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Development of an MEG-based brain–computer interface

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Abstract

Brain–computer interfaces (BCI) have recently gained interest both in basic neuroscience and clinical interventions. The majority of noninvasive BCIs measure brain activity with electroencephalography (EEG). However, the real-time signal analysis and decoding of brain activity suffer from low signal-to-noise ratio and poor spatial resolution of EEG. These limitations could be overcome by using magnetoencephalography (MEG) as an alternative measurement modality. The aim of this thesis is to develop an MEG-based BCI for decoding hand motor imagery, which could eventually serve as a therapeutic method for patients recovering from e.g. cerebral stroke. Here, machine learning methods for decoding motor imagery -related brain activity are validated with healthy subjects' MEG measurements.

The first part of the thesis (Study I) involves a comparison of feature extraction methods for classifying left- vs right-hand motor imagery (MI), and MI vs rest. It was found that spatial filtering and further extraction of bandpower features yield better classification accuracy than time–frequency features extracted from parietal gradiometers. Furthermore, prior spatial filtering improved the discrimination capability of time–frequency features.

The training data for a BCI is typically collected in the beginning of each measurement session. However, as this can be time-consuming and exhausting for the subject, the training data from other subjects' measurements could be used as well. In the second part of the thesis (Study II), methods for across-subject classification of MI were compared. The results showed that a classifier based on multi-task learning with a $l_{2,1}$ -norm regularized logistic regression was the best method for across-subject decoding for both MEG and EEG.

In Study II, we also compared the decoding results of simultaneously measured EEG and MEG data, and investigated whether the MEG responses to passive hand movements could be used to train a classifier to detect MI. MEG yielded altogether slightly, but not significantly, better results than EEG. Training the classifiers with subject's own or other subjects' passive movements did not result in high accuracy, which indicates that passive movements should not be used for calibrating an MI-BCI.

The methods presented in this thesis are suitable for a real-time MEG-based BCI. The decoding results can be used as a benchmark when developing other classifiers specifically for motor imagery-related MEG data.

Keywords magnetoencephalography, brain–computer interface, MEG, BCI, motor imagery, sensorimotor rhythm

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Tiivistelmä

Aivo-tietokone -käyttöliittymät (brain-computer interface; BCI) ovat viime aikoina herättäneet kiinnostusta niin neurotieteen perustutkimuksessa kuin kliinisissä interventioissakin. Suurin osa ei-invasiivisista BCI:stä mittaa aivotoimintaa elektroenkefalografialla (EEG). EEG:n matala signaali-kohinasuhde ja huono avaruudellinen resoluutio kuitenkin hankaloittavat reaaliaikaisia signaalianalyysia ja aivotoiminnan luokittelua. Nämä rajoitteet voidaan kiertää käyttämällä magnetoenkefalografiaa (MEG) vaihtoehtoisena mittaussuomenetelmänä. Tämän työn tavoitteena on kehittää käden liikkeen kuvittelua luokitteleva, MEG:hen perustuva BCI, jota voidaan myöhemmin käyttää terapeuttisena menetelmänä esimerkiksi aivoinfarktista toipuvien potilaiden kuntoutuksessa. Tutkimuksessa validoidaan terveillä koehenkilöillä tehtyjen MEG-mittausten perusteella koneoppimismenetelmiä, joilla luokitellaan liikkeen kuvittelun aiheuttamaa aivotoimintaa.

Ensimmäisessä osatyössä (Tutkimus I) vertailtiin piirteennirrotusmenetelmiä, joita käytetään erottamaan toisistaan vasemman ja oikean käden kuvittelu sekä liikkeen kuvittelu ja lepotila. Havaittiin, että avaruudellisesti suodatettujen signaalien taajuuskaistan teho luokittelupiirteinä tuotti parempia luokittelutarkkuuksia kuin parietaalisista gradiometreistä mitatut aika-taajuuspiirteet. Lisäksi edeltävä avaruudellinen suodatus paransi aika-taajuuspiirteiden erottelukykä luokittelutehtävissä.

BCI:n opetusdata kerätään yleensä kunkin mittauskerran alussa. Koska tämä voi kuitenkin olla aikaavievää ja uuvuttavaa koehenkilölle, opetusdatana voidaan käyttää myös muilta koehenkilöiltä kerättyjä mittaussignaaleja. Toisessa osatyössä (Tutkimus II) vertailtiin koehenkilöiden väliseen luokitteluun soveltuvia menetelmiä. Tulosten perusteella monitehtäväoppimista ja $l_{2,1}$ -regularisoitua logistista regressiota käyttävä luokittelija oli paras menetelmä koehenkilöiden väliseen luokitteluun sekä MEG:llä että EEG:llä.

Toisessa osatyössä vertailtiin myös samanaikaisesti mitattujen MEG:n ja EEG:n tuottamia luokittelutuloksia, sekä tutkittiin voidaanko passiivisten kädenliikkeiden aikaansaamia MEG-vasteita käyttää liikkeen kuvittelua tunnistavien luokittelijoiden opetukseen. MEG tuotti hieman, muttei merkittävästi, parempia tuloksia kuin EEG. Luokittelijoiden opetus koehenkilöiden omilla tai muiden koehenkilöiden passiiviliikkeillä ei tuottanut hyviä luokittelutarkkuuksia, mikä osoittaa että passiiviliikkeitä ei tulisi käyttää liikkeen kuvittelua tunnistavan BCI:n kalibrointiin.

Työssä esitetyjä menetelmiä voidaan käyttää reaaliaikaisessa MEG-BCI:ssä. Luokittelutuloksia voidaan käyttää vertailukohtana kehitettäessä muita liikkeen kuvitteluun liittyvän MEG-datan luokittelijoita.

Avainsanat magnetoenkefalografia, aivo-tietokone -käyttöliittymä, MEG, liikkeen kuvittelu, sensorimotorinen rytmi

Preface

The work for this thesis was conducted at the Department of Neuroscience and Biomedical Engineering (NBE) of Aalto University School of Science. All measurements were carried out at the MEG Core of the Aalto NeuroImaging infrastructure. My research was financially supported by Emil Aaltonen foundation, and conference travels were funded by the Doctoral Programme Brain and Mind.

First and foremost, I would like to thank professor Lauri Parkkonen for patience and flexibility with regard to this thesis and my scientific work in general. Thank you for all the expert advice and, most importantly, thank you for giving me the permission for writing this thesis.

I thank Dr. Alexandre Gramfort for pre-examination and constructive comments that helped me make minor improvements to this thesis.

