Fig 6), portraying the following movements of computer-generated models: rotation of the wrist, elbow, knees and ankle anteriorly and an arm flexion towards the spectator. The videos displayed the movements from the perspective of the participant to encourage the feeling that each participant was moving their own limbs. At the end of each video a 6 s recording phase started, with a blank screen being presented during this phase. During this recording period, participants were requested to replicate subsequently the just observed movement by motor imagery. The task was to perform a kinesthetic rather than visual motor imagery (Neuper et al., 2005). Instructions were important during this experiment, as the participants only received offline feedback before the motor imagery phase. Participants were instructed to feel the just observed motion in their muscles and they should vividly remember a situation in which they performed a given movement before imagining it during the subsequent EEG recording phase. This should activate their prior experience with the task they will imagine, which is expected to make the learning easier (Merrill, 2007). Data collection lasted 45 min, with participants performing three runs of 10 min each, with five-minute breaks between each run” (Sollfrank et al., 2015a).

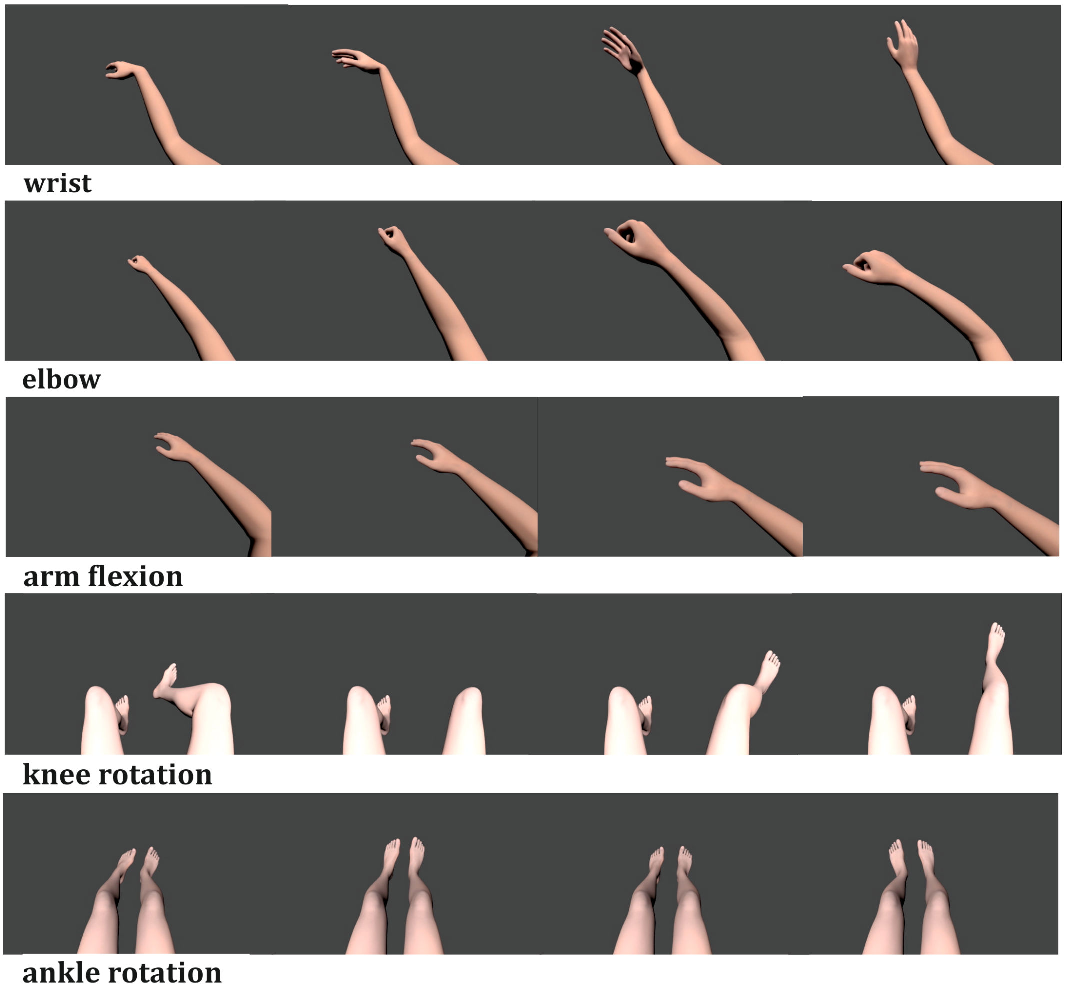

Figure 6: Limb movement visualizations. Five different limb movements were animated: wrist movement, elbow rotation, arm flexion, knee and ankle rotation. All movements were shown for the left and right limb, except the ankle rotation, which showed both feet rotating simultaneously. All videos were displayed randomized in 2D and 3D. Figure reproduced with permission from Sollfrank and colleagues (2015a), Copyright Frontiers Media SA. The publication is available online at http://www.ncbi.nlm.nih.gov.

6.3.3 Data acquisition

"The EEG was recorded from 40 channels located over the sensorimotor cortex. The locations of the Ag/AgCl electrodes were based on the modified 10-20 system of the American Electroencephalographic Society (Sharbrough et al., 1991). Each channel was referenced to the left and grounded at the right mastoid. Impedances were kept below 5kΩ via application of conductive gel. Data were collected via Neuroscan EEG equipment and signals were amplified using NuAmps amplifier.

Data were sampled at 1000 Hz and bandpass filtered between 0.1-70 Hz with an additional notch filter applied to remove 50 Hz noise. A program algorithm was written to determine the presence of eye-blink artifacts; if identified, data from these periods were deleted. Data processing and storage were performed on a conventional laptop with an additional external monitor" (Sollfrank et al., 2015a).

6.3.4 ERD/ERS analyzes

"EEG signals were visually inspected and trials contaminated with muscle or eye movement activity were discarded. ERD/ERS calculation was undertaken by bandpass filtering of each trial, squaring of samples and subsequent averaging over trials and over sample points (Graimann et al., 2002). The ERD/ERS were expressed as proportional power decrease (ERD) or power increase (ERS) of the imagery period in the upper alpha frequency band (10-12 Hz) and were calculated relative to the baseline, in relation to a 1-s reference interval before the imagery period started. Topographical maps were generated averaged for all participants for each task and visualization modality. The resulting maps represent plots of significant ERD within the given frequency range of 10-12 Hz. Based on the results of the topographical maps, mean ERD/ERS in the alpha frequency band were computed with the traditional ERD/ERS method proposed by Pfurtscheller and Lopes da Silva (1999). For statistical analyzes, ERD/ERS values obtained from the right (C_4) versus left sensorimotor cortex (C_3) temporally aggregated over the imagery period (1-6 s) were used (Fig 7). In order to analyze the potential influence of the visualization modality on the ERD/ERS patterns during task performance a repeated measure ANOVA was performed using the visualization modality, task, electrode position and task side as within-subjects variables. The probability of a Type I error was maintained at 0.05" (Sollfrank et al., 2015a).

6.4 Results

"The topographical maps of the mean ERD values for the two visualization modality groups are compared in Figure 7, separately for the respective tasks (rotation of the wrist, elbow, knees and ankle in front and arm flexion towards the spectator) and pooled for both left and right motor imagery in the upper alpha frequency band (10-12 Hz). In general, the results show a strong increase of the characteristic patterns of sensorimotor ERD of the upper alpha band components for left and right limb motor imagery present over the sensorimotor areas in both visualization conditions. On basis of these findings electrode positions C_3 and C_4 were selected for further analyses, which is in accordance to other motor imagery studies (Ron-Angevin and Diaz-Estrella, 2008; Neuper et al., 2009; Ono et al., 2013). A repeated measures ANOVA was performed on the ERD/ERS data using the visualization modality (VM, 2 levels: 2D vs. 3D), task (5 levels: wrist movement, elbow rotation, arm flexion, knee and ankle rotation), electrode position (2 levels: C_3 vs. C_4) and task side (2 levels: left vs. right) as within-subjects variables, in order to analyze the potential influence of the visualization modality on the ERD patterns during motor imagery. In addition, two 5x2x2 ANOVAs were performed using the variables task, EP and task side as within-subjects variables for the two VM groups separately. Table 1 provides an overview of the significant ANOVA effects. Overall, significant differences were observed as a function of visualization modality. This main effect is primarily due to the larger ERD during motor imagery after 3D feedback. The significant main effect of Task indicates that ERD varied upon the different tasks. The averaged data for all upper limb (wrist rotation, elbow rotation, arm flexion) and lower limb MI tasks (knee rotation, ankle rotation) separated for the 2D and 3D condition were checked for normal distribution. Afterwards a post hoc paired sample t-test revealed significant smaller ERD values for lower limb MI tasks compared to upper limb MI tasks for the 2D ($t_{(368)}=3.74$, $p=.041$) and for the 3D ($t_{(368)}=4.21$, $p=.0433$) visualization modality. A significant interaction between electrode position and the task was found, which established the contralateral dominance of ERD. This analysis revealed significant interactions involving the factors visualization modality, task, electrode position and task side (Table 1). Post hoc paired t-test comparison indicated that the largest upper alpha band power decrease during motor imagery was obtained subsequent to the three-dimensional visualization averaged or all tasks and both electrode positions ($t_{(1007)}$=3.126, p=.002)" (Sollfrank et al., 2015a).

Table 1: ANOVA analysis. Summary of significant F-values[a] for ERD/ERS analyses for the whole sample and separated for each visualization modality (VM). Table reproduced with permission from Sollfrank and colleagues (2015a), Copyright Frontiers Media SA. The publication is available online at http://www.ncbi.nlm.nih.gov.

	ANOVA effects		
	Whole sample (N=35) VM (2) x Task (5) x EP (2) x Task Side (2)	2D VM (N=35) Task (5) x EP (2) x Task Side (2)	3D VM (N=35) Task (5) x EP (2) x Task Side (2)
VM	F(1.73)=20.48**		
VM x Task	F(1.73)=9.12**		
VM x EP	F(1.73)=8.54**		
VM x Task x EP	F(1.73)=4.57**		
VM x Task x Task side	F(1.73)=4.32*		
Task	F(1.73)=6.90**	F(1,73)=2.69*	F(1,73)=12.51**
Task x EP	F(1.73)=2.95**		F(1,73)=5.81**
Task x Task Side	F(1.73)=4.72**		F(1,73)=6.89**
EP x Task Side	F(1.73)=4.08*		F(1,73)=4.78*
Task x EP X Task Side	F(1.73)=8.21**		F(1,73)=6.57**

[a]p-values 5 % (*) and 1 % (**). All repeated measures tests are Huynh-Feldt corrected.
EP = Electrode position

"A detailed overview of the mean ERD/ERS values, with standard deviation, is presented in Figure 8. For t-test post hoc comparisons a conservative significance level of 0.01 was used, since no correction was done for multiple comparisons for the two visualization modalities (2D and 3D), separately for the different task, task side (left and right motor imagery) and electrode position (C_3 and C_4). A difference between the visualization modalities can be seen in almost all tasks, depending on the electrode position and side of the movement. In total in 12 out of 20 tasks the end-user of the 3D visualization group showed an enhanced upper alpha ERD relative to 2D visualization modality group, with statistical significance (although not corrected for multiple comparisons) in nine tasks. The pattern of results suggests a generally higher ERD over the right (as compared to the left) sensorimotor region" (Sollfrank et al., 2015a).

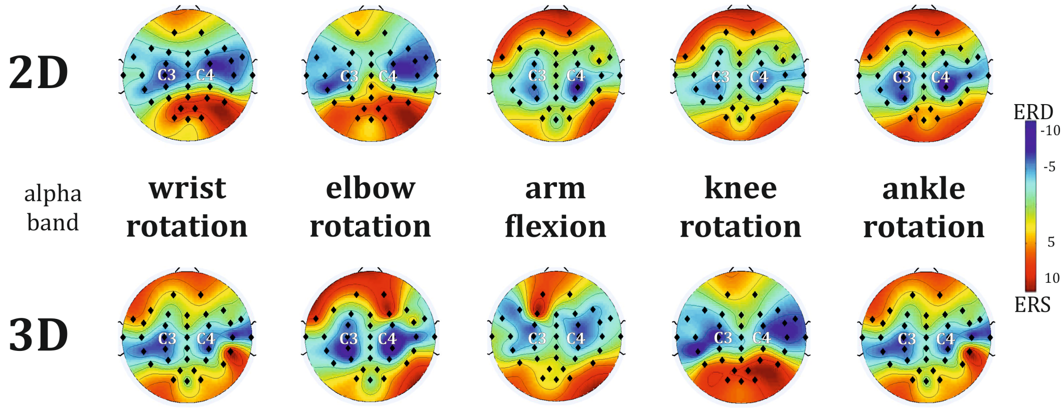

Figure 7: Topographical maps. ERD/ERS patterns averaged over all end-users for the five motor imagery tasks (averaged across left and right limb movements) for 2D and 3D visualization modality in the upper alpha frequency band (10-12 Hz). Note: ERD is indicated in blue and ERS is indicated in red. The black dots represent the electrode positions. Figure reproduced with permission from Sollfrank and colleagues (2015a), Copyright Frontiers Media SA. The publication is available online at http://www.ncbi.nlm.nih.gov.

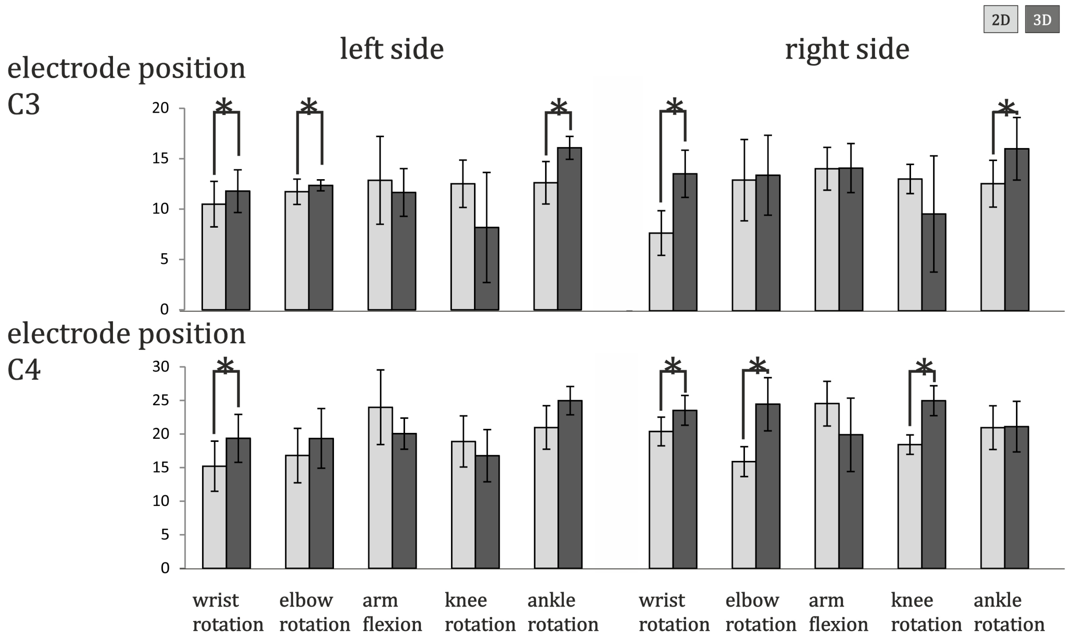

Figure 8: Mean ERD/ERS values. Mean ERD/ERS values and standard deviation obtained for the left (left panel) and right (right panel) limb motor imagery side of the 10-12 Hz upper alpha frequency band for all subjects with the two visualization conditions (2D, light grey bar; 3D, dark grey bar) on electrode position C_3 and C_4. Significant differences between the visualization modalities are indicated (p-value, * <.01). Figure reproduced with permission from Sollfrank and colleagues (2015a), Copyright Frontiers Media SA. The publication is available online at http://www.ncbi.nlm.nih.gov.