I wish to thank Helge Kainulainen, Veikko Jousmäki, Joel Salminen and Janne Peuraniemi for designing and constructing the pneumatic hand stimulators used in Study II. I thank Tuomas Tolvanen, Veikko Jousmäki and Petteri Räisänen for helping me with my countless MEG hardware and software problems, and NBE-IT personnel for dealing with my SSH issues. I want to warmly thank Mia Illman for assistance with the measurements of Study II. I wish to thank Katri Seitsonen and Mari Dagnall for help with the bureaucracy related to the licentiate thesis.

This thesis will be the final step on my path to becoming a certified medical physicist. I'd like to thank all my colleagues at Helsinki University Hospital for teaching, guidance and peer support during recent years.

Last, my family and friends deserve huge thanks for listening to my endless whining about research and work. Special thanks to my dear husband Anton Laitinen for love and support, as well as being a subject in all my experiments and sharing his expertise in clinical neurophysiology.

To be continued...

Helsinki, April 3, 2019,
Hanna-Leena Halme

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List of Publications

This thesis consists of an overview and of the following publications which are referred to in the text by their Roman numerals.

- I** Hanna-Leena Halme, Lauri Parkkonen. Comparing Features for Classification of MEG Responses to Motor Imagery. *PLOS ONE*, 11(12): e0168766, 2016.
- II** Hanna-Leena Halme, Lauri Parkkonen. Across-subject offline decoding of motor imagery from MEG and EEG. *Scientific Reports*, 8(1): 10087, 2018.

Author's Contribution

In both studies, I designed the experiment together with the other author. I implemented the real-time stimulation and analysis system, performed the measurements and analysed the data. I had the main responsibility of writing the manuscripts.

List of abbreviations

BCI	Brain–computer interface
CNN	Convolutional neural network
CSP	Common spatial patterns
EEG	Electroencephalography
ERD	Event-related desynchronization
ERS	Event-related synchronization
FBCSP	Filter bank common spatial patterns
HPI	Head position indicator
ICA	Independent component analysis
LDA	Linear discriminant analysis
MEG	Magnetoencephalography
MI	Motor imagery
M1	Primary motor cortex
MTL	Multi-task learning
OPM	Optically-pumped magnetometer
PAM	Pneumatic artificial muscle
PCA	Principal component analysis
PM	Passive movement
PSD	Power spectral density
SAM	Synthetic aperture magnetometry

List of abbreviations

SQUID Superconducting quantum interference device

SMA Supplementary motor area

SMR Sensorimotor rhythm

SSD Spatio-spectral decomposition

SSS Signal space separation

STFT Short-time Fourier transform

SVM Support vector machine

1. Introduction

Brain–computer interfaces (BCI) translate brain activity in real time into commands for external devices. Noninvasive BCIs have various applications in both basic and clinical neuroscience, including communication and movement assistance devices for disabled people and tools for neurological rehabilitation [1,2]. For example, hemiparetic patients can learn to control an orthosis attached to the paretic hand using motor imagery (MI) and concurrent feedback. Several studies have suggested that this kind of closed-loop feedback training boosts neurological recovery [2–6], albeit most of the studies involve only small groups of patients and no control group. In spite of the substantial advancements in the field during the last decades, there is still need for improvement of both the experimental protocols and usability of BCIs.

Electric brain activity can be measured noninvasively with electroencephalography (EEG) and the corresponding magnetic fields with magnetoencephalography (MEG). During the last decade, MEG has gained attention in the context of BCI and closed-loop neurofeedback studies [7–12]. The advantages of MEG compared to EEG are better signal-to-noise ratio (SNR) and spatial resolution, which are crucial for BCI applications in which the signal is analyzed in real time. Due to these benefits, MEG can be used e.g. to assist the development of eventually EEG-based BCIs. MEG-based BCIs can also be used in basic neuroscientific research.

The core component of a BCI is signal classification, i.e. the automatic detection of predefined brain states, such as motor imagery vs resting state. Machine learning methods are typically employed for this classification task, either in a supervised or unsupervised manner. Regardless of the classification algorithm, successful decoding requires that relevant signal features are extracted from the raw data. Optimal features should accurately discriminate between the brain states of interest and, even more importantly, they should generalize across sessions and subjects in order to enable successful inter-session and inter-subject classification. Feature extraction is an elementary part of a BCI, and selecting optimal features can significantly improve the classification accuracy.

The state-of-the-art BCIs typically require dozens or even hundreds of samples of each subject's neurophysiological signals for training the classifiers to decode the user's brain states with an accuracy exceeding chance level. Due to large inter-subject variability of these signals, user-specific brain responses are usually collected in the beginning of each session for calibrating the BCI. Because of the calibration, the total time spent for each BCI practice session can be quite long. The training can be exhausting for the BCI users, especially for patients suffering from neurological disorders. Therefore, there is a need for robust classifiers that can be trained in advance with other subjects' data and generalized to new subjects. With these generalized classifiers, the laborious BCI calibration session could be omitted.

This thesis presents methods for optimizing the accuracy and usability of MEG-based BCI systems utilizing hand MI. Specifically, methods for feature extraction and inter-subject decoding are considered. The long-term goal of this research is to develop an MEG-BCI that could be used for rehabilitation of hand function after e.g. cerebral stroke.

2. Aims of the thesis

The main goal of this licentiate thesis was to develop an MEG-based MI-BCI and search for solutions to issues related to the usability of noninvasive BCIs. The aims of the thesis were:

- 1.** Finding optimal MEG signal features for within-subject classification of MI (Study I),
- 2.** Validating methods for inter-subject classification of MI (Study II),
- 3.** Comparing MEG and EEG in within- and inter-subject classification of MI (Study II), and
- 4.** Investigating the use of passive movements for training a MI-BCI instead of MI (Study II).

3. Background

3.1 Motor system

The neural structures controlling voluntary movements involve several cortical and subcortical areas as well as peripheral nerves. The primary motor cortex sends movement commands to the peripheral muscles via nerve tracts in the brainstem and spinal cord. The cerebellum and basal ganglia are also involved in movement control, and the motor cortex has reciprocal connections to other regions of the cerebral cortex. Cooperation of many sensory and associative cortical areas is required to perform delicate, coordinated movements.