6.5 Discussion

“The present study was performed to investigate whether a three-dimensional visualization of upper and lower limb movements can amplify motor cortex activation during a subsequent motor imagery phase. Little is currently known about the impact of such a ‘realistic’ visualization modality. The mu rhythm in humans can characteristically be found over the sensorimotor area with peaks around 10–12 Hz (Kuhlman, 1978b; Hari et al., 1998; Pfurtscheller and Neuper, 2001). This frequency shows typical reactivity in association with motor imagery (Pfurtscheller et al., 1997; McFarland et al., 2000; Wolpaw et al., 2002; Blankertz et al., 2010). In the present study, discernable decrease of the mu rhythm (10-12 Hz) was detectable during imagery of limb movements over sensorimotor areas that significantly increased in the 3D visualization condition. The results showed in both VM conditions a more pronounced ERD for motor imagery of the upper limbs compared to the lower limbs. This could be explained with the fewer difficulties that the MI-based BCI naïve participants have in imagining hand and arm movements. In daily life, we pay more attention to our movements of the upper limbs than conscious movements with the foot or knees and could explain the effect on motor cortex activation during motor imagery.

The visualization of the different limb movements in a first person perspective was supposed to facilitate the task of performing motor imagery. One potential limitation of the realistic video presentation was due to the fact that computerized limb models were used. We tried to create them as realistic as possible with skin color, texture, and anatomical correct movement sequences. Especially for rehabilitation a computer-animated version can give the advantage to adapt the limb to each individual end-user. Although a lot of effort was contributed in video programming still a visible difference exists compared to a video of a real limb movement. We refrained from using videos of taped limb motion, as this would not be an option for impaired patients. Previous work has suggested an important role for the perception of the body within a three-dimensional environment (Slater et al., 1995). The body should be used naturally and should be anchored into the feedback for a successful ERD reproducibility. A possible explanation for this effect is the activation of the sensorimotor rhythm, which is in correspondence to the human mirror neuron system. This system matches action observation and execution and is capable of performing a simulation of just observed actions (Pineda, 2005; Neuper et al., 2009) and some researchers proposed a functional link between the observation of an action, the internal simulation, motor imagery and the execution of the motor action (Grezes and Decety, 2001; Neuper et al., 2005). The execution, imagination or observation of motor actions produces asynchronous firing in the mirror neurons and causes a suppression or desynchronization of the mu rhythm (Lopes da Silva, 2006). To exclude an overlaying effect of 'motion observation' on the ERD in the alpha band (Muthukumaraswamy et al., 2004; Hammon et al., 2006; Perry and Bentin, 2009) a short pause between the videos and the motor imagery phase was integrated, where the screen turned blank. How long the ERD of such a motion observation can last is not yet known. To be sure that the effects on the upper alpha band are only due to actual motor imagery, the motor imagery phase was expanded to 6 s. The current findings indicate that a three-dimensional realistic presentation of movements to support a subsequent motor imagery phase seems to be a suitable strategy to achieve locally restricted activation patterns for MI-based BCI use.

In a study by Friedmann and colleagues (2007), participants tried to control an MI-based BCI in a CAVE system and showed that navigation was possible. Participants reported afterward that they were more motivated in this kind of task compared to the training on a conventional visual monitor. They reported that the interaction seemed more natural to them than traditional BCI. Virtual reality (VR) and 3D non-VR visualization are powerful tools with significant possibilities to improve BCI-feedback presentation (Pineda et al., 2003; Pfurtscheller et al., 2006b; Ron-Angevin and Diaz-Estrella, 2008). With this technology immersive and motivating environments can be created, which can positively influence a successful training (Leeb et al., 2007b). A study by Gruzelier and colleagues published in 2010 could show that sensorimotor rhythm neurofeedback training in virtual reality could enhance the artistic performance of actors more successfully than training with a 2D feedback rendition. The efficacy of this training was attributed to the psychological engagement through the ecologically relevant learning context of the immersive VR technology.

The three-dimensional visualization enhanced ERD in the upper alpha band in some but not in all motor imagery tasks. Eleven tasks showed no significant differences in the mean ERD values however, a high variance in this data can be found. A study by Neuper and colleagues (2009) compared the effects of abstract and realistic feedback on MI-based BCI performance and could not find any significant differences between the two groups. One explanation for that was that feedback stimuli seem to become closely associated with the action goal during motor imagery and, therefore, both feedback types were able to enhance the desired electrophysiological signals for individuals to perform accurately. This could also be true for our experiment. Most of the present studies compared 'abstract' versus 'realistic' feedback (Neuper et al., 2009), presented activation maps during BCI training (Hwang et al., 2009) or game-like feedback in VR (Ron-Angevin and Diaz-Estrella, 2008; Scherer et al., 2008; Zhao et al., 2009). This study compared for the first time the actual effects of 2D and 3D visualization on motor imagery during the same limb motion tasks." (Sollfrank et al., 2015a).

6.6 Conclusion

"In future studies, the influence of these two visualization modalities have to be further investigated as it is possible that the effect can be increased in an online setting where the end-user imagined movements affect the animated limb in real time. Following the herein presented results, we can conclude that visualization modality plays an important role in a BCI controlled with motor imagery. Providing a realistic three-dimensional presentation of limb movements may help the end-user to get a concrete feeling of kinesthetic motor imagery and exerts significant effects on motor cortex activation" (Sollfrank et al., 2015a).

7 Study II - The effect of multimodal and enriched feedback on motor imagery (MI)-based BCI performance

The data presented in the following study have been published elsewhere (Sollfrank et al., 2015b). Several parts of this publication were adapted. Study 1 revealed that an enriched visualization supports end-users in a single offline training session to achieve characteristic event-related desynchronization patterns during motor imagery. Study 2 connects to these findings and investigates the elicitation of ERDs while controlling a motor imagery based BCI during several online training sessions with visually enriched and multimodal feedback.

7.1 Introduction

Feedback is a necessary feature for initial learning of the BCI skill (Brown, 1970; Kuhlman, 1978a; McFarland et al., 1998; Wolpaw et al., 1991, 2002). The end-user have to be properly trained to be able to successfully control their EEG signals, especially for the use of a BCI based on the recognition of mental imagery tasks (e.g., motor imagery, Neuper and Pfurtscheller, 2010). Unimodal visual feedback is usually provided in order for the subject to learn how to modulate mu band power. The end-user receives feedback by an extending bar or a moving cursor in one or two dimensions according to the classification results (Pfurtscheller, 2004; Neuper and Pfurtscheller, 2010; Schreuder et al., 2010). It provides no information about the quality of the mental imagery as it provides feedback only about which MI is classified at any one point in time. This presentation can be inaccurate because often the input signal contains a degree of uncertainty, which can make a precise classification difficult (van Beers et al., 2002; Hattie and Timperley, 2007; Shute, 2008).

The crucial step is to reliably extract the relevant information from EEG signals, although only a limited amount of data is available which includes various noises and a signal non-stationarity (McFarland and Wolpaw, 2011; van Erp et al., 2012) and to give meaningful and precise feedback (Hattie and Timperley, 2007; Shute, 2008). Uncertainty is not static and can vary substantially over time. Therefore, we created the visually enriched 'funnel feedback' to provide more information about the quality of the EEG signal: A liquid cursor model was implemented in a funnel shape that can provide the end-user with additional information about their input signal. The stability of the EEG was mirrored by the speed of the liquid cursor through the funnel. Being not in control of a BCI can make its use frustrating (Holz et al., 2015). Frustration has been experienced as problematic in BCI use (Curran and Stokes, 2003) and further Kleih and colleagues (2010, 2013) further demonstrated that learning an SMR-BCI task is facilitated by increased motivation. If the enriched funnel feedback allowed for better learning, frustration may be lowered and motivation increased.

Although the most common feedback is visual, there is evidence that training can be enhanced by providing multimodal feedback with the same granularity and specificity for each modality (Ainsworth, 2006). Kaufman and colleagues (2011) provided their BCI users with a cursor indicating the integrated classifier output, as well as the instantaneous sign and absolute value, coded as the color and intensity of the cursor. Results suggested that the end-user could handle a multi-dimensional feedback although no significant increase in performance was found. Auditory feedback provides an alternative to a visually based BCI system (McCreadie et al., 2012; Simon et al., 2014), specifically for those potential end-user with impaired vision. Nijboer and colleagues (2008a) found that although the initial BCI performance in the visual feedback group was superior to the auditory feedback group, there was no significant difference in performance at the end of training. A study by Schreuder and colleagues published in 2010 illustrated that the combination of audio and visual feedback did not lead to an enhancement in BCI performance, whereas Gargiulo and colleagues (2012) concluded that multimodal feedback could increase performance in some naïve subjects and could relieve the sense of frustration that came from the feeling of not being in control of the visual cue. Thus, studies provided mixed results and further investigation are warranted to elucidate the effect of multimodal feedback on SMR-BCI performance.

7.2 Study aims

The goal of this study was to investigate the effects of a visually enriched and multimodal feedback on performance and user satisfaction during MI-based BCI control in a between-subject design. This study should clarify, if end-user can learn to control a motor imagery based BCI in several operant conditioning training sessions with online feedback. It should investigate if an informative visual feedback can facilitate the learning process in MI-based BCIs. Furthermore, the study includes the comparison of unimodal (visual) and multimodal (visual and auditory) feedback and attempts to identify the effects on BCI performance and user satisfaction.

Although a number of end-users are not able to control a BCI (Kübler et al., 2011) it is expected that around 70 % can learn to control the BCI across five training sessions, but differential effects of the feedback types were expected. The visually enriched feedback, which contains information about the quality of the input signal, is expected to facilitate the learning process and enhance end-user performance as compared to the conventional cursor bar feedback. The presentation of uncertainty information should render end-users confident toward the functionality of the MI-based BCI, especially during the training phase, where the subject tends to explore different mental strategies to determine the optimal one for achieving control (Lotte et al., 2013). The combination of auditory and visual feedback is expected to motivate end-users while controlling the BCI and, therefore, enhance the satisfaction with the BCI system.

7.3 Methods

7.3.1 Participants

“Thirty healthy MI-based BCI novices took part in the study which was approved by the Ethical Review Board of the Medical Faculty, University of Tübingen. Each participant was informed about the purpose of the study and signed informed consent prior to participation. None of the participants was excluded from analysis. Of the 30 participants 20 were women, and mean age of the sample was 27.73 years (SD 6.57, range 19–51); six were left-handed" (Sollfrank et al., 2015b).

7.3.2 Experimental set-up

"The participants were seated in a comfortable chair approximately 1 m away from the computer screen. Participants were asked to sit relaxed with eyes open and to avoid any eye and body movements. After the specific task instruction, all participants underwent a screening session (0.5 h). During this period, end-users were instructed to perform kinesthetic imagery (Neuper et al., 2005) of a movement with their right or left hand, with their arms relaxed. They had to perform three runs with individual breaks in between. Every run consisted of 30 trials with 15 trials per class (left vs. right) presented in random order. The trial started with the presentation of a fixation cross (2 s). Afterwards, one of the two visual cues (arrows pointing left and right) indicated to the participant which type of motor imagery task to perform (2 s, Fig 9). The period of movement imagery lasted for four seconds and the end-users could control a cursor bar to the left and to the right side until the screen turned blank. After a two-second pause the next trial started.

After the screening session, following a between-subject design, participants were randomly assigned to three feedback groups with ten subjects each. Multimodal funnel feedback: six female, aged between 23-51, mean age 30.2 ±7.8 SD; unimodal funnel feedback: six female, aged between 19-46, mean age 27.1 ±7.5 SD; conventional cursor bar feedback: eight female, aged between 23-38, mean age 25.9 ±4.4 SD. They then performed the first training session, consisting of six runs with 20 trials each. The timing was the same in all feedback groups (Fig 9): Each started with the presentation of a fixation cross at the center of the monitor. For two seconds, a visual cue indicated to the participants which type of motor imagery task to perform (left or right hand). The duration of online feedback depended on the end-user's ability to control the BCI. It terminated when the decision threshold (classification values: left/right, cursor hit one of the corners of the lower part of the funnel visualization) was reached or by timeout after 15 s.

During the last two seconds of the trial, the screen was blank. There were breaks of 5-10 min between the runs, depending on the participants' individual needs. The subsequent four training sessions were performed on different days over a period of two to three weeks. No classifier adaptation or retraining occurred at any time" (Sollfrank et al., 2015b).

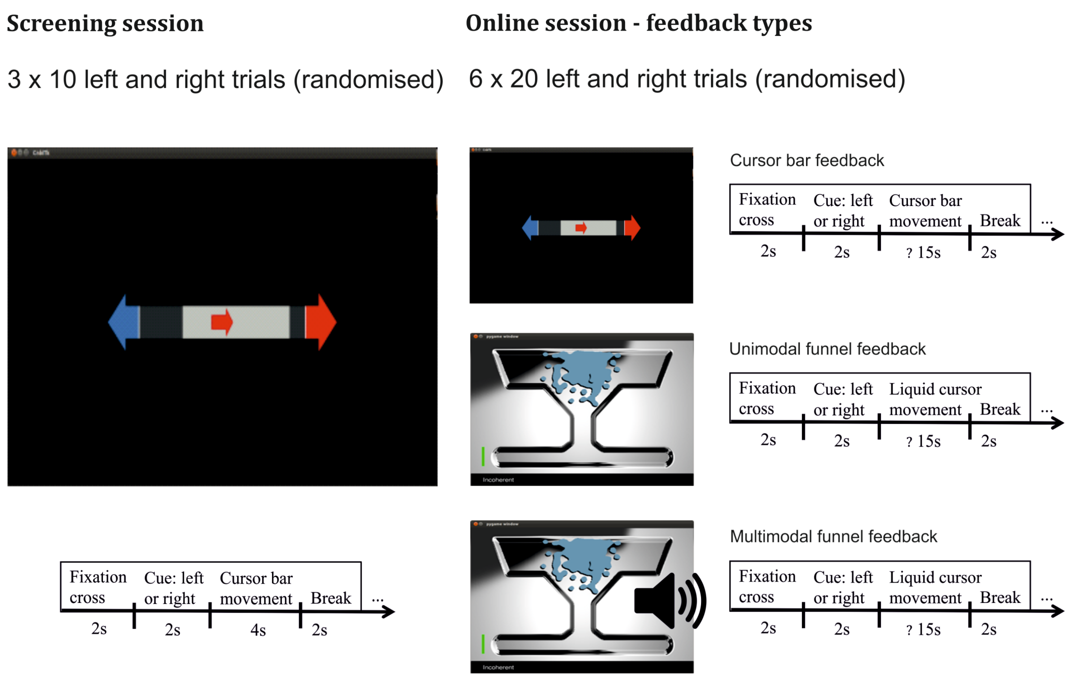

Figure 9: Experimental design. Timing of the paradigm used in the screening session and in the online session with the three different feedback types: cursor bar feedback, visual unimodal funnel feedback and multimodal funnel feedback. Figure reproduced with permission from Sollfrank and colleagues (2015b), Copyright Elsevier E.V. The publication is available online at http://www.sciencedirect.com/.

7.3.3 Feedback modalities

- "**Cursor bar (CB) feedback:** Visual feedback was provided by a cursor bar that moved to the left and right according to the classification values along a horizontal line between two arrows (Fig 10 upper left). It provided feedback about which MI was classified at any one point in time (further details on classification in section 7.3.5).

- **Visual unimodal funnel (UF) feedback:** Visualization of a liquid cursor moving in a funnel shape connected to a 'test tube' at the bottom (Fig 10 right). The BCI provided two types of information: an estimate of how stable the end-user's control was and a left/right MI classification value. The respective quality of the EEG was visualized as the dispersion of the cursor. The liquid cursor began in an amorphous, diffuse state (Fig 10, mode of control: incoherent) and remained like this until the stability estimate of the end-user's EEG signal increased. With larger steadiness in the input signal, the liquid condensed and altered into a transitional mode while it moved to the lower region (mode of control: transitional). The cursor could shift between the two modes of control according to the classification values. When the liquid cursor reached the 'test tube', it remained in a stabilized mode and could not return to one of the previous states, independent of the signal quality, to avoid any negative feedback (mode of control: stabilized). As the input signals became more accurate to discriminate between the two (left and right hand motor imagery) classification values, the end-user could control the liquid cursor to the left and to the right (mode of control: controlled).

- **Multimodal funnel (MF) feedback:** In addition to the described visual feedback participants were provided simultaneously with auditory feedback: The 'incoherent' to 'transitional' visual state was acoustically discernible by bubble sounds (Fig 10). Metal sounds were presented while the liquid cursor was in a 'stabilized' mode and the movement of the liquid cursor to the left and to the right was supported by the sound of clinking glasses. No sounds were played when moving from 'transitional' to 'incoherent' or from 'controlled' to 'stabilized' " (Sollfrank et al., 2015b).

7.3.4 Data acquisition

"The EEG was recorded from 16 channels located over the sensorimotor cortex (F_z, FC_3, FC_1, FC_z, FC_2, FC_4, C_3, C_1, C_z, C_2, C_4, CP_3, CP_1, CP_z, CP_2, CP_4). The locations of the Ag/AgCl electrodes were based on the modified 10-20 system of the American Electroencephalographic Society (Sharbrough et al., 1991). Each channel was referenced to the left and grounded at the right mastoid. Impedances were kept below 5kΩ. The EEG was recorded using a g.USBamp amplifier (manufactured by g.tec Medical Engineering GmbH, Austria), notch filtered at 50 Hz and sampled at 512 Hz. Data processing, storage, and online display were performed on a conventional laptop with an additional external monitor" (Sollfrank et al., 2015b).

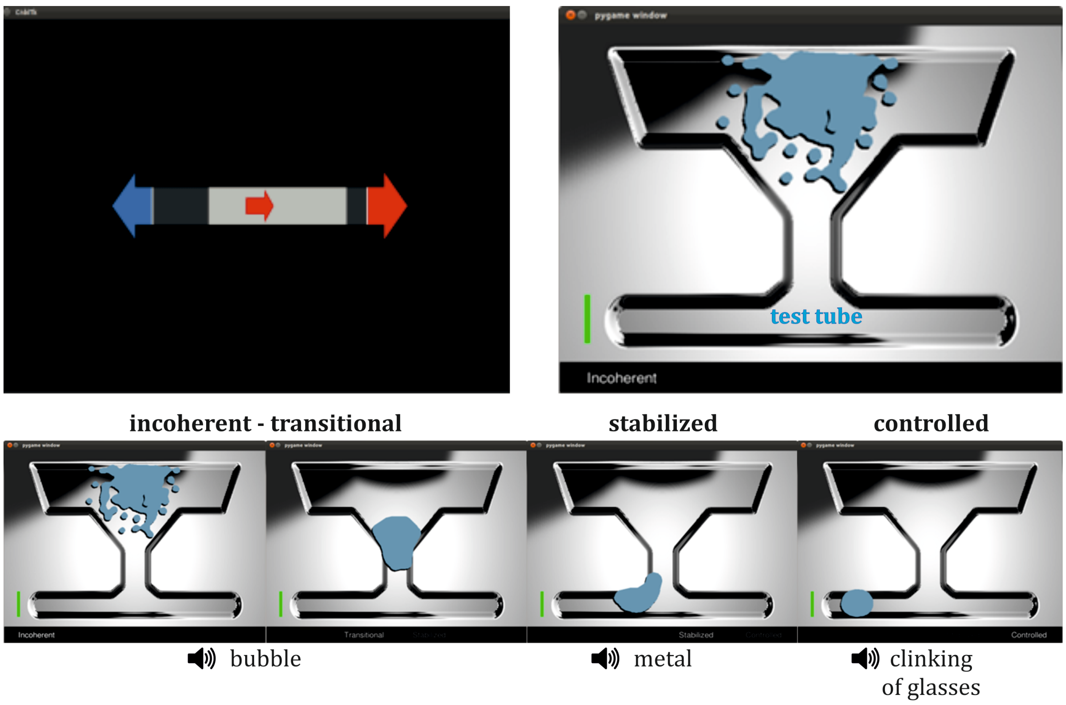

Figure 10: Visual feedback. Top left: conventional cursor bar feedback, top right, and bottom: visualization of the funnel feedback and the feedback sequence of the unimodal and multimodal funnel display. Multimodality: Each of the three different modes of control corresponded to specific sounds. Auditory feedback was provided simultaneously to changes in the visual display. Figure reproduced with permission from Sollfrank and colleagues (2015b), Copyright Elsevier E.V. The publication is available online at http://www.sciencedirect.com/.

7.3.5 Feature extraction, selection and classification

"After the screening session, power spectral density (PSD) features were computed in 1-second sliding windows (Polat and Güneß, 2007; Leeb et al., 2013). EEG signals were first spatially filtered with a local Laplacian derivation and the PSD was estimated within 4–48 Hz with 2 Hz resolutions, accounting for 23 frequency bands per channel. The PSD was computed every 62.5 ms using the Welch method (five 25 %–overlapping internal Hanning windows of 500 ms) and was log-transformed to better comply with the normality assumption of the classification method subsequently employed. The overall candidate feature vectors were thus 368 (16x23) band power estimated on combinations of channels and frequency bands. For the classification of left versus right hand motor imagery trials Fisher's linear discriminant analysis (LDA) was applied. Three to six features were identified as optimal using the Canonical Discriminant Spatial Patterns (CDSP) method, which best discriminated between the two classification values (left versus right hand) within the motor imagery period (Leeb et al., 2013). A classifier was then built for each pair of MI tasks, with the selected MI pair (highest controllability), and the corresponding EEG channels and PSD features identified by the feature selection process, which were used online to control the BCI. In the online feedback sessions, the BCI used the individual classifier of each participant to translate the end-users' EEG over the sensorimotor area during motor imagery into a continuous output on the computer screen.

For the cursor bar feedback, the LDA classified a single sample (decision = +-1) and then the bar moved from its current position x, as x = x + decision*dx. dx was adjusted per subject obtaining a movement to the threshold in 0.5-2 s, depending on individual performance.

In the visual unimodal and multimodal funnel feedback, uncertainty in the input signal was displayed by the combination of two visualizations: the liquid cursor that could be moved and deformed by pseudo-physical forces, that was basically a Monte Carlo visualization, where 60 particles represented the state of the classifiers input: Each particle had a Gaussian density field around it. The physics were defined by attractive and repulsive fields around each particle, which had an inverse-square-exponential falloff such that there was an equilibrium point at a set inter-particle spacing. As the strength of the forces increased, the points coalesced into a single blob and eventually into a fairly solid object. The implementation used an Euler integrator to provide the physics functionality. The second visualization of uncertainty in the end-users input signal was the movement speed of the liquid cursor along the vertical axis in the funnel shape to the 'test tube'. The uncertainty index was computed by calculating the Euclidian distance of the sample from the global mean. The dispersion was a complex nonlinear and time-varying function of the distance; but the cohesive force in the liquid varied monotonically with d_c(x): The classifier assumed a Gaussian distribution N(μ_c, M_c) for each prototype of the class c and then, a feature vector x was assigned to the class that corresponded to the nearest prototype, according to the so-called Mahalanobis distance dc(x) (Lotte et al., 2007).

$$d_c(x) = \sqrt{(x-\mu_c)M_c^{-1}(x-\ \mu_c)^T} \qquad (1)$$

The user interface and the interface to the incoming BCI signal were written as a Python module, using TOBI interfaces C and D, which were established during the TOBI project (EU grant FP7-224631, Tools for Brain-Computer Interaction, http://www.tobi-project.org/)" (Sollfrank et al., 20015b).

7.3.6 BCI performance

"Accuracy was calculated as the ratio between the number of correct selections and the total number of selections. The maximum duration of each motor imagery period was up to 15 s. If the target side was not reached within this time window, the trial was terminated and separately counted as a 'time out' (miss). To decide whether the performance was above chance level, indicating that the cursor control and classification rates exceeded chance level and reached statistical significance, the number of trials has to be taken into account. Kübler and Birbaumer (2008) stated that for the two-choice MI-based BCI the observed frequencies (of hits (cursor into the correct target) and misses) have to be compared to the expected frequencies given chance performance and can be tested for significance as follows:

With

$$x^2 = \sum \frac{(f_0 - f_e)^2}{f_e} \tag{2}$$

more than 75 trials (f_0, observed frequency; 63 % correct trials in one session) have to be hits to get performance above chance level with f_e as the expected frequency of 60 hits in 120 trials and a x^2 value with a probability of 0.05 (df=1)" (Sollfrank et al., 2015b).

7.3.7 ERD/ERS analyses

"EEG signals were visually inspected and trials contaminated with muscle or eye movement activity were removed. The ERD/ER was quantified in the artifact-free EEG in the following steps: The ERD/ERS was expressed as percentage powers decrease (ERD) or powers increase (ERS) and were quantified relative to the baseline (in relation to a 1 s reference interval before the imagery period) for the upper alpha frequency band (10-12 Hz) and beta (13–25 Hz). The ERD/ERS values of the imagery period were calculated by the squared value of the raw EEG over a 250 ms non-overlapping interval across 8 s of each tasks. The natural log ratio of the EEG power value and the baseline power was estimated for all sample points and the ERD was represented as the mean of these. For statistical comparison a 3x5 repeated measures ANOVA was computed, with the ERD values of the imagery period as dependent variable and sessions (5) as within and feedback type (3) as between subjects factors" (Sollfrank et al., 2015b).

7.3.8 Questionnaires

"After the last training session, subjects were asked to rate five questions by assigning a score between one and ten (1 = not at all, not very likely and 10 = a lot, very much likely). Questions were related to the subjective feeling of the subject during and after the experiment (see Table 3). There was no time constraint for answering the questions, and the questionnaire was completed immediately following the experiment while the subject was still in the lab. A one-way analysis of variance was conducted to evaluate significant differences in the ratings of the different feedback groups. Tuckey HSD was used for post hoc pairwise comparisons" (Sollfrank et al., 2015b).

7.4 Results

7.4.1 Performance

"Feedback accuracy varied largely between participants (mean 62.29 % ± 16.1 %), covering the full range from chance-level performance (63 %) to perfect control (100 %). For most participants, performance varied strongly between sessions. More specifically, the intra-participant performance variability between the five training sessions ranged from 3.5 % to 21.3 % (mean 6.2 % ± 4.4 %, Fig 11). Above-chance level performance (>63 % hits) was reached by the end-users in 21 training sessions (42 %) in the MF group, in 17 sessions (34 %) of the UF group and in 15 sessions (30 %) of the CB group (Table 2).

One-way ANOVA for the classification results of the screening session did not reveal any significant main effect, indicating that the performance was similar in all three groups. Mean MI-based BCI performance as a function of feedback in the online training sessions is summarized in Table 2. For the online classification in the feedback sessions, a classifier, built on a distinctive data set was applied. The 3x5 repeated measures ANOVA with feedback and number of sessions as independent variables yielded a significant main effect of Session ($F_{4,236}$=3,00; p=.019) and a significant session x feedback interaction ($F_{8,472}$=2,11; p=.034). Post hoc comparisons revealed weakest performance for all feedback groups in session 2 (Tuckey HSD test, p=.005) as compared to the initial training session. The cursor bar (CB) feedback group revealed the lowest level of performance during the first session (58.40 ± 16.05 SD) but could afterwards continuously increase the level with significantly best results during session 4 compared to the initial session (64.64, SD ± 15.03; p=.037). In session 1 the funnel feedback groups, both unimodal (66.25 ± 18.47 SD) and multimodal (66.40 ± 20.02 SD) could achieve a significantly better performance as compared to the cursor bar feedback group (MF*CB, $t_{(118)}$=-2,96; p=.004; UF*CB, $t_{(118)}$=2,53; p=.013). This effect vanished during the following training sessions (Fig 12). A significant higher occurrence of 'time outs' was present in the funnel feedback group across all training sessions (Table 2, $F_{3,255}$= 1,89; p=.012)" (Sollfrank et al., 2015b).

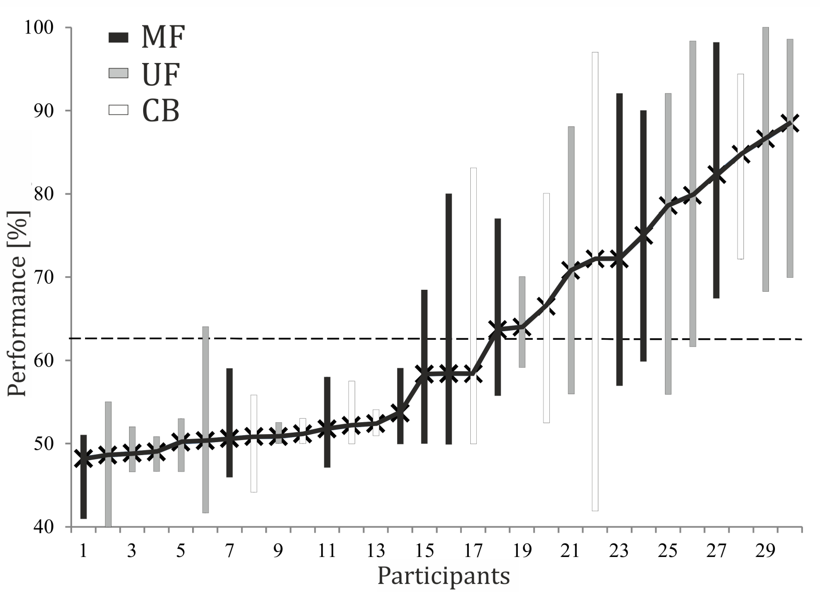

Figure 11: Feedback performance. The black crosses show the feedback performance averaged across all recorded sessions for each end-user. Vertical lines indicate performance range for every end-user and the horizontal line indicates above chance level performance). End-users were re-ordered by increasing performance. Figure reproduced with permission from Sollfrank and colleagues (2015b), Copyright Elsevier E.V. The publication is available online at http://www.sciencedirect.com/.