3.1.1 Motor cortex

The motor cortical areas include the primary motor cortex (M1), the premotor cortex and the supplementary motor area (SMA). M1 is located in the precentral gyrus in the frontal lobe and extends to the central sulcus. M1 sends movement commands to neurons in the corticospinal tract, and is thus involved in initiating voluntary movements. The premotor cortex is located anterior to M1 and is responsible of planning and sensory guidance of movement. SMA is also located anteriorly to M1, and its functions include postural stabilization as well as coordination of bilateral movements and complex movement sequences. In addition, SMA is suggested to play a role in internal generation of movements, i.e. those not triggered by a sensory stimulus. SMA and premotor cortex are adjacent to each other: SMA is located medially and premotor cortex laterally.

The motor cortical areas receive input from the thalamus, mainly the ventral lateral nucleus, and from association areas of the cerebrum. Correspondingly, output signals are sent from the motor cortex to several cortical and subcortical areas. The primary motor cortex is organized such that different muscles are controlled by different parts of M1. The size of

the cortical representation is proportional to the precision of movements performed by the corresponding body part: a larger cortical area allows more detailed control of movements. The representation areas are also slightly different in each individual, depending on the learned motor skills.

3.1.2 Motor pathways

The corticospinal tract originates primarily in M1. Neurons of the corticospinal tract have their cell bodies in the cortex, and the axons descend towards the brainstem and spinal cord, going through the internal capsule and the cerebral peduncle, and further into the brainstem and anterior medulla oblongata. Below that point, most of the axons (about 80%) cross over, or decussate, to the opposite side and form the lateral corticospinal tract, which controls movements of lateral muscles. The anterior tract, containing about 10% of the corticospinal fibers, does not cross over and controls the muscles in the proximal parts of the body. The rest of the corticospinal tract's fibers do not cross over at brainstem, but instead join the lateral tract in the spinal cord. The axons of corticospinal neurons synapse at spinal cord with alpha motoneurons either directly or via interneurons. The alpha motoneurons are connected to skeletal muscles. A single alpha motoneuron and the muscle fibers connected to it form a motor unit.

The anatomy of motor cortical areas and corticospinal tract is illustrated in Fig. 3.1.

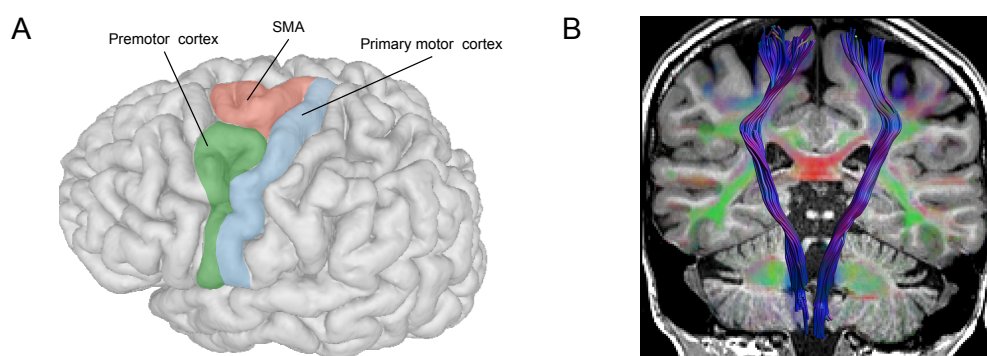


Figure 3.1. Anatomy of the human motor system. A) Motor cortical areas, B) A diffusion tensor image of the corticospinal tract extending from the primary motor cortex (MR tractography of the author's brain, image by V. Sairanen).

3.1.3 Motor cortical plasticity

Neural plasticity refers to the brain's ability to reshape itself in response to environmental and behavioral changes. Plasticity involves e.g. changes in the amount of gray matter in certain brain areas, weakening or strengthening of synapses, or even relocation of entire functional brain areas. Plastic

changes occur throughout life, although some areas remain unchanged after childhood development.

The core principle underlying neural plasticity is Hebbian learning, i.e. the activity-dependency of synaptic connections. The rule often summarized as “neurons that fire together, wire together” does not actually mean that two neurons have to fire action potentials simultaneously – it rather implies that if a presynaptic neuron is repeatedly stimulating a postsynaptic neuron, these two are more likely to form a strong connection. This phenomenon can emerge between multiple neurons as well if the same activation pattern involving several cells is repeatedly fired.

Reorganization and functional changes in the motor system can occur during practising of new motor skills or spontaneously when recovering from neurotrauma [13]. In neurological rehabilitation of the motor system after e.g. cerebral stroke, physical therapy is often exploited to guide the reorganization of the injured brain areas. Motor imagery (MI), i.e. the mental simulation of movements without actually performing them, activates partially the same areas as the execution of the same movements. Thus, plastic changes of the motor cortex can be expected in response to practising MI. However, performing MI without any external feedback can be challenging, and without simultaneous neurophysiological measurements it is impossible for the clinician to observe the patient’s performance. Therefore, MI combined with (noninvasive) measurement of brain activity and real-time activity-induced feedback could be a more engaging and motivating task. Furthermore, the concurrent activation of both motor cortical areas with MI as well as afferent pathways with proprioceptive feedback could re-establish sensorimotor integration.

3.1.4 Sensorimotor rhythms

The sensorimotor rhythm (SMR), also referred to as rolandic mu rhythm, is the oscillatory activity occurring in the primary somatosensory and motor cortices [14]. The rhythm is most prominent during rest, and therefore the oscillations are thought to correspond to idling of the somatosensory and motor cortices [15]. SMR consists of two distinct frequency components in the alpha and beta band, centered at approximately 10 Hz and 20 Hz. The 10-Hz oscillation originates predominantly in the primary somatosensory cortex, whereas the 20-Hz component originates mainly in the primary motor cortex [16]. The center frequencies of these components vary between individuals.

The power of SMR is suppressed (event-related desynchronization, or ERD) primarily during voluntary movements. After termination of movement, SMR power returns back to baseline via a transient rebound (event-related synchronization, or ERS). Besides voluntary movements, SMR modulation is also observed during passive movements and somatosensory

stimulation [17], as well as MI [18–20]. Furthermore, mere observation of movements can affect the modulation of SMR by decreasing the strength of rebound [21]. The resting state power of SMR, as well as the degree of suppression and rebound, can vary substantially between individuals and also as a function of age [22]. SMR modulation can also change in response to motor practice and during neurological recovery; for instance, the rebound of the 20-Hz rhythm has been found to increase during the course of stroke recovery [23, 24].