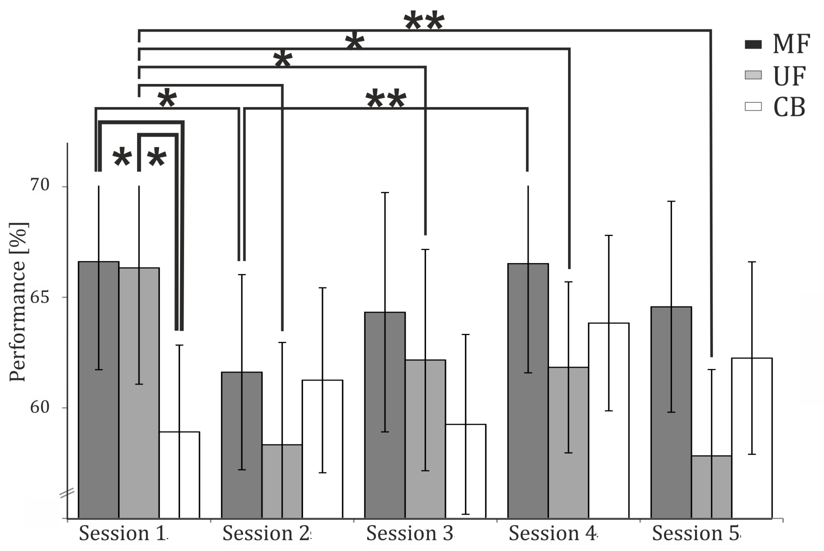

Figure 12: Mean performance. Mean performance values and SE obtained for the three feedback groups during five training sessions. Significant differences between sessions are indicated: p –values 5 % (*) and 1 % (**) level. Figure reproduced with permission from Sollfrank and colleagues (2015b), Copyright Elsevier E.V. The publication is available online at http://www.sciencedirect.com/.

"The grand average time-frequency representations (0-30 Hz) of significant ERD/ERS values at electrode position C_z for all five training sessions for the two tasks (right and left hand motor imagery together) are shown in Figure 13. The differentiation of the frequencies between ERD and ERS revealed a mean frequency of the desynchronized components of 10.1 Hz ± 1.0 (CB), 10.2 Hz ± 1.0 (UF) and 10.2 Hz ± 1.1 (MF) and a corresponding frequency of the synchronized components of 12.5 Hz ± 1.4 (CB), 12.4 Hz ± 1.4 (UF) and 12.5 Hz ± 1.2 (MF). This difference was significant for all feedback groups for the alpha band (t(149)=-16,23, p=0), but not for the beta band (13–25 Hz; $t_{(149)}$=-1,69, p=.108), that is why the beta band was excluded from further analysis. In order to analyze the potential influence of the feedback on the ERD/ERS patterns during task performance in the different sessions, a 3 (feedback) x 5 (session) repeated measures ANOVA was performed. The feedback x session interaction and the main effect of feedback were not significant. The main effect of session was significant ($F_{4,36}$=3,35; p=.023) with higher ERD values in session 1 compared to session 2 ($t_{(29)}$=2,75; p=.010) and session 4 ($t_{(29)}$=3,96; p=0) for all feedback groups" (Sollfrank et al., 2015b).

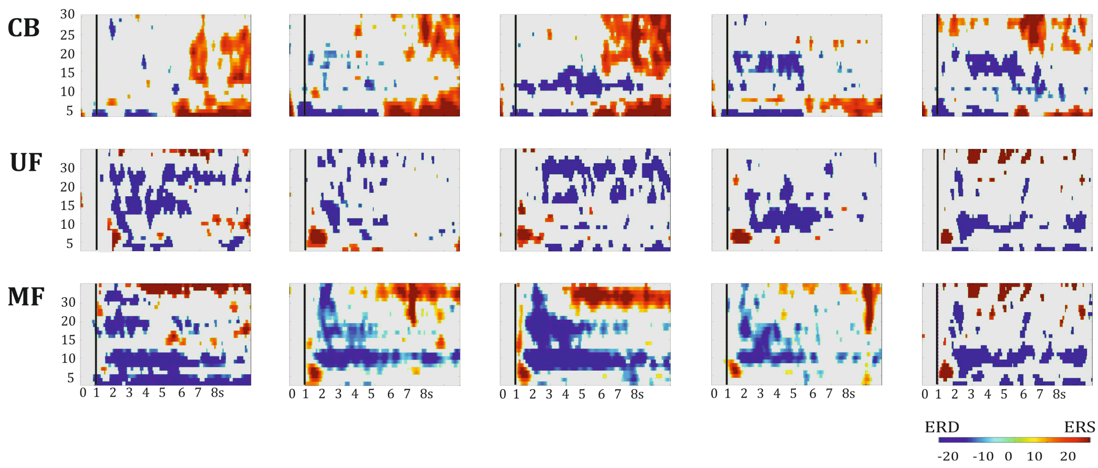

Figure 13: Grand average time-frequency maps. Representation of significant ERD values (marked in blue, p<0.01) at electrode position C_z pooled for the left and right hand motor imagery periods, for all five training sessions, separately for the three feedback groups. The maps are plotted for the mean duration of a whole trial (0-8 s; x-axis) and for the frequency range of 0-30 Hz (y-axis). A vertical line indicates the cue onset level. Figure reproduced with permission from Sollfrank and colleagues (2015b), Copyright Elsevier E.V. The publication is available online at http://www.sciencedirect.com/.

7.4.2 Questionnaire and end-user satisfaction

"Quantitative analyses of the questionnaire are shown in Table 3. Post hoc comparisons to evaluate pairwise differences among group means were conducted with the use of Tuckey HSD test since equal variances were tenable. The visualization of the funnel feedback was rated as more helpful than the CB feedback (MF*CB feedback group, p=.002 and UF*CB p=.006). The MF group reported less frustration (MF*CB feedback group, p=.009) and was afterwards more motivated (MF*CB feedback group, p=.033) as compared to the CB group" (Sollfrank et al., 2015b).

Table 2: Mean performance. Mean values of accuracies (%) of participants of the three different feedback groups for the offline screening session and across the five training sessions level. Figure reproduced with permission from Sollfrank and colleagues (2015b), Copyright Elsevier E.V. The publication is available online at http://www.sciencedirect.com/.

Type of feedback	CB	UF	MF
N	10	10	10
Mean screening performance[a] ±SD	55.05 ±13.43	55.33 ±17.23	57.55 ±15.22
Mean online performance[a] ±SD	61.04 ±16.53	61.36 ±15.85	64.84 ±17.02
Range online performance	40.00 – 97.00	41.67 – 99.17	44.17 – 98.33
Time out trials[b]	16 %	27 %	25 %
***Above chance level* performance[c]**	30 %	34 %	42 %

[a] percentage of correct responses,
[b] percentage of 'time out' trials,
[c] percentage of sessions, where performance was *above chance level.*

Table 3: Average ratings per question. Every question could be rated between one and ten (1= not at all, not very likely and 10= a lot, very much likely). Standard deviations are noted in brackets. Quantitative analysis shows that the one-way ANOVA was significant for Question 2 ($F_{(2,17.9)}$=8,756, p=.001**), Question 4 ($F_{(2,17.1)}$=5,33, p=.011**) and Question 5 ($F_{(2,15.9)}$ =3,649, p=.040*), level. Table reproduced with permission from Sollfrank and colleagues (2015b), Copyright Elsevier E.V. The publication is available online at http://www.sciencedirect.com/.

	Question	CB	UF	MF
1.	Did you find the task difficult?	7.71 (±1.29)	7.11 (±1.21)	6.23 (±1.42)
2.	Did you find the visualization helpful?	5.33 (±1.41)	7.56 (±1.37	7.87 (±1.64) **
3.	Did you find the sound helpful?			6.34 (±1.14)
4.	Did you feel frustration during the experiment?	8.34 (±1.50)	6.45 (±1.92)	5.23 (±2.81) **
5.	How motivated are you to be test end-user for this kind of experiment again?	5.34 (±1.56)	6.55 (±2.05)	7.21 (±1.71) *

p-values 5% (*) and 1% (**) level.

7.5 Discussion

"We investigated the MI-based BCI performance as a function of feedback type. The performance was measured as the percentage of correct responses during motor imagery tasks. Averaged for all feedback groups 56 % of the end-user performed at least one session above chance level with more than 63 % correct responses and could, thus, achieve significant control over the required brain response.

During the initial training session, significant better performance was measurable in the MF and UF groups as compared to the conventional CB group. It seems that the enriched unimodal and multimodal online feedback, with information about the quality of the input signal, supports an easier approach for BCI control. The two modalities of auditory and visual feedback seemed to be not as important as the enriched information of the feedback, as there was no significant difference in performance of the two funnel feedback groups. This is in accordance with Schreuder and colleagues (2010) who also found no effect of multimodal (auditory and visual) feedback on performance with a BCI using slow cortical potentials as input signal. An efficient feedback should not be too complex, and should be provided in manageable pieces (Lotte et al., 2013). It may be that the visual feedback was too dominant such that the simultaneous auditory feedback did not provide any beneficial information. However, in line with results of Gargiulo and colleagues (2012) we could show that multimodal feedback can reduce frustration and enhance motivation, making the use of a BCI more enjoyable. Learning to control a BCI is a complex task and psychological factors like motivation and frustration may play an important role (Nijboer et al., 2010; Kleih et al., 2010; Kleih and Kübler, 2013). Such psychological factors could be influenced by the choice of feedback presentation. An engaging, stimulus-rich feedback (Pineda et al., 2003; Pfurtscheller et al., 2006b, 2007) might, in turn, increase the success in controlling a BCI application. A study by Gruzelier and colleagues published in 2010 showed that neurofeedback training in virtual reality (VR) enhanced the artistic performance of actors more successful than training with a 2D feedback rendition. The efficacy of this training was attributed to the psychological engagement through the ecologically relevant learning context of the immersive VR technology. The liquid cursor in combination with sounds was judged more helpful and descriptive than the conventional CB feedback and the motivation for participating again in another BCI experiment was higher for the MF group than for the CB group. However, on the physiological level the ERD analyses revealed no significant difference between the ERD in the alpha band of sensorimotor areas between the three feedback groups. Significantly highest values of performance and ERD were present only in the first session in all feedback groups and along with training, performance and ERD values of the feedback groups converged. Thus, we may cautiously conclude that the funnel feedback may support the initial training phase and represents an alternative feedback for BCI-controlled by motor imagery.

Another explanation for the significantly better performance during the initial training session could be due to the fact that no online adaptation was included. Classification accuracy is certainly affected by inter-session non-stationarity of brain patterns and the uncertainty metric used for the funnel might be even more affected by this issue. This may explain the drop of performance in subsequent sessions of the funnel feedback group, which did not occur in the conventional cursor bar group.

In each group were end-users who did not achieve any significant cursor control. This phenomenon is known as BCI inefficiency (Kübler and Müller, 2007; Vidaurre and Blankertz, 2010; Hammer et al., 2012), and it seems to be present in 10-30 % of potential BCI end-users (Guger et al., 2003; Blankertz et al., 2010). Approaches to alleviate this phenomenon have been explored, such as improved signal processing (Blankertz and Vidaurre, 2010). Blankertz and colleagues (2007) demonstrated that participants, who had no peak of the sensorimotor idle rhythm at the beginning of the experiment, could develop such peak during the course of the session with an end-user-optimized state-of-the-art classifier. They developed the BBCI – a machine learning BCI approach – which provides BCI control during the first session after 20 min screening period. A statistical analysis of the screening measurement is used to adapt the system to the specificities of the end-user`s current brain signals. Kindermans at al. (2010) could show that a combination of Reservoir Computing and a feature selection algorithm based on Common Spatial Patterns can be used to improve performance in an non-cued motor imagery based BCI. They enhanced the discrimination of the motor imagery classes that made the system more robust against potential changes in the environment. Besides online, or even offline adaptation in the classifier, other factors like training, new task instructions and feedback (Pfurtscheller et al., 2006b, 2007; Allison and Neuper, 2010) can also play an important role in learning to control a BCI. We decided to train end-user with a non-adaptive classifier to focus on the potential effect of an enriched feedback and to be able to exclude any other factors besides the type of feedback.

A rather unexpected result was that there was no improvement of classification accuracy with training and overall performance in all groups was surprisingly low. Contrarily, all four patients with amyotrophic lateral sclerosis of a study by Kübler and colleagues published in 2005 were able to achieve regulation of their sensorimotor rhythm of more than 75 % accuracy within less than 20 training sessions. The performance was around chance level during the first ten sessions but increased significantly during the last ten sessions. A study by Nijboer and colleagues (2008a) also showed that healthy participants were able to control an MI-based BCI with solely auditory feedback. Although BCI performance in the visual feedback group was superior to the auditory feedback group there was no difference in performance at the end of the third training session. Participants in the auditory feedback group learned slower, but four of eight end-users reached an accuracy of more than 70% correct responses in the last session which was comparable to the visual feedback group. Both studies have in common that the participants had to perform a high number of trials: In the study of Nijboer and colleagues (2008b) around 2070 trials were conducted in three sessions, and Kübler and colleagues (2005) included a minimum of 3200 to even 10500 trials in 20 sessions, depending on the physical and psychological condition of the patient. For end-user with low control the duration of a trial was maybe too long. In some trials the liquid cursor remained in the center of the test tube and it was not possible or too exhausting for the end-user to maintain motor imagery over the 15 s before the 'time out' occurred. A higher number of 'time outs' were found in the funnel feedback groups compared to the CB group and every 'time out' was rated as a miss, even though the tendency of the cursor was toward the correct target. On average, the experiment for the funnel feedback took 2.2h, whereas the same number of trials in the CB feedback training was often faster. This may have had a negative impact on the accuracy results of the funnel feedback groups" (Sollfrank et al., 2015b).

7.6 Conclusions

"Taken together, healthy participants were able to control a BCI when presented with multimodal funnel feedback including information about uncertainty. The enriched visual feedback in combination with auditory feedback leads to a significantly better performance in the initial training session. Such feedback may boost initial performance, but beneficial effects were not maintained. Studies possibly with more training sessions are required to replicate this finding and to elucidate the long-term effect. Independent of performance, multimodal funnel feedback was rated more helpful, more motivating, and less frustrating than the unimodal and cursor bar feedback. Especially in the operant conditioning approach feedback plays an important role in learning to control a BCI. The herein presented results can partly support our hypothesis and contribute to the idea that an enriched feedback can support end-users in learning to control an MI-based BCI. Thus, the multimodal funnel feedback represents an alternative approach for training end-users to modulate their SMR and may be advantageous for training adherence. It can facilitate the initial training phase and render end-users confident toward the functionality of the BCI controlled by motor imagery. Combined with adaptive classification and feature selection approaches, more distinct differences might arise between feedback types" (Sollfrank et al., 2015b).

8 Study III – Alpha neurofeedback training in patients with schizophrenia

Study 1 and 2 could show that healthy participants were able to get in control of their alpha rhythm over the sensorimotor cortex to control a BCI. It revealed that feedback can play an important role by supporting the end-user with various information but has to be distinct to not distract from the actual task. Study 3 builds upon these results and attempts to bring the BCI to the end-user – the patient. This study is investigating if patients with schizophrenia can learn to control their alpha rhythm in several online training sessions in a clinical setting.