Representative time–frequency patterns corresponding to SMR suppression and rebound during passive hand movements and hand MI followed by proprioceptive feedback are illustrated in Fig. 3.2. Importantly, the passive movements activate only the alpha-band SMR component (centered at 12 Hz), whereas MI and the corresponding feedback activate both the alpha- and beta-band (centered at 16 Hz) components, shown by a power suppression shortly after the beginning of the epoch. In both cases, SMR rebound is observed after termination of the motor task.

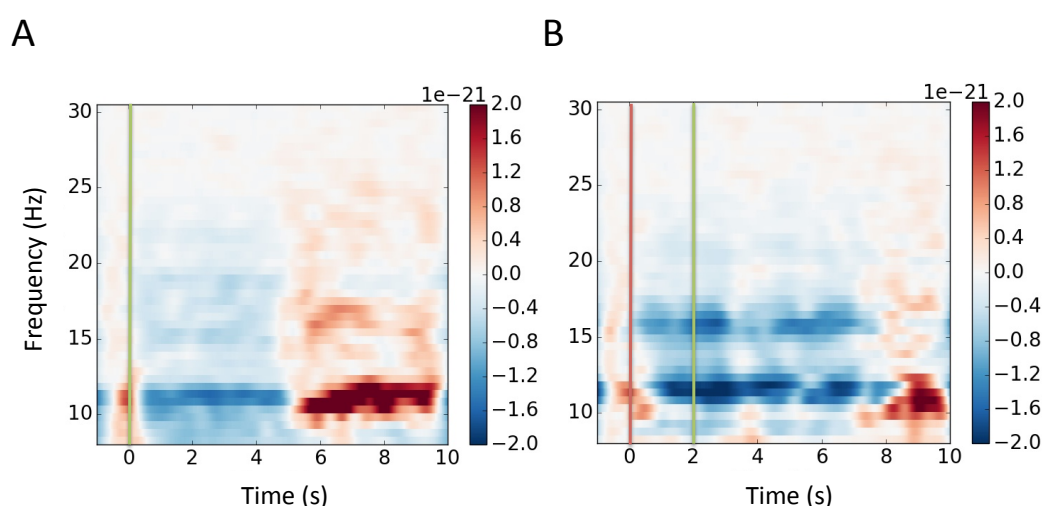


Figure 3.2. The time–frequency plot of SMR modulation measured with MEG during (A) passive hand movements (start indicated by the green line), and (B) hand motor imagery (start indicated by the red line) followed by proprioceptive feedback (green line). The signal is measured from a single subject and averaged over 52 parietal gradiometers and 50 epochs of left- and right-hand activity.

In addition to the approximately 10- and 20-Hz oscillations included in the SMR, the motor cortex is also found to elicit high frequency gamma-band activity. Both low-gamma (30–60 Hz) oscillations [25–29], and transient high-gamma (60–90 Hz) bursts [30, 31] have been found to occur during movements. Also MI can elicit gamma-band activity, as shown by Miller and colleagues in an electrocorticography study [32]. They found that high-gamma power is increased in a similar manner both during movements and MI, and that the gamma-band activity is more localized in

the cortex than the suppression of SMR.

3.2 Magnetoencephalography

Magnetoencephalography (MEG) measures noninvasively the magnetic fields generated by electrical brain activity [33]. The first MEG signal was measured in 1968 with a single induction coil [34]. Later, superconducting quantum interference devices (SQUID) became the state-of-the-art MEG sensors. First whole-head SQUID array was developed in the 1990's [35], and nowadays most commercial MEG devices involve a sensor helmet covering the whole head with hundreds of SQUID sensors. Quite recently, optically-pumped magnetometers (OPM) [36] have been developed in order to overcome certain limitations of SQUIDs.

One of the advantages of MEG compared to other neuroimaging methods is excellent temporal resolution, which allows capturing brain dynamics even in sub-millisecond scale. Another benefit of MEG is spatial resolution superior to that of EEG due to the fact that magnetic fields are not distorted by the high conductivity difference of skull and scalp.

3.2.1 Signal generation

The neurophysiological signal measured by MEG is mostly generated by synchronous activity of cortical pyramidal neurons. Signals in neurons are conveyed via action potentials, which are triggered when the membrane potential exceeds a certain threshold, resulting in depolarization. When the action potential in a presynaptic neuron reaches a synapse, neurotransmitters are released into the synaptic cleft. The neurotransmitters bind to the receptors of the postsynaptic neuron, which results in opening of ion channels and subsequent change of the membrane potential, i.e. depolarization or hyperpolarization depending on the neurotransmitter. The change of potential at the postsynaptic cell membrane causes a graded postsynaptic potential along the dendrite, and related intracellular current.

In a presynaptic axon, the intracellular currents associated with action potential flow in opposite directions and thus the generated magnetic fields cancel each other out. In addition, the extracellular electric and magnetic fields generated by the action potential attenuate rapidly as a function of distance, and therefore are not detectable outside of the head. In the postsynaptic dendrite, the intracellular current flows in one direction, thus producing a magnetic field that can be measured outside the cell. In addition, currents related to postsynaptic potentials are slower than those related to action potentials and therefore easier to measure. The MEG signal reflects the net magnetic field of tens of thousands of postsynaptic currents. MEG is most sensitive to currents oriented parallel to the scalp,

corresponding to the current sources in the walls of sulci where apical dendrites are positioned tangential to the scalp [37].

3.2.2 Physics and instrumentation

The strength of magnetic fields measured by MEG is typically 100-500 fT, being orders of magnitude weaker than Earth's magnetic field. Therefore, in order to detect the neural signals and avoid interference from external sources, the measurements must be conducted with highly sensitive sensors in a magnetically shielded room. The SQUIDs are kept below critical temperature by embedding them in a large dewar containing liquid helium for maintaining superconductivity.

In SQUID-MEG, magnetic fields are picked up by flux transformers, which can be configured as magnetometers or gradiometers. A magnetometer comprises a single coil which measures the magnetic flux component perpendicular to its surface. A gradiometer measures the magnetic flux difference, or gradient, between its two loops, which can be arranged along the same radial axis (axial gradiometer) or in the same plane as a figure-of-eight shape (planar gradiometer). Magnetometers are sensitive to both deep and superficial sources, whereas gradiometers are most sensitive to nearby superficial sources and their sensitivity decreases rapidly as a function of distance. On the other hand, gradiometers often have better signal-to-noise ratio [37].

The measured magnetic field induces a current in the flux transformer circuit. This current is further converted into magnetic flux through the SQUID loop. The SQUID converts the flux to a voltage, which is amplified and digitized.

In this thesis, the MEG measurements were conducted using Elekta Neuromag Vectorview device (Elekta Oy, Helsinki, Finland), comprising 102 magnetometers and 204 gradiometers arranged in a helmet-shaped array as elements consisting of two planar gradiometers and one magnetometer. In both studies, only the signals from the gradiometers were utilized in the analyses.

3.2.3 Data analysis

A crucial part of MEG analysis is reduction of artifacts originating from both the subject and environment. A powerful method for artifact removal is signal space separation (SSS) [38], which is based on separation of signal and noise subspaces by utilizing the physical properties of the magnetic fields. SSS is particularly well suited for suppressing signals from sources outside of the head. Interference related to physiological processes, such as cardiac and muscle artifacts as well as eye blinks, cannot be suppressed by magnetic shielding, and usually not even with SSS. Thus, they have to

be eliminated by other means. An effective way to suppress artifacts is to decompose the multi-channel signal into additive subcomponents with e.g. principal component analysis (PCA) or independent component analysis (ICA) and omit the artifactual components.

In order to increase the SNR, the raw MEG data can be filtered before further analyses. It is usually appropriate to band-pass filter the signals such that only the frequencies corresponding to the neural activity of interest are included in the passband.

Another approach to increase SNR is spatial filtering, i.e. creating linear combinations of the sensor-level signals such that the SNR of the signal of interest is maximized. Supervised machine learning methods, such as common spatial patterns (CSP) and linear discriminant analysis (LDA), can be used to project the data such that they most effectively discriminate between the classes of interest.

If the location of the signal source of interest is known in advance, beamformers [39] can be used to suppress activity originating outside that source. A beamformer is based on a spatial filter that selectively blocks the contributions from all other sources except the predefined source. For calculation of beamformers, also the estimate of the data covariance matrix is required.

In most offline analyses, SNR is further increased by averaging over epochs. It is assumed that noise is uncorrelated with the signal, and thus averaging multiple stimulus-time-locked responses will reduce the effect of noise and thus make the neural response more discernible. However, in real-time signal analysis averaging is not feasible since it would increase the latency of feedback. Furthermore, in the analysis of SMR modulations averaging in time domain should not be done, since the rhythms are not phase-locked to external events and averaging would distort the phase and amplitude information of SMR. Instead, averaging in frequency or time–frequency domains can reveal SMR modulation over epochs, sessions and subjects.

3.3 Brain–computer interfaces

Brain–computer interfaces (BCI) are systems in which the user’s brain activity is measured in real time and utilized to control an external device or to provide feedback. These closed-loop systems have a variety of applications from pure entertainment to basic neuroscience and clinical interventions. During the last decades, the computing power and measurement technology have developed sufficiently to enable robust real-time signal analysis and translation into meaningful feedback for the user.

The setup of a BCI varies greatly depending on the application, but in general all BCI systems consist of the following elements: 1) signal

acquisition, 2) signal processing, 3) interpretation of the ongoing signal, and 4) feedback for the user. Parts 2) and 3) may involve feature extraction and classification using various machine learning methods, and in some cases they can be combined. As the recorded signals are usually high-dimensional, many BCI applications involve some form of dimensionality reduction in the signal processing phase.

BCIs can be designed as permanent neuroprostheses, usually involving electrodes implanted on the cortical surface, or noninvasive rehabilitation tools, in which the neural signals are measured from head surface. It is important to make a distinction between these two types of BCI; the former replace the lost brain functions by bypassing the damaged brain areas, whereas the latter aim at recovery of the neural pathways via training and activity-induced brain plasticity. In this thesis, the focus is solely on the noninvasive, rehabilitative BCIs.

3.3.1 BCIs based on motor imagery

The modulation of SMR in response to MI has inspired the development of MI-based brain–computer interfaces. The core idea of MI-BCIs is that users who have lost the ability to perform voluntary movements can control the interface by performing MI, and successful SMR modulation is rewarded with appropriate feedback.

In the early days of SMR-based BCIs, the level of SMR suppression was calculated from EEG signals and linearly translated to e.g. movement of a cursor on a screen [40, 41]. The subjects could thus learn to modulate their SMR via operant conditioning. However, this straightforward approach was problematic because the SMR varied substantially between measurement sessions, and minor power changes were easily masked by noise, which made the learning process difficult for the user.

In order to overcome this issue, the next generation of MI-BCIs relied on machine learning and automatic classification algorithms. In these approaches, the classifiers are trained such that the subject performs the requested task, e.g. left- and right-hand MI, in a calibration session, and the parameters of the classifier are adjusted in accordance with the subject’s individual task-specific signal features.

3.3.2 Common spatial patterns

A popular method for reducing the dimensionality of multi-channel signals is spatial filtering, i.e. weighting of signals measured at different locations such that the difference between two classes is maximized. Common spatial patterns (CSP; [42]), based on simultaneous diagonalization of two covariance matrices, has for some years been more or less the state-of-the-art spatial filtering technique in two-class EEG classification. Using

the training data, CSP computes a set of spatial filters that maximize the variance for signals in one class and minimize it for the other class. The method is described in detail below.

First, the covariance matrices for two signals \mathbf{X}_1 and \mathbf{X}_2 , corresponding to two classes, are computed:

$$\mathbf{R}_1 = \frac{\mathbf{X}_1 \mathbf{X}_1^\top}{t_1} \quad (3.1)$$

$$\mathbf{R}_2 = \frac{\mathbf{X}_2 \mathbf{X}_2^\top}{t_2} \quad (3.2)$$

where t_1 and t_2 are the numbers of time points in \mathbf{X}_1 and \mathbf{X}_2 , respectively. CSP finds eigenvector \mathbf{w} such that the ratio of variances is maximized:

$$\mathbf{w} = \underset{w}{\operatorname{argmax}} \frac{\|\mathbf{w} \mathbf{X}_1\|^2}{\|\mathbf{w} \mathbf{X}_2\|^2} \quad (3.3)$$

The simultaneous diagonalization of the two covariance matrices is done by finding eigenvectors of \mathbf{R}_1 and a corresponding diagonal matrix of eigenvalues \mathbf{D} , sorted in decreasing order such that \mathbf{w}^\top is the first column of \mathbf{P} and following equations hold:

$$\mathbf{P}^{-1} \mathbf{R}_1 \mathbf{P} = \mathbf{D} \quad (3.4)$$

and

$$\mathbf{P}^{-1} \mathbf{R}_2 \mathbf{P} = \mathbf{I}_n \quad (3.5)$$

where \mathbf{I}_n is the identity matrix.