8.1 Introduction

Alpha oscillations are of special interest because they are largely associated with attentional, cognitive and verbal memory processes (Lecomte and Juhel, 2011). The magnitude of activation, meaning the amount of alpha suppression, is an index of cortical activation and Alexander and colleagues (2006) could demonstrate that patients with cognitive impairments show a decreased activation compared to healthy able-bodied participants. Several studies suggest that a large alpha resting power can be a predictor of good cognitive performance (Doppelmayr et al., 2002; Hanslmayr et al., 2005; Zoefel et al., 2011; Klimesch, 2012; Wan et al., 2014). Alpha band neurofeedback (NF) training has successfully been used to enhance attention and memory performance in healthy younger subjects (Vernon et al., 2003; Angelakis et al., 2007; Escolano et al., 2011; Zoefel et al., 2011; Nan et al., 2012a,b; Dekker et al., 2014; Gruzelier, 2014) and in elderly subject groups (Angelakis et al., 2007; Gruzelier, 2014). Those subjects who were able to enhance their alpha power during training performed better in attention, short-term memory and working memory tasks. The better subjects were able to increase their alpha power the larger was the improvement in cognitive performance after NF training (Hanslmayr et al., 2005). NF has mainly been used as a therapeutic tool to treat different types of disorders such as attention deficit hyperactivity disorder

(Butnik, 2005; Strehl et al., 2006; Friel, 2007; Arns et al., 2009; Escolano et al., 2014), addictive disorder (Trudeau, 2000; Sokhadze et al., 2008), autistic spectrum disorder (Coben et al., 2010) and epilepsy (Rockstroh et al., 1993; Kotchoubey et al., 1999; Walker and Kozlowski, 2005; Sterman and Egner, 2006).

Worldwide around 21 million people suffer from schizophrenia (World Health Organization, 2015). This disease comprises a wide spectrum of symptoms such as delusions, hallucination, depression or avolition (Kay et al., 1987). It is a chronic and devastating brain disorder and even after pharmacological treatment, not all symptoms disappear and can still negatively influence the patient`s social and occupational lives (Ritsner et al., 2003; Harvey and Strassing, 2012; Keefe and Harvey, 2012). Besides these core symptoms, 73 % of the patients` further experience cognitive deficits (Palmer et al., 1997) such as reduced attention, working memory, verbal learning and short-term memory performance (Gold and Harvey, 1993; Heinrichs and Zakzanis, 1998; Lesh et al., 2010; Fioravanti et al., 2012; Keefe and Harvey, 2012). These deficits are relatively stable over time and independent of the symptomatic manifestations of the illness (Gold, 2004). Oscillatory abnormalities in the EEG of these patients seem to play an important role in this dysfunctional information processing (Haenschel et al., 2009; Uhlhaas and Singer, 2010, 2015; Phillips and Uhlhaas, 2015). Abnormalities in the oscillatory activity of patients with schizophrenia include less well-organized alpha activity as compared to healthy subjects (Itil, 1977), a reduced event-related alpha desynchronization (Higashima et al., 2007; Ikezawa et al., 2011; Popov et al., 2012; Ilana and Gomez-Ramirez, 2014) and a reduced frontal EEG alpha power (Boutros et al., 2008; Koh et al., 2011; Popov et al., 2011b).

Neurofeedback is an operant conditioning procedure in which individuals learn to regulate their brain activity, i.e., to increase or decrease the power of one or two specific frequency bands (Lubar, 1997) or the amplitude of specific potentials measured with EEG. Electrodes are placed on the scalp at locations linked to the specific EEG activity. Cognitive remediation in patients with schizophrenia is an increasingly prominent goal of rehabilitation programs (Popov et al., 2011a) and different therapeutic approaches may be needed to address the different aspects of the illness (Gold, 2004). A daily alpha neurofeedback training that focuses on the increase of alpha resting power to improve cognitive performance could be effective, inexpensive and easy to handle for the patients and for the clinical staff (Weber et al., 2011). Alpha neurofeedback training can consist of tasks to either enhance, suppress or both enhance and suppress the individual's mean level of alpha amplitude (Cho et al. 2008). Whereas most studies learn to consciously enhance alpha (Hanslmayr et al., 2005; Zoefel et al., 2011; Lopez-Larraz et al., 2012), it has been suggested that incorporating both the suppression and enhancement into the training procedure is more beneficial for learning overall control (Plotkin, 1976). The alternation between alpha enhancement and suppression enables participants to gain an understanding of how each direction feels, which facilitates the learning process of having a conscious control over their alpha activation.

To date, little is known about the effects of such an alpha NF training in patients with schizophrenia. Nan and colleagues (2012a) published data of a single patient with schizophrenia who could learn to increase individual alpha power in four sessions and simultaneously enhance short-term memory. This single case study gives an example of a successful NF training, but further data of more patients is missing. In another study by Bolea (2010) more than 70 patients with chronic schizophrenia were involved in mixed neurofeedback training on different frequency bands (alpha, beta, delta) with temporal stages and altering electrode recording sites. The author obtained positive progress in the EEG patterns and in cognitive, affective and behavioral patterns of the schizophrenic inpatients. Furthermore, a two-year follow-up found that these improvements were sustained. Due to the complex procedure of the presented neurofeedback training it is not quite clear which frequency band training led to these positive results. The author holds the opinion that the reinforcement of the right parietal alpha and inhabitation of the frontal delta and fast beta activity obtained the determining effects.

8.2 Study aims

Alpha NF seems to be a promising technique for the cognitive rehabilitation of patients with schizophrenia, but to date only little is known about the ability of those patients to control their alpha amplitudes. This study attempts to clarify how the alpha neurofeedback training should be designed to fulfill the patient's specific needs with respect to training time and feedback type. Furthermore, it shall be investigated whether (1) these patients are able to get in control of their alpha rhythm (10-12 Hz) over the sensorimotor cortex, (2) the amplitude of the alpha resting power increases within and across the training sessions, and (3) if an increase in alpha resting power has positive effects on the patients' cognitive performance.

It is assumed that schizophrenic patients can learn to get in control of their alpha rhythm but due to their lack in concentration a higher training effort is needed (Gold, 2004). These patients react sensibly to visual input as some suffer from hallucination (Kay et al., 1987). It is predicted that a simple but distinct informative online feedback can support the training progress. In a successful training, where patients learned to enhance and suppress their alpha power it is expected that effects on the resting alpha power are detectable associated with positive effects on behavioral performance (Zoefel et al., 2011).

8.3 Methods

8.3.1 Participants

This study was approved by the Ethical Review Board of the Psychology Faculty of the University of Konstanz. In-patients were recruited at the Center of Psychiatry Reichenau, Konstanz, Germany. Inclusion criteria were an ICD diagnosis of paranoid-hallucinatory schizophrenia (code number 10.0). All patients were receiving psychoactive medication and were trained with neurofeedback in a clinically stable state. A total of six patients and four healthy controls took part in the experiment (see Table 1). The t-test for independent samples showed no significant difference in age between the patient and the control group $t(7) = 2.065$, $p=.078$. Each participant gave written informed consent, the procedure was explained in detail to them and they received monetary reward for participation. One patient had to be entirely excluded from training (dropout) and another one was included in the neurofeedback training but could not participate in the behavioral test due to insufficient German language skills.

Table 4: Demographic variables for schizophrenic patients and healthy controls. PANSS= positive and negative syndrome scale (Kay et al., 1987): P=positive, N=negative, G=general psychopathology; F=female, M=male.

Subject	Gender	Age	PANSS-Score		
			P-scale	N-scale	G-scale
Patient #1	M	39	9	8	19
Patient #2	F	36	24	23	44
Patient #3	M	24	8	16	29
Patient #4	M	24	10	27	42
Patient #5*	F	43	25.5	11	31
Control #1	F	24			
Control #2	M	25			
Control #3	F	24			
Control #4	M	23			

* Insufficient German language skills

8.3.2 Design

For each participant, the experiment consisted of 22 appointments with two pre and post behavioral test sessions and 20 neurofeedback training sessions within three to five weeks, with one or two sessions each day. A baseline of 3.5 min with alternating eyes open and eyes closed intervals of 15 s each was recorded before and after each training session (Fig 14). Each session comprised three runs of 75 trials and lasted 10 min, with short breaks in between.

8.3.3 EEG recordings

EEG was measured with five Ag/AgCl electrodes (F_z, C_3, C_z, C_4, P_z), placed in an elastic cap according to the international 10-20 system, grounded to the left and referenced to the right mastoid. A large Laplacian spatial filter was applied, with the values on electrode location C_z used for online feedback, calculated by combining the value at that location with the values of a set of the surrounding next-nearest-neighbor electrodes F_z, C_3, C_4 and P_z (McFarland et al., 1997). The signals were amplified by a g.tec amplifier system (g.tec, medical engineering, Austria). The EEG signals were analogue filtered between 0.1 and 30 Hz and digitally stored at a sampling frequency of 256 Hz. The raw EEG data was inspected for signal quality and further processed using a custom-made software programmed in BCI2000. EEG power was calculated by means of a sliding FFT algorithm, updated every 0.5 s during each training run. Every 12 s the past data was included into statistic to update the gain and offset of the online feedback. This calculation of alpha frequency-specific EEG-power (10-12 Hz) was used during training sessions to provide a fast and reliable feedback. During the pre and post baseline, raw EEG signals with eyes open and eyes closed were recorded for offline statistical analyses.

8.3.4 Neurofeedback training

The NF training was consistently performed with eyes open. Subjects trained to regulate their alpha band (10-12 Hz) amplitude. Participants received instructions drawn from the literature. Alpha rhythms are often said to be associated with feelings of calmness, pleasant relaxation, and increased inner awareness (Beatty, 1972, Holmes et al., 1974) and patients had to produce this particular state of mind. The trial started with the presentation of four arrows on the screen (2 s) which pointed inward or outward indicating the task direction to either decrease or increase alpha amplitude (Fig 14). The 4 s feedback phase started with a vertical grey bar that appeared in the middle of the screen. This bar could be extended and contracted in real time according to the online classification results by means of a sliding FFT algorithm. Positive feedback was either given by the change of the color of the bar, which turned green when it was controlled to the requested direction and by a smiley which appeared at the end of each successful trial, indicating that the user controlled the bar > 50 % of the feedback phase time into the requested direction. To avoid negative feedback, the bar remained grey when the correct alpha regulation could not be achieved. Increase and decrease trials occurred randomly, but not more than two times the same consecutive in each run.

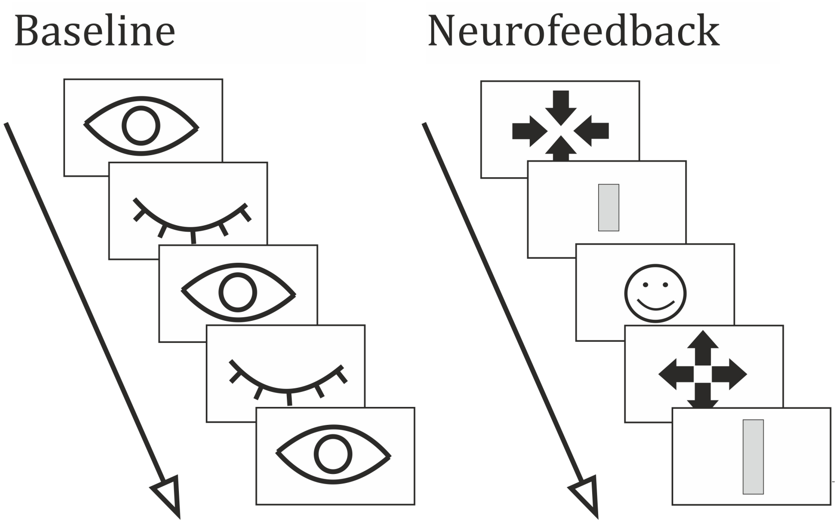

Figure 14: Illustration of the baseline and neurofeedback measurements. Each trial segment was initiated by a visual cue.

8.3.5 Data analysis

Performance

The level of performance for both subject groups was calculated as the percentage of correct selections across all runs per session. Due to the small sample size it was not possible to assume normal distribution of the data across the subjects. The nonparametric Wilcoxon signed-rank test for paired samples was applied to compare means. Further, to measure of the development of power the slope of the linear trend of the performance curves was considered.

Physiological data

The alpha amplitude was calculated for the training and the pre and post session baseline data sets in EEGlab, an open source Matlab toolbox. Raw EEG data was inspected by eye and artefacts were rejected. The data set of the training runs was split in 'up' and 'down' trial segments. Afterwards the mean power for each segment was calculated and averaged for each session. To investigate changes in alpha power over time, a Spearman correlation was calculated between the power in the alpha band and the number of sessions. The Mann Whitney U Test for independent data sets was used to compare alpha amplitude power means for the patient and the control group.

For the pre and post baseline measurements the 'eyes open' segments were extracted. The average alpha amplitude power of the 'eyes open' segments was calculated for each baseline before and after each NF session to detect changes in alpha resting power. Due to the small sample size the Wilcoxon signed-rank test for paired samples was calculated to compare means of the pre and post segments for each subject and for the averaged values for the patient and for the control group.

8.3.6 Cognitive performance

Cognitive performance of all patients was assessed by the German version of the California Verbal Learning Test (CVLT), the digit span and the d2 test of attention before the first and after the last NF session. All tests were conducted with pencil and paper. The procedure and the targeted cognitive function are presented in Table 5. The test analysis was conducted with the respective test manual.

Table 5: Cognitive tests. Pencil-and-paper tests conducted to evaluate three aspects of cognitive performance (verbal learning, short-term memory and attention), which are known to be reduced in patients with schizophrenia.

Cognitive test	Cognitive function	Procedure
CVLT German Adaptation, (Niemann et al., 2008)	Verbal learning	- serial learning of a word list with 15 items immediate recall: number of words recalled after the first presentation working memory: number of successfully recalled items after five repetitions delayed recall: intermission after 30 min including the distraction of a second word list
Digit Span (Conway et al., 2005)	Short-term memory	- series of trials presenting random digits at the rate of 1 digit/s - number of digits is increased by one in each trial until the participant failed twice to recollect everything correct - digits are repeated with the same (forward digit span) or with the inverse order (backward digit span)
d2 test (Brickenkamp, 2000)	Attention	- 14 test lines with 47 characters in each line - each character consists of a letter, 'd' or 'p' marked with one, two, three or four small dashes - lines must be scanned and all occurrences of the letter 'd' with two dashes must be crossed out while ignoring all other characters

8.4 Results

8.4.1 Neurofeedback training

The NF training could be integrated into the daily clinical routine. Five patients managed to attend all 22 appointments. Patients were motivated and accepted the NF, but reported that training was challenging depending on their mental and physical condition on each day.

Performance

The averaged performance values separated for the patient and for the healthy control group are shown in Figure 15. Patients and controls started at the same level of performance (patient: $M=.671$; control: $M= .652$). Both groups showed a positive linear trend across the 20 training sessions with an enhancement of the performance scores of up to $M=.7136$ in the patient group and $M=.8251$ in the control group. The slope of this trend was larger for the healthy control group ($m=.002$) than for the patient group ($m=.000$). The overall average performance in patients ($M=.692$) was significant lower than in healthy control groups ($M=.791$, $Z=-11.525$, $p<.001$).

Furthermore, the separation in 'up' and 'down' trials could show that the control group performed better than the patient group in both tasks (up: $Z=-6.653$, $p< .001$; down: $Z=-11.547$, $p< .00$). Both groups revealed a better performance for the 'up' trials than for the 'down' trials (patients: $Z=-6.648$, $p<.001$; control group: $Z=-3.662$, $p<.000$).