The original signals are projected, i.e. multiplied with these filters, typically using the two largest and two smallest eigenvectors in \mathbf{P} . Thereafter, the band powers of the filtered signals are usually averaged, log-transformed and classified using e.g. linear discriminant analysis (LDA) or support vector machine (SVM).

The downside of CSP and other spatial filters is that the frequency band and time window for the signal of interest have to be predetermined. Thus, it is not very robust to subtle variations in task-specific parameters, let alone to outliers or extremely noisy trials. Some modifications are developed in order to increase the robustness of CSP, such as filter bank CSP (FBCSP; [43]) and common spatio-spectral patterns (CSSP; [44]). Furthermore, EEG and MEG classification based on Riemannian geometry has been suggested as an alternative for CSP-based methods [45–47].

3.3.3 Inter-subject decoding

The aforementioned subject-specific BCIs require large amounts of neurophysiological data from each user for training the classification algorithms

to decode the user's brain states. Due to substantial inter-subject and inter-session variability of these data, the common approach is to collect user-specific brain responses in the beginning of each session for calibrating the BCI. Therefore, the total calibration time per subject can be significant, which makes the calibration process exhausting especially for patients recovering from neurotrauma. In addition, when employing neurofeedback for rehabilitation, the feedback should drive brain activity towards that of a healthy brain and not reinforce the prevailing pathological state as a patient-specific BCI might do. In order to overcome these issues, several research groups have developed inter-subject-generalized classifiers [48–52]. With such an approach, the classifier can be trained in advance using other subjects' data and a new BCI user can begin the BCI practice immediately without the initial calibration session, which saves both time and effort of the patients.

Successful inter-subject classification requires that globally relevant signal features are extracted from each training subject. Multi-task learning (MTL; [53, 54]) aims at selecting a few relevant features from a large feature set such that these features are shared across multiple related tasks; in the case of BCI training, the tasks are usually measurements from different subjects. MTL is beneficial for learning problems in which the number of samples is much lower than the number of features, since it effectively reduces the dimensionality of the feature space. In addition, MTL finds a sparse feature set that is correlated across tasks instead of optimizing features for each individual task, which makes the method robust to outliers. In case of inter-subject classification, MTL considers decoding of each subject's data as a separate task. In contrast to data pooling, MTL does not assume equal distributions for all training data, which allows variability between subjects.

Logistic regression with $l_{2,1}$ -norm regularization is found to be efficient for selecting a small number of relevant features from a high-dimensional feature space shared across subjects [55]. Already in 2010, Alamgir and coworkers showed the efficacy of this method in multi-subject EEG-BCI [48]. Recently, MTL based on logistic regression regularized with $l_{2,1}$ -norm minimization was successfully used for inter-subject classification of MEG signals [56].

The optimization problem for $l_{2,1}$ -norm regularized MTL can be formulated as:

$$\min_{\mathbf{W}, \mathbf{c}} \sum_{i=1}^t \sum_{j=1}^{n_i} \log(1 + \exp(-Y_{i,j}(\mathbf{W}_i^\top X_{i,j} + \mathbf{c}_i))) + \rho \|\mathbf{W}\|_{2,1} \quad (3.6)$$

where $X_{i,j}$ is sample j of the i th task, $Y_{i,j}$ denotes the corresponding label (-1 or 1), \mathbf{W}_i and \mathbf{c}_i are the model for task i , parameter ρ controls the

sparsity of the feature space and $\|\mathbf{W}\|_{2,1}$ is the $l_{2,1}$ -norm of \mathbf{W} :

$$\|\mathbf{W}\|_{2,1} = \sum_{j=1}^{n_i} \|\mathbf{W}_{j,:}\|_2 \quad (3.7)$$

During recent years, convolutional neural networks (CNN) have been studied in classification of MI-related EEG [57, 58] and MEG [59] signals. Regarding the SMR-based BCIs, CNNs provide several advantages compared to traditional classification methods. First, whereas CSP and logistic regression can (without further extensions) only discriminate between two classes, CNNs are able to perform multi-class decoding. Second, CNNs are usually more robust to measurement noise and intra- and inter-subject variations, thus providing better generalization than other types of classifiers. The downside of CNNs is the requirement of large amounts of training data, while the number of training samples from each user is typically limited in traditional BCI paradigms. However, CNNs are well suited for inter-subject learning, which allows using large databases of previously recorded signals and thus omitting the collection of training data from each user. Deep learning in general has gained increased interest in BCI research over the last years, and many studies demonstrate improved decoding accuracy using deep learning compared with other machine learning methods (for MI-BCI applications, see e.g. [60, 61]; for a comprehensive review about deep learning for EEG, see [62]). Besides these complex machine learning methods, Riemannian geometry has been successfully used for inter-subject classification [63].

3.3.4 Clinical applications

Regarding the clinical applications of MI-BCI, the benefit of BCI-based motor function rehabilitation is that the repeated feedback training can induce brain plasticity via simultaneous activation of both afferent and efferent pathways. In contrast to the traditional physiotherapy, which relies mostly on passive manipulation of the paretic limbs, BCI therapy engages the patient's own top-down modulation of motor activity. The voluntary activation of motor cortex together with tactile or proprioceptive feedback "closes the sensorimotor loop" [64], which is fundamental to the sensorimotor integration and eventual reorganization of the injured motor cortical areas.

There is evidence that BCI therapy improves motor function [3–6], but further evidence about its long-term clinical effect is still needed. In addition, certain recovery-related neurophysiological phenomena should be taken into account while designing rehabilitative BCIs. Many stroke patients with motor disabilities have difficulties in modulating SMR in the affected hemisphere. Instead, the unaffected hemisphere shows increased motor-related activity due to reduced intracortical inhibition. Therefore,

discriminating between MI and resting state is not necessarily an optimal goal for a rehabilitative BCI, since the activity in the unaffected hemisphere can be erroneously recognized as activity of the target area. As a result, neural plasticity during recovery might only enhance the activity of the healthy motor cortex and thus result in decreased functionality of the affected limb. Decoding left- vs right-hand MI instead of MI vs rest is a better option, since it encourages the user to produce SMR modulation with motor areas in the affected hemisphere.