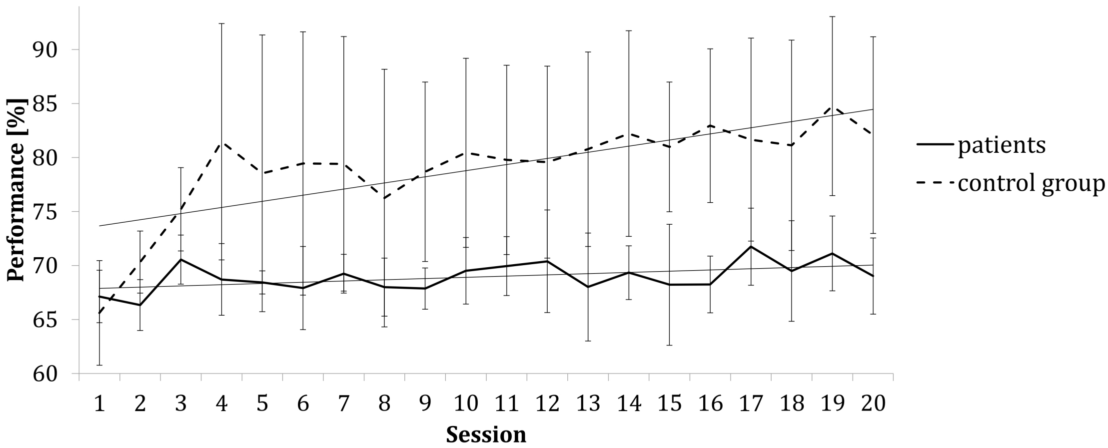

Figure 15: Mean performance values. Performance of the patient and control group with linear regression and standard deviation across all training session.

Physiological data

The average of the amplitude power in the alpha band during NF training for each patient is shown in Figure 16. Four of the five patients showed a positive correlation of the alpha amplitudes with the training session (patient: #1 r=.676; p=.001; #3 r=.465; p=.039; #4 r=.724; p=.001; #5 r=.587; p=.01). Patient ##2, #4 and #5 show a power trend indicating a strong improvement of performance during session one to five followed by an asymptotic performance with practice.

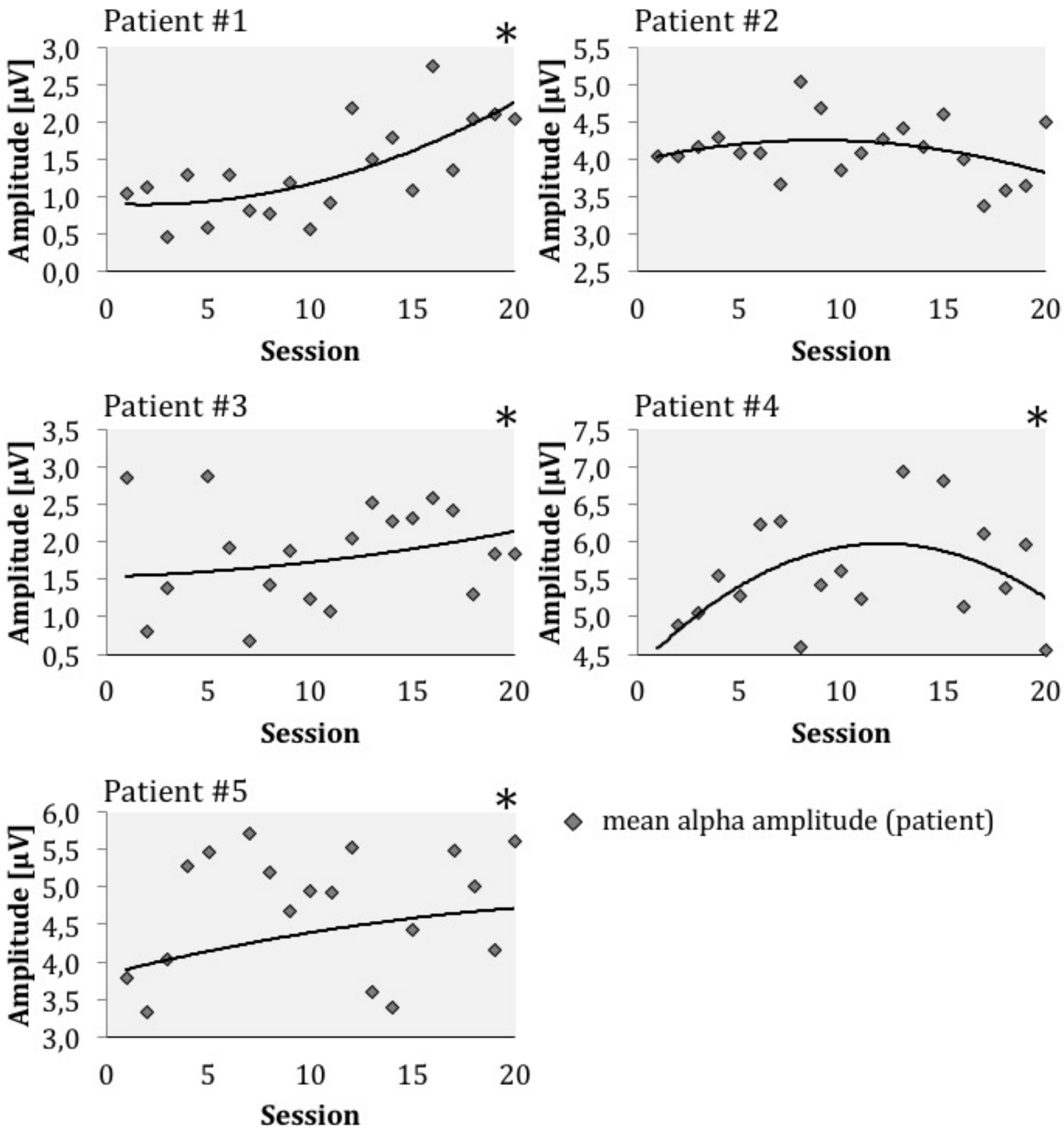

Figure 16: Mean amplitude values during training. Average alpha (10-12 Hz) amplitudes during training across each patient according to the temporal course of the study. The polynomial trend line results from a regression and indicates the temporal course of the amplitude values over sessions. Significance values p<.05 are marked with ∗.

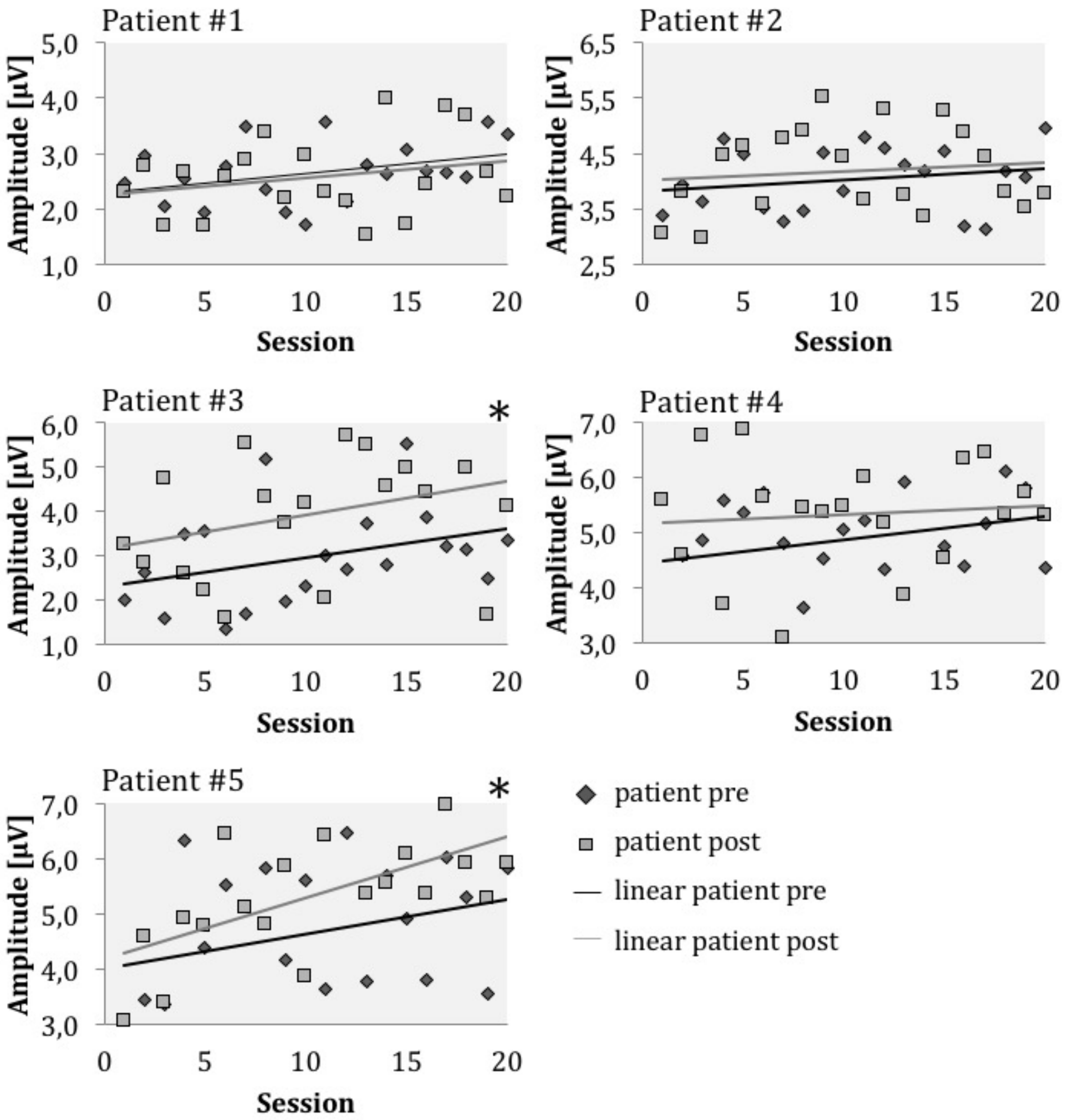

Figure 17: Mean alpha amplitude values during baseline. Alpha (10-12 Hz) amplitude power of the baseline before and after each trainings session and across all 20 NF sessions for each patient. Significant differences (p<.05) in pre and post baseline values are indicated by *.

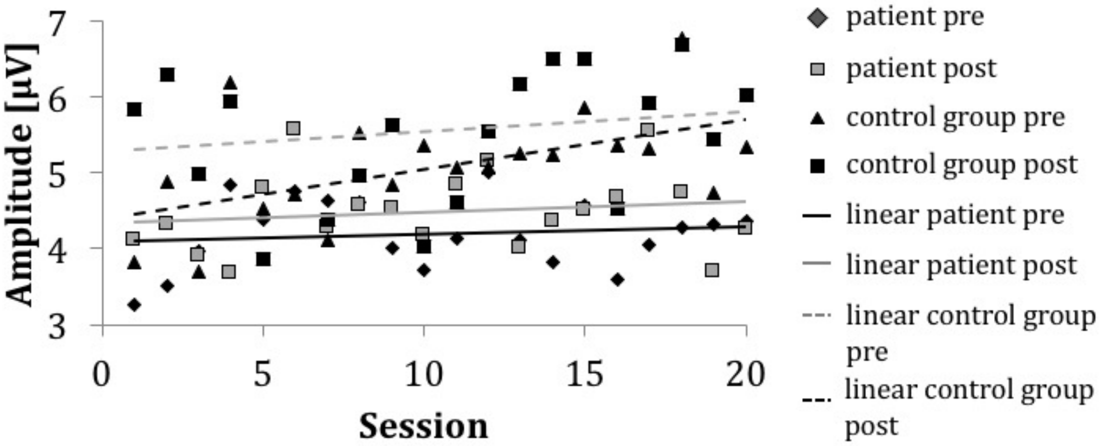

Figure 18: Averaged mean alpha amplitude values during baseline. Averaged mean alpha amplitude values for all patients and for the control group according to the temporal course of the study. The straight line results from a regression and indicates a linear increase in amplitude values over sessions.

The amplitude values of each patient during baseline measurements (eyes open) recorded before and after each training session and across the 20 NF training sessions are presented in Figure 17. Regarding the eyes open resting baseline four patients showed lower amplitudes in the baseline pre compared to the baseline post training with statistical significance in patient #3 ($Z=-2.240$; $p= .025$) and patient #5 ($Z=-2.320$; $p=.024$; Wilcoxon signed-rank test for paired samples, *= $p<.05$).

Figure 18 gives an overview of the averaged baseline values for both the control and the patient group before and after each training session and across the 20 training sessions. Both groups had significant lower amplitudes in their baseline pre compared to the baseline post (patients: $Z=-1.941$, $p=.05$; control: $Z=1.979$, $p=.048$; Wilcoxon signed-rank test for paired samples). The overall amplitude values for the pre ($U=-3.841$, $p=.000$) and post ($U=-3.327$, $p=.001$) measurements during the baseline were significantly smaller in patients than in controls (Mann Whitney U Test for independent samples).

8.4.2 Cognitive Performance

Descriptive results of the cognitive test scores both before and after NF training were available for four patients and are represented in Figure 19. Patient #5 had to be excluded due to insufficient German language skills. Whereas patient #1 and #2 showed strongest improvements in digit span and CVLT post tests, patient #3 and #4 could not enhance their performance in the cognitive tests. The results of the cognitive performance tests are not in accordance with the physiological data of the training or baseline alpha amplitude measurements.

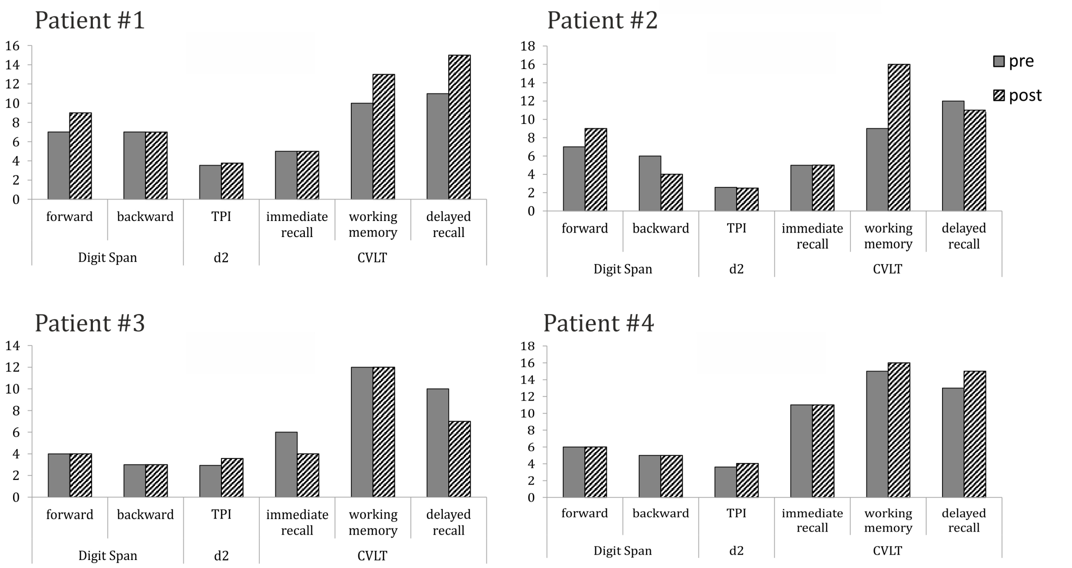

Figure 19: Cognitive performance. Test scores of each patient before and after the alpha neurofeedback training. Performance is represented separately for the three cognitive tasks and their respective subtests. Ordinate denotes the number of items recalled. TPI = total performance index.

8.5 Discussion

In line with our hypothesis the trainability of the alpha frequency amplitude of patients with schizophrenia was confirmed. Patient #3 and #5 could learn to regulate their brain activity with an effect on pre and post session baseline. Across the session, patients achieved higher alpha resting amplitudes and according to findings of Zoefel and colleagues (2011) significant differences between the baseline values pre and post each training session can be measured.