3.3.5 MEG in BCI research

To date, a vast majority of noninvasive BCIs involves EEG as the measurement method. However, MEG has recently gained interest in the context of BCI as it is well suited for closed-loop experiments [65]. In fact, several groups have developed real-time signal processing [66, 67] and artefact removal [68] methods specifically for MEG with regard to possible usage in closed-loop paradigms. A number of studies have also investigated the feasibility of MEG in real-time neurofeedback experiments [7–12, 69–71]. According to these studies, both sensor- and source-level MEG can be used for providing the user with feedback that is used for modulating his/her brain activity. Indeed, the high temporal and spatial resolution of MEG make it inherently suitable for real-time measurements.

Although MEG outperforms EEG in terms of SNR and spatial resolution, certain technical challenges are specifically emphasized with MEG-BCIs. One of these issues is head position: changes in the position of the subject's head and thus the signal sources with respect to the sensor array might impair the real-time signal decoding. The reason for this effect is that classifiers optimized for a certain fixed head position cannot accurately decode signals measured with a different head position. Even BCIs trained and tested with the same subject may therefore yield poor results, especially if the subject is removed from MEG between the training and testing sessions. Head position is not as critical for EEG, because the electrodes are attached to the scalp, in contrast to the helmet-like MEG sensor array. This difference between modalities should be considered when designing BCI studies, as the decoding methods well suited for EEG might not yield as good results with MEG. Changes in head position in MEG should be either corrected online, or taken into account by designing classifiers that are robust to small head movements. In the future, OPMs [72], already available as multi-channel arrays [73–75], might solve this problem and additionally improve SNR as the sensors are placed on scalp.

Portability, low price and better availability are common reasons for preferring EEG over MEG in BCI applications. Nevertheless, MEG-based BCIs have been studied in post-stroke motor function rehabilitation [8, 12], and the results suggest good usability of MEG in clinical studies.

Furthermore, the neurophysiological effects of long-term BCI training, such as changes in functional connectivity, can be more reliably estimated using MEG. Studies by Fukuma and coworkers [70, 71] suggest that MEG-BCI can be also used to evaluate whether a patient would be able to control an invasive neuroprosthesis. Besides clinical applications, real-time MEG analysis and closed-loop feedback experiments have wide potential in basic neuroscience. MEG-based BCIs can also assist the development of eventually EEG-based BCIs.

4. Methods

This thesis comprises two studies on healthy participants. Both studies were approved by the Aalto University Research Ethics Committee. The research was carried out in accordance with the guidelines of the Declaration of Helsinki, and all subjects gave written informed consent prior to the measurements.

4.1 Measurements

In both studies, MEG was recorded with a 306-channel Elekta Neuromag Vectorview (Elekta Oy, Helsinki, Finland) located at the MEG Core of Aalto Neuroimaging, Aalto University. During signal acquisition, the signals were filtered to 0.1–330 Hz and digitized at the rate of 1 kHz. Four head-position indicator (HPI) coils were attached to the subject’s scalp for head position estimation and alignment to a common coordinate frame. The visual cues and feedback were delivered on a screen located approximately 1 m in front of the subject’s eyes by a projector outside the shielded room. During the recording, the raw MEG data were continuously written in 300-ms segments to a network-transparent rtMEG ring buffer [66, 76] hosted by the MEG acquisition workstation (6-core Intel Xeon CPU at 2.4 GHz, 64-bit CentOS Linux, version 5.3). This buffer was read over a local network connection by another computer (64-bit Ubuntu Linux, version 12.04-LTS), which processed the data in real time using functions implemented in the MNE-Python [77] software and presented the visual stimuli using PsychoPy [78] version 1.83.

In Study II, EEG was measured simultaneously with MEG using an MEG-compatible cap with 60 electrodes. EEG was used only in offline analyses, and the real-time feedback was determined using MEG signals only.

The measurement setup is illustrated in Fig. 4.1.

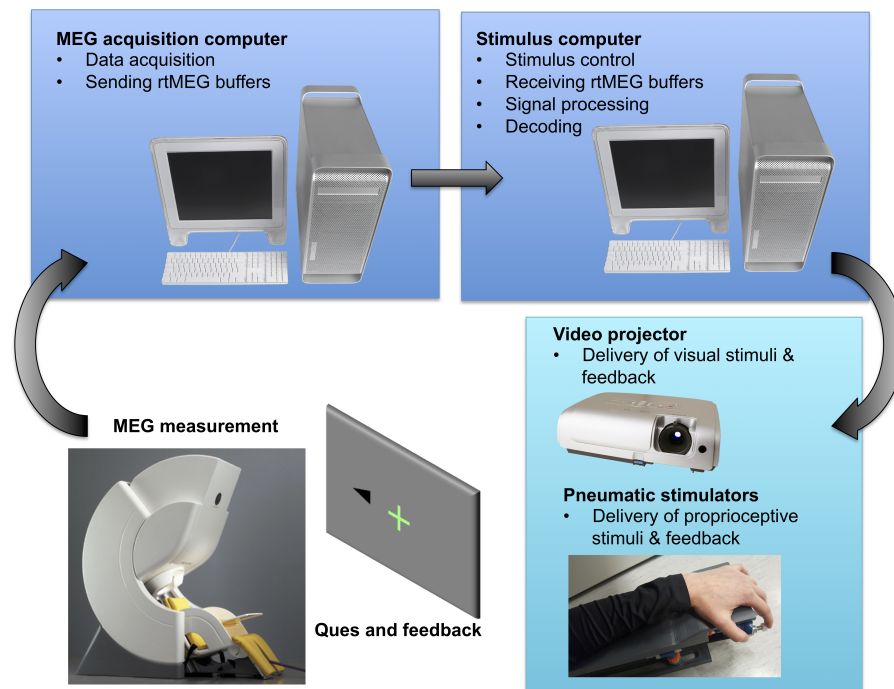


Figure 4.1. The setup for real-time MEG experiments.

4.2 Pneumatic hand stimulators

The proprioceptive stimulators used in Study II consisted of two plastic frames supporting each hand, and of 8 elastic pneumatic artificial muscles (PAM; DMSP-10-100 AM-CM, diameter 10 mm, length of the contracting part 100 mm; Festo AG & Co, Esslingen, Germany) attached to fingers 2–5 of both hands with tape. During the experiment, the subject's hands and arms were resting on the plastic frames, and the PAMs were touching the fingertips horizontally from beneath the frame. The PAMs were connected to the frame via moving hinges, so that the stimulator system could be adjusted to fit the subject's hand.