It is highly discussed how to most effectively measure alpha modulation. Three methods have been proposed: the individual alpha peak frequency (Angelakis et al., 2004), the mean peak frequency within a fixed bandwidth (Hooper, 2005) and the individual alpha peak at the center of gravity within the individual alpha frequency range (Klimesch et al., 1993). According to the established method by Dempster and Vernon (2009) the herein presented study used a fixed predefined bandwidth for alpha modulation. This approach can minimize the time of the session due to the no longer required pre-calibration. It simplifies the handling of equipment and software, especially for BCI untrained clinical staff, and it adjusts the same training for every participant. Other research groups claimed that the large inter-individual differences in the alpha frequency band can be problematic and therefore, suggested to train subjects instead with their individual alpha frequency (IAF) band (Klimesch, 1999; Vernon, 2005; Zoefel et al., 2011). We cannot exclude that training with the individual alpha frequency could have been more successful or if it would have shortened the overall training time. To clarify the potential of these alternative alpha measurement methods it would be necessary to implement further studies detecting differences in performance or training times with an IAF training.

In the herein presented study four out of five patients learnt to regulate the fixed alpha frequency range across 20 training sessions. Huge differences in the suggested number of session for NF exist in the published literature. Whereas some studies with healthy participant showed that 10-20 lessons are necessary to learn to regulate brain activity (Dempster and Vernon, 2009; Nan et al., 2012; Dekker et al., 2014), others could show differences in EEG activity and behaviour were detectable within less than ten sessions (Hanslmayr et al., 2005; Zoefel et al., 2011). Depending on the signal of interest and classification approaches, significant regulation can be even achieved in the first session (Blankertz et al., 2010). The two studies published on alpha neurofeedback training in patients with Schizophrenia applied different training times: Whereas Nan and colleagues (2012b), could report positive training effects in cortical activity and short-term memory after only four sessions on consecutive days, Bolea (2010) conducted a study with more than 140 sessions within 1,5 years. Our results could show that patients featured the strongest enhancement in performance and an increase in their amplitudes in the first five sessions, followed by an asymptotic performance across the following sessions. This is in accordance to findings by Kübler and colleagues (2010). They compiled an overview of existing literature and concluded that studies that rely on neurofeedback and operant conditioning to achieve self-regulation on a specific oscillation feature performance followed a power trend indicating a strong improvement of performance at the beginning of the training. Cho and colleagues (2008) pointed out that there is likely to be a limit on how many sessions can be undertaken before there is no more improvement to be made and the learning curve flattens out.

In the cognitive performance tests, only four patients could be included. The remaining data set for the behavioral tests can only be seen with a descriptive interpretation without statistical evaluation due to the small sample size. Nonetheless, it is possible to see trends in this preliminary data set with a shift towards better tests scores after NF in verbal learning and attention. This is in accordance to findings of other studies with healthy participants (Vernon et al., 2003; Escolano et al., 2011; Zoefel et al., 2011; Nan et al., 2012a; Dekker et al., 2014). The CVLT was tested with different pre and post versions with a minimum of three weeks in between. However we cannot exclude training effects as patients got used to the surrounding, the test situations, procedure and requirements.

Another important aspect that has to be kept in mind when interpreting the results is that all patients were on medication and took part in the rehabilitation program at the clinic for psychiatry Reichenau. Cordes and colleagues (2015) noted in their study that cognitive therapy usually addressed patients on antipsychotic medications. Therefore, this present sample represents a realistic treatment setting of patients with schizophrenia that may be more relevant to study than a group of non-medicated patients.

8.6 Conclusions

The herein presented work is the first study that investigated the implementation of alpha neurofeedback training in several patients with schizophrenia in a clinical setting. Cognitive remediation in patients with schizophrenia is an increasingly prominent goal of rehabilitation programs (Popov et al., 2011a) and our results are promising that a daily alpha NF training that focuses on the increase of alpha resting power can be effective, inexpensive and easy to handle for the patients and for the clinical staff.

9 General Discussion and perspectives

For successful and efficient alpha neurofeedback training, the following questions have to be answered: In which way, how often, and how long has to be trained for to detect changes over time. The fundamental objective of this thesis was to examine the relationship between alpha frequency band modulation recorded over the sensorimotor cortex and training efficiency. The studies sought to isolate the effect of feedback and training time on cortical activation patterns and BCI performance. Healthy participants, as well as patients suffering from schizophrenia, were trained to intentionally regulate their alpha amplitude in a single or several training sessions.

The following is a summary of the major findings, including a discussion of the results in the light of published research and, lastly, limitations as well as clinical implications are reviewed.

The herein presented studies demonstrated that participants were able to enhance the desired electrophysiological modulation, which was an increase or decrease of their alpha amplitude recorded over the sensorimotor cortex in a user centered design . In study I, averaged data of 35 participants revealed characteristic mu rhythm ERD patterns during motor imagery. In study II, the performance was measured as the percentage of correct responses during motor imagery tasks. In 56 % of all feedback group's end-users performed at least one session above chance level with more than 63 % correct responses and could, thus, achieve significant control over the required brain response. In study III, in line with our hypothesis, the trainability of the alpha frequency amplitude of patients with schizophrenia was confirmed. Patients were able to learn to alter their alpha activity, enhancing it in the desired direction with an effect on the baseline during rest. In accordance with the findings of Zoefel and colleagues (2011), significant differences between the baseline values pre- and post-training session were measurable and the alpha resting amplitudes increased across the 20 training sessions.

9.1 Instructions and feedback in alpha activity

Current BCI training protocols rarely include a detailed overview of the instructions provided to the end-user and several studies exist that even omit any kind of guidance during NF training. In that case, training is thought to be self-guiding and participants should intuitively find a way to control their brain oscillation, just relying on the feedback (van Boxtel et al., 2012; Dekker et al., 2014).

In the herein presented studies, participants were instructed to feel a kinesthetic experience while imagining movements of their limbs but avoiding any muscle tension. The objectives of the training were explicitly mentioned to the end-users to help to produce clear, specific and stable brain patterns (Neuper et al., 2005). In that way, the end-user could benefit from the realistic pre-visualizations. Further, we investigated the effects of enriched feedback on BCI performance. Instructions were carefully made to the end-user in order to explain them the meaning of this abstract feedback. Comparable to a study by Dempster and Vernon in 2009, the feedback loop was explained to each participant, which involved instructions about the goal of the task. It was therefore explicitly mentioned to the end-user what was expected from him/her. This seems particularly important if the feedback is related to a classifier output whose actual meaning, in this case, the movement of a liquid cursor through a funnel shape is unlikely to be intuitive for people not familiar with the classification of motor imagery and BCI (Lotte et al., 2013). In the alpha NF training patients were instructed by explaining the BCI system and the goal of the training. Examples were given on how different states in their brain oscillations can be elicited and what could alter the amplitude power, such as different states of alertness. At the beginning of each session, participants were instructed to imagine a realistic situation in which they felt concentrated or relaxed, before imagining it during the subsequent NF training. Merrill (2007) recommended that this would activate their prior experience, facilitating the learning process. After the instruction, participants seemed to feel more confident with the task. Naïve end-users are often not aware on how the BCI system works, and often tend to control it with eye movements, breathing techniques or muscle tension. Our findings support the importance of instructions provided to the end-user before the actual training to improve BCI learning approaches and making feedback more efficient (Hattie and Timperley, 2007; Shute, 2008). The effect of instructions and feedback are not yet completely understood, but earlier studies focused on the interplay between these two features on NF performance.

Studies by Beatty (1972) and Holmes and colleagues (1980) could show that subjects who were carefully instructed how to modulate their alpha amplitude were as effective at increasing alpha as subjects who were both instructed to increase alpha and given feedback to aid them. The feedback itself did not seem to have any effect on alpha production at all. It appears, then, that the subjects who received the instructions simply put themselves into the alpha-related emotional state that was described to them and that they could do that without the feedback to guide them. Prfwett and colleagues (1976) could show that alpha enhancement was associated with instructions but was independent of feedback. However, alpha activity suppression needed both, accurate instructions and a meaningful feedback.

From our results, we can conclude that feedback is a necessary feature to support end-users in the initial contact with the BCI system. Moreover, several studies underline the hypothesis that providing meaningful feedback to an end-user leads to efficient and faster learning (Hattie and Timperley, 2007; Shute, 2008). Feedback can benefit from improved technical capabilities that are nowadays available to make it more meaningful and descriptive. Especially for several sessions and longer trial length it can keep the participant involved and motivated by applying different mediums like virtual reality (VR) or 3D games characteristics (Pfurtscheller et al., 2007; Leeb et al., 2007b; Scherer et al., 2008). However, this holds not true for any kind of feedback. Protocols that are poorly designed could actually deteriorate motivations and impede a successful learning (Shute, 2008).

9.2 Choice of feedback

During the online feedback studies the end-users received continuous feedback of their alpha activity in real time in form of an expansible moving bar or liquid cursor that changed its color or velocity when controlled in the right direction. The participant was aware of when the desired aspect of their alpha activity, in this case the amplitude, increased or decreased. The feedback should enable them to attempt the most effective way at influencing this process so that they could learn to alter their alpha power in the desired direction. To date, the majority of BCIs controlled by motor imagery employ continuous process control. This means that the signal obtained primarily from the cortex is used to determine the position, velocity and/or acceleration of the controlled cursor. The end-user receives continuous feedback regarding the input signal and must encode the details necessary to achieve that action. A study of Neuper and colleagues (1999) suggested that continuous feedback can have facilitating effects depending on the end-user and can lead to more efficient BCI learning than delayed discrete feedback. According to Guger and colleagues (2000) instantaneous feedback information can lead to an improvement in the differentiation of left versus right hand motor imagery in the EEG. An alternative control strategy is a discrete goal selection, in which the BCI uses the signal it obtains to determine the selection of the desired target to the end-user. The end-user must only encode the desired action to achieve the target (Wolpaw 2007). This feedback is not very common in MI-based BCIs, but several studies have demonstrated that control is possible (Friedrich et al., 2009; McFarland et al., 2008). Royer and He (2009) affirmed that goal selection leads to more hits per run, was faster, more accurate and had a higher information transfer rate than process control. However, a study by Middendorf and colleagues (2000) failed to support these findings and found no difference between discrete and proportional feedback.

Regardless of whether feedback is continuous or contingent, it has been suggested that including a scoring system in addition to the feedback could help to improve participants' performance. Kübler and colleagues (1999) established a combination of both a continuous feedback during cursor movement and a discrete delayed feedback at the end of each trial and demonstrated that all patients suffering from Amyotrophic lateral sclerosis (ALS) could achieve self-control in a training of SCP. We followed this suggestion in study III and provided a continuous feedback in form of a moving bar and a smiley presented at the end of successful trials. Preliminary studies could show that patients seemed to be very insecure about their NF performance. They reported to have difficulties to judge their own performance but a score gives them guidance to measure their performance. Hardt and Kamiya (1976) affirmed that using a scoring system helps to motivate participants and helps to keep them on task and alert.

Rather than just indicating whether the task was done correctly or not (Hattie and Timperley, 2007), feedback should be specific, that means explanatory, and should suggest how the end-users could improve the task. Given feedback could benefit from more engaging environments and additional information, describing the actual quality of the performed mental task in order to enhance the end-users motivation and engagement. The herein presented results support the positive effects of enriched feedback presentation on BCI performance during the initial training session. A realistic feedback in form of a three-dimensional visualization of upper and lower limb movements could amplify motor cortex activation during a subsequent motor imagery phase. This is in accordance with previous findings: Pfurtscheller and colleagues (2007) have argued that observing a realistic moving hand should have a greater effect on the desynchronization than watching an abstract feedback in the form of a moving bar. A study by Ono and colleagues (2013) could show that anatomically congruent feedback produced the highest reproducibility of ERD with the smallest inter-trial variance. However, Neuper and colleagues (2009) proposed some limitations of the positive effects: They suggested that the type of task is of prime importance as the processing of such a realistic feedback stimulus may interfere with the mental motor imagery task and can therefore, in some cases, impair the development of EEG control. Furthermore, they argued that when the feedback contains equivalent information on both the continuous and final outcomes of mental actions, the form of presentation, if it is abstract or realistic, does not influence the performance in a BCI, at least in initial training sessions. Some promising results were found for the effect of an enriched feedback presentation. 3D and VR feedback environments have been shown to increase BCI performances (Pfurtscheller et al., 2007; Leeb et al., 2007b; Scherer et al., 2008). This technology has the capability of creating immersive and motivating environments in order to improve the effectiveness of the training process and reduce training times (Ron-Angevin and Diaz-Estrella, 2009).

The results in study II revealed significantly better performance scores measurable in the enriched feedback group as compared to the conventional group during the initial training session. It seems that the enriched online feedback, with information about the quality of the input signal, supports an easier approach for BCI control. This is an alternative method to enrich visual feedback proposed by Kaufmann and colleagues (2011b). They provided their BCI end-users with multidimensional feedback information regarding the classifier output, decoded in the color of the cursor, and the strength of the absolute value of the classifier output, decoded in the intensity changes of the cursor. The preliminary results demonstrated that participants were able to control the BCI with the same accuracy as compared to a conventional cursor feedback. By providing the end-users with the information about how well he/she is controlling at any point in time during the trial, the BCI feedback could facilitate the learning process in the initial training session and, therefore, minimize frustration and increase motivation.

The two modalities of auditory and visual feedback seemed to be not as important as the enriched information, as there was no significant difference in the performance of the two funnel feedback groups. Ainsworth (2006) suggested that the content of the representations might be more important than the modalities used for each representation. A multimodal BCI feedback has to follow some guidelines to be meaningful for the end-user. Furthermore, the paired modalities should have a similar specificity, using the same amount of details of explanatory content, so that the end-user can easily relate them. The missing effect in performance our study may either be due to an overflow of information which distracts the subject from the specific task or due to the visual feedback being too dominant to such an extent that the simultaneous auditory feedback did not provide any beneficial information (Hinterberger et al., 2004). However, participants objectively judged the combination of liquid cursor and sounds to be more helpful and more descriptive than the unimodal funnel feedback and the motivation for participating again in another BCI experiment was rated higher.

As explained previously, NF training allows the end-user to receive real-time feedback of their alpha activity. The participant should be aware of when the desired aspect of their alpha activity, e.g. the amplitude, increases or decreases. The feedback should enable them to attempt the most effective way at influencing this process so that they can learn to alter their alpha in the desired direction. Some patients with schizophrenia suffer from delusions, hallucinations and deficits in their perception (Kay et al., 1987). The feedback used should be carefully adjusted to this patient group. The effects of different types of visual feedback have not been established; however, in order to neither distract or to irritate patients, it seems beneficial to support them with simple but meaningful feedback, to help the user in producing clear, specific and stable brain pattern. The results of the herein presented studies suggest that feedback is an important feature when learning to control a BCI.

9.3 Effect of training time

As mentioned in section 4.3.3 different amounts of sessions are proposed to train end-users to modulate their alpha oscillation. Issues relating to how long each session should last and how many sessions are needed to detect enhancement in NF performance are of major interest. In the machine learning approach, participants learned in a single session to gain control over an MI-based BCI (Vidaurre and Blankertz, 2010), whereas neurofeedback studies with an operant learning approach exist with more than 50 training sessions over a period of several years (Rockstroh et al., 1993; Birbaumer et al., 1999; Fuchs et al., 2003; Kübler et al., 1999, 2005, 2008; Kouijzer et al., 2009; Dehghani-Arani et al., 2013; Escalano et al., 2014). The causes for the diverse training times can be various. Variables that influence performance are i.e. the frequency bandwidth that was chosen; whether it is an operant conditioning or a machine learning approach; whether healthy subjects or patients are participating; and whether the training is performed with eyes open or eyes closed, etc.

Still no recommendations exist on how long a single training session should take. The herein presented results showed that healthy participants were able to take part in sessions that took around 1.5 h, but patients with schizophrenia often suffer from attention deficits due to the disease and medication. Therefore, we recommend shorter training times (30–40 min) with longer breaks in between. How long each session should last should be closely tied up to the targeted group and their capabilities in concentration.

The issue of how many sessions are needed to learn to exert a conscious control over the alpha oscillation, and how many sessions are needed that such training has the desired effect on optimal performance, is not uniform and needs to be individually answered. Whereas in study I, healthy participants were able to elicit characteristic event-related desynchronization of the mu rhythm in a single session in accordance to other studies (Hanslmayr et al., 2005, Vidaurre and Blankertz, 2010), some researcher groups argue that more than one session is needed to detect the progress of learning (e.g. Schneider et al., 1992; Egner and Gruzelier 2004; Raymond et al. 2005; Dempster and Vernon, 2009; Nan et al., 2012b; Dekker et al., 2014). In study III, patients learned to control their alpha rhythm across 20 sessions. Performance increased significantly with time for both the patient and the control group. Whereas, the control group showed a fast increase from session one to three, the patient group showed a slow continuously increase from session one to twenty. Nowlis and Wortz (1973) found similar results. They trained their participants between five and 52 sessions and found that their degree of control over their alpha increased with the number of sessions. Cho and colleagues (2008) pointed out that there is likely to be a limit on how many sessions can be undertaken before there is no more improvement to be made and the learning curve flattens out.

In study II, unexpectedly no improvement of classification accuracies were found across the five training sessions and the overall performance in all groups was surprisingly low. The significantly highest values of performance and ERD were present only in the first session in all feedback groups. Along with training, performance and ERD values of the feedback groups converged and maybe more training sessions would have been necessary to detect learning. Other studies also failed to detect learning across multiple training sessions (Lynch et al., 1974; Vernon, et al., 2003). The training duration might be relevant in detecting learning effects (Pichiorri et al., 2011) but the issue of how much learning is involved in BCI control still remains an open question. Participants often report that as training proceeds, the task itself, e.g. the imagined movement or state of alertness, becomes less important and the use of a BCI system becomes more automatic (Daly and Wolpaw, 2008). Kübler and colleagues (2010) compiled an overview of existing literature and concluded that studies that rely on neurofeedback and operant conditioning to achieve self-regulation on a specific oscillation feature performance followed a power trend indicating a strong improvement of performance at the beginning of the training followed by an asymptotic performance with practice.

In general, healthy end-users learned faster to achieve control over a BCI than patients. This is in accordance to findings in other studies: Patients suffering from ALS needed more training time and did not show asymptotic behavior (Kübler et al., 1999). Overall, the level of BCI performance seems to be diminished in those patients compared to healthy controls (Nijboer et al., 2008b). Only studies including a long-term training could report linear or power trends in the performance of severely motor impaired end-users, indicating either a constant improvement of performance or a strong improvement of performance at the beginning of training (Kübler et al., 2004).

Slower learning progress in patients can be explained by recording difficulties, such as noisy data and large electromyogenic artifacts due to the restless behavior of patients with schizophrenia or neurodegeneration as a consequence of the ALS disease (Mateen et al., 2008). Furthermore, patients suffer from cognitive impairment and psychological problems and may be in need of antipsychotic medication that affects attention, concentration or even directly individual EEG components (Nijboer et al, 2010). The success of studies, especially in a clinical setting, may be diminished by several factors and further limitations are presented in the next chapter.

9.4 Limitations

Although each study was planned and conducted with greatest diligence some aspects of the proposed hypotheses reveal a lack of statistically significant results. Therefore, it is important to consider several limitations, such as sample characteristics and medication effects.

9.4.1 Sample Characteristics

A relatively small sample size in study II and III must be considered as a possible explanation for the lack of statistically significant results. Each feedback group in study II included ten subjects, but the performance within the groups showed a high variability between the end-users. Only four patients could be included in the cognitive performance tests in study III. The data set for the behavioral tests can only be seen with a descriptive interpretation without statistical evaluation due to the small sample size. The small sample size is due to the time-consuming work with patients in the clinic: Not all patients fulfilled the requirements for this study and they had to agree to take part in more than 20 appointments that took a minimum of three weeks. It was not possible to simultaneously measure more than three patients as the experiment could only be conducted in time slots between clinical interventions. Sometimes patients had to cancel at short notice due to changes in their clinical timetable. Conducting studies in a clinical setting with patients are always more time consuming and elaborate and a huge effort must be put in the scheduling and appointment management.

9.4.2 Medication effects

All participants of study III were taking medication at the time the NF training was conducted. Antipsychotic medications, especially neuroleptics, can alter resting EEG activity, introducing a potential confound into the EEG (Hammond and Gunkelman, 2001; Surmeli et al., 2012). Since the effects of medication on alpha activity are uncertain, this represents a threat to internal validity. In addition, certain medications may have influenced participants' attention and alertness. In this study we tried to control for medication by keeping it constant during the experiment time. Cordes and colleagues (2015) took up the position that cognitive therapy usually addressed patients on antipsychotic medications. Therefore this present sample represents a typical clinical population that may be more relevant to study than a group of un-medicated patients, thereby increasing the generalizability of results.

9.5 Clinical Implications

9.5.1 MI-based BCIs for communication

Study II could show that healthy participants were able to control a cursor on a computer screen through modulation of their mu rhythm amplitude of the sensorimotor area with motor imagery (MI). Such MI-based BCI enables communication in healthy end-users (Millán and Mourino, 2003; Birbaumer, 2006; McFarland and Wolpaw, 2011) as well as in patients with severe motor impairments. Kübler and colleagues (2005) could show that four ALS patients acquired control over their sensorimotor rhythms. Furthermore, the performance of all patients achieved over 20 sessions exceeded the 70 % accuracy that is sufficient for using a language support program. A study by Neuper and colleagues (2003) showed a case study where a completely paralyzed patient, diagnosed with severe cerebral palsy, could learn to gain control over a BCI-controlled spelling device.

However, the MI-based BCI is not always the first choice for communications in patients. Nijboer and colleagues (2010) compared the performance level of six participants with advanced ALS that were trained for a block of 20 sessions with a BCI based either on sensorimotor rhythms or on event-related potentials (P300-BCI). The MI-based BCI required more training than the P300-BCI and the information transfer rate was higher with the P300-BCI (3.25 bits/min) than with the SMR-BCI (1.16 bits/min). Nevertheless, it seems justifiable to enhance MI-based BCIs because of the advantage that it relies on the modulation of the mu rhythm. Even when control is poor in the first session, it can be learned by means of operant conditioning, which is not an option for the BCIs relying on the P300 signal feature (Neuper et al., 2010). The MI-based BCI used in this thesis relies on learning via neurofeedback training to train the ability to self-regulate alpha rhythms (Kübler et al., 2001a; Wolpaw et al., 2002), which is a skill that can be achieved through practice.

9.5.2 MI-based BCIs for motor rehabilitation

In recently published literature BCIs that are controlled by motor imagery are used in a therapeutic approach. It can be used as a training tool for stroke rehabilitation, in order to restore the impaired motor function (Grosse-Wentrup et al., 2011; Pichiorri et al., 2014; Keng-Ang and Guan, 2013; Ramos-Murguialday et al., 2013). MI-based BCIs might restore motor function by inducing activity-dependent brain plasticity to induce recovery of normal motor control and restore more normal brain function. They could help to guide brain plasticity by affecting motor learning, for example by demanding close attention to a motor task or by requiring the activation or deactivation of specific brain signals (Daly and Wolpaw, 2008). During motor imagery BCI training end-users mentally rehearse the function, behavior and performance of a movement like they are actually performing them (Lotze and Cohen 2006). Motor imagery training in an early stage of recovery allows patients to practice and exercise movements, which they cannot carry out physically due to their motor impairment (for Review see Zimmermann-Schlatter et al., 2008; Sharma et al., 2006).

Several studies could report the successful implementation of such training for stroke rehabilitation (Page, 2000, 2001, 2005; Daly et al., 2009; Pichiorri et al., 2013). And first results indicate that patients are able to regain control over volitional motor movement within this BCI intervention. The review by Zimmermann-Schlatter and colleagues found modest evidence supporting the additional benefit of motor imager training compared to only conventional physiotherapy in patients with stroke.

Therefore, we support the use of a more realistic feedback especially for BCI use for rehabilitation. In stroke patients, motor imagery may, therefore, provide a promising alternative to motor rehabilitation intervention that is not dependent on residual function but still incorporates voluntary drive (for Review see Sharma et al., 2006).

9.5.3 Neurofeedback and cognitive rehabilitation in schizophrenia disease

Around 73 % of the patients with schizophrenia have cognitive impairments (Palmer et al., 1997) and abnormal EEG findings are common in 20 % to 60 % of these patients (Ellingson, 1954; Itil, 1977). Most often the EEGs are characterized by decreased resting alpha activity (Sponheim et al., 1994; Saletu, et al., 1990; for review see Boutros et al., 2008). Currently, the treatment of choice for the symptoms of schizophrenia is an antipsychotic medication, but the effects of these medications are not consistent and the side effects can be severe, especially when used long term. Findings indicate that neurofeedback (NF) training can be an alternative or at least complementary intervention that has clinical significance for patients with schizophrenia (Schneider et al., 1992; Gruzelier, 2000; Bolea, 2010; Nan et al., 2012b). The aim of NF training is to teach the individual how to modify aspects of their own brain activity and, in doing so, potentially influence their behavior.

Of interest to NF clinicians is whether the alpha rhythms recorded over the sensorimotor cortex should be targeted in EEG training. Results of study III suggest that the training of the alpha frequency band should be considered in developing and executing NF training protocols. Studies with patients suffering from autism spectrum disorder (ASD) have begun to examine the effects of NF training on the alpha rhythm recorded over the sensorimotor cortex: Coben and Hudspeth (2006) demonstrated that operant training of the alpha rhythm resulted in a significantly reduced alpha activity and improved social and emotional functioning in these patients. A study by Pineda and colleagues (2008) demonstrated that alpha NF training could induce EEG changes and enhance attention in children diagnosed with ASD.

As suggested in our hypothesis, the trainability of the alpha frequency amplitude of patients with schizophrenia was confirmed. Patients could learn to regulate their brain activity with an effect on the pre- and post-session baseline. This is in accordance with the findings of Zoefel and colleagues (2011). Across the sessions, patients achieved higher alpha resting amplitudes. The self-regulation of the alpha rhythm seems to be a viable training modality and, taken together, these findings suggest that alpha neurofeedback offers a promising alternative as a cognitive rehabilitation technique. With the growing importance of personalized medicine, this type of treatments may become more common in the future.

9.6 Conclusive recommendations and perspectives

In summary, this thesis successfully targeted factors improving alpha modulation training, thereby increasing the understanding of the role of training in practical, clinically useful BCIs. The herein presented studies revealed a high individual variability in the performance demands and abilities of each end-user. These findings support the need of an iterative process in BCI development, in which the researchers and end-users communicate about the requirements of a product and its implementation. This seems beneficial especially when the final product is thought to be used in the daily life of the target population or in a clinical setting as for cognitive and motor rehabilitation.

On the basis of the herein presented results, several recommendations can be proposed to increase the efficiency of an alpha rhythm training over the sensorimotor cortex in an operant learning approach.

Guidelines to improve training of alpha modulation with regard to performance and activation patterns:

Feedback
- Realistic feedback to support motor imagery
- Enriched multidimensional feedback: Quality of the input signal
- Continuous feedback (moving shape, color change etc.)
- Positive reinforcement (smiley, score system, etc.)
- Multimodal feedback is not a necessary feature

This thesis provided proof that feedback and training time have an influence on the performance and the activation patterns observed during BCI control and several recommendations for future research follow from the results of these studies.

First, the presented MI-based BCI systems should be transferred from the laboratory to the end-users home in order to reach the targeted group that is in actual need of a reliable BCI training, namely the patients. It has to be verified if patients could benefit from realistic enriched feedback with an enhancement in performance and activation patterns, without being overwhelmed with information or distracted from the actual motor imagery task. A larger sample size is needed for the alpha neurofeedback training in patients with schizophrenia. This would make it possible to statistically verify not only changes in the amplitude values across the training session but also for variances in behavioral data, e.g. cognitive performance including short-term memory and attention. In order to make reliable statements regarding the effects of neurofeedback training it is necessary to exclude the impact of medication and psychological intervention, especially in studies that are made in a clinical setting over longer periods of time. Therefore, we recommend controlling for medication effects. Furthermore, several measurements after a longer period of time are necessary to detect long-term effects on cognitive performance. This would prove the relevance of alpha neurofeedback training as a successful rehabilitation intervention.

The recent improvements of the efficiency and reliability of BCI systems are promising and they have the potential to support various aspects such as communication and rehabilitation in patients with disabilities. The importance of a correct training procedure, with regard to efficiency and comfort, cannot be overestimated. In the worst case, training success can be diminished and end-users are dissatisfied with the BCI system or with their own performance. The BCI – end-user interaction is a closed loop and all aspects have to be carefully adjusted in order to transfer BCIs successfully into the clinical setting.

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11 Appendix

A: Eidesstattliche Erklärung

B: Curriculum Vitae

Appendix A: Eidesstattliche Erklärung

Affidavit

I hereby confirm that my thesis entitled „Feedback efficiency and training effects during alpha band modulation over the human sensorimotor cortex" is the result of my own work. I did not receive any help or support from commercial consultants. All sources and/or materials applied are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor similar form.

Würzburg, 04.12.2015

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Place, Date **Signature**

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation " Die Wirksamkeit von Feedback und Trainingseffekte während der Alphaband Modulation über dem menschlichen sensomotorischen Cortex" eigenständig, d.h. insbesondere selbstständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Würzburg, 04.12.2015

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Ort, Datum **Unterschrift**

Appendix B: Curriculum Vitae

MRS TERESA SOLLFRANK

PERSONAL DATA

Residential address	Juliuspromenade 64a, 97070 Würzburg
Phone	0931 3189115
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Date of birth	23.03.1985

EDUCATION/STUDY

2007 – 2011	Study of biology (Diploma) at the Julius-Maximilians University Würzburg; Degree: Diploma of Biology
2005 – 2007	Study of biology (BSc) at the Friedrich Alexander University Erlangen
1996 – 2005	Matthias Grünewald Gymnasium Würzburg; Degree: Abitur

PROFESSIONAL EXPERIENCE

Since 08.2013	Associate member of the Graduate School of Life Sciences, University of Würzburg Associate member of the GK Emotion, Research Training Group 1253
01.2013 – 07.2013	Research associate at the Department of Mechanical Engineering, Workgroup of Prof. Tele Tan, Curtin University Perth/Australia
Since 02.2012	Research associate at the Institute of Psychology, Workgroup of Prof. Kübler, University of Würzburg

PUBLICATIONS

Sollfrank, T., Hart, D., Goodsell, R., Foster, J., Kübler, A. & Tan, T. (2014) 2D vs 3D visualization modalities and their effects on motor related potentials. *J Vis 14* (10): 311; doi:10.1167/14.10.311.

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Würzburg, 04.12.2015

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Place, Date **Signature**