During the stimulation paradigm, the PAMs produced horizontal movements according to the internal air pressure (max 4 bar). The pressure to each PAM was switched on and off by a solenoid valve (SY5220-6LOU-01F-Q, SMC Corporation, Tokyo, Japan) controlled by trigger pulses. The valves were placed outside the magnetically shielded room, and 3.5-m long semi-elastic tubes (internal diameter 2.5 mm) conveyed the pressurized air to the PAMs. A computer controlled the valves such that all the four PAMs for either left or right hand contracted sequentially (each for 500 ms) at intervals of 500 ms and flexed the fingers. After the contraction, each PAM returned to its resting length and extended the corresponding

finger, returning it back to the initial position. This four-finger movement sequence was repeated twice during each epoch.

The stimulator for one hand is shown in Fig. 4.2.

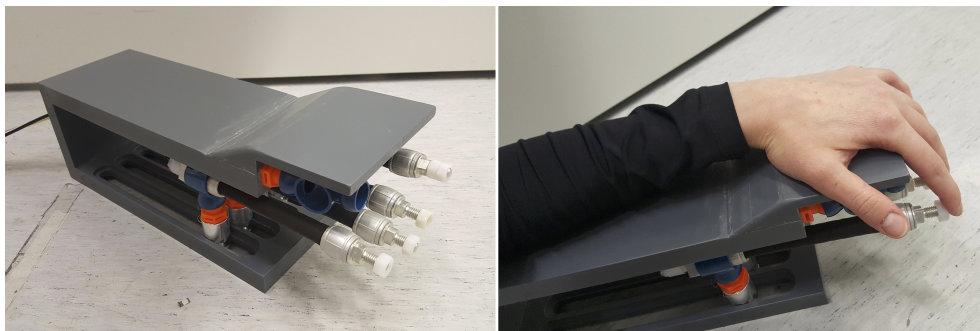


Figure 4.2. Pneumatic stimulator.

4.3 Data preprocessing

In both studies, before offline analyses the MEG data were preprocessed with MaxFilter [38], involving removal of bad channels, signal space separation, and head position transformation into the default position and orientation. Only signals from gradiometers were retained for further analysis. In the online analyses, the signals were split to epochs of 3 (Study II) or 4 seconds (Study I) and filtered to 8–30 Hz.

In Study II, EEG was referenced to the common average.

5. Summary of studies

5.1 Study I

Motivation

In Study I, we evaluated several feature extraction methods for discriminating 1) left- and right-hand MI, 2) MI and rest. The aim was to find features that are both discriminative and fast to compute, and thus usable in a real-time MEG-based BCI.

Methods

The study involved nine healthy volunteers (5 females, 4 males, age 25.8 ± 1.4 yrs, all right handed by self-report). None of the subjects had previous experience in BCI training.

In the experimental paradigm, the task was to imagine finger tapping with either left or right hand, directed by visual cues. An online classifier was trained with the first 40 epochs and tested with the following 40 epochs, during which the subjects received feedback. For the online feedback, power spectral densities in 8–30 Hz were calculated over the 3-s MI epoch and 64 parietal gradiometers, and 50 most relevant features were retained for classification with LDA. After MI, visual feedback presenting a hand grasp was shown. The feedback was graded with 20 levels between a resting open hand and a fully closed fist, based on a linear transformation of the classification probability, and it was given separately for the left and right hand. The experimental paradigm is illustrated in Fig. 5.1.

As most of the subjects did not achieve good (>70%) online decoding accuracy, we performed an offline analysis to find more efficient decoding methods. The evaluated features were power spectral density (PSD), Morlet wavelets, short-time Fourier transform (STFT), common spatial patterns

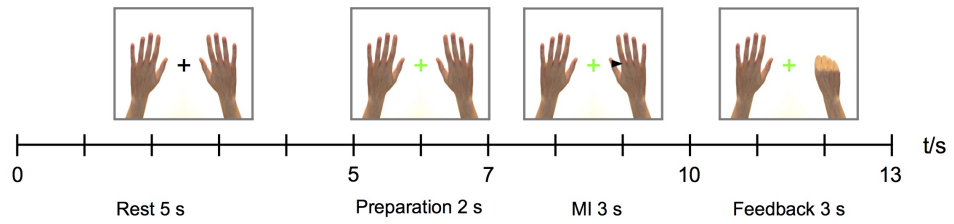


Figure 5.1. Stimulus paradigm.

(CSP), filter bank common spatial patterns (FBCSP; [43]), spatio—spectral decomposition (SSD; [79]), and combinations of SSD+CSP, CSP+PSD, CSP+Morlet, and CSP+STFT. In addition, we compared four classifiers applied to single trials using 5-fold cross-validation for evaluating the effect of classification algorithm to decoding performance.

Results & conclusions

We found that the combination of SSD and CSP filters yielded the best accuracy in both left vs right (mean 73.7%) and MI vs rest (mean 81.3%) classification. The combination of SSD and CSP outperformed other popular decomposition methods (CSP and FBCSP) in both left vs right and MI vs rest classification. CSP has been found efficient for discriminating single-trial MI patterns in EEG, and our results agreed with these findings, since CSP alone yielded accuracies above chance level. However, adding SSD filtering prior to CSP improved the classification. The increase in classifier performance was most likely due to decreased overfitting compared to CSP alone. The reasonable performance of SSD+CSP on both left vs right and MI vs rest indicates the flexibility of the method in discriminating the relevant oscillatory activity from noise.

There were large inter-subject differences in classification accuracy; some subjects barely got over chance level accuracies whereas others yielded over 85% regardless of the extracted features. The level of beta-band suppression correlated significantly ($p=0.037$) with the subjective MI vs rest accuracy. On the contrary, no correlation between suppression in either alpha- or beta-band and left vs right classification was found.

5.2 Study II

Motivation

The main motivation for Study II was to improve the BCI usability by developing a BCI that requires zero training data from the user. Furthermore, in many clinical studies the training data is collected from the patients

whose brain function is severely disturbed, and the BCI is trained to recognize and reward this activity. Although this kind of protocol might lead to improved BCI performance over time, it does not necessarily support recovery of neurotrauma since the patient is guided to enhance the disturbed brain activity. Therefore, a BCI trained with healthy participants' data might better guide the patient to achieve normal brain function.

Methods

We evaluated methods for inter-subject decoding of MI from MEG and EEG in healthy people. In addition, we compared the decoding performance of simultaneously recorded MEG and EEG. Furthermore, as it has been suggested that responses to passive movements (PM) could be used for training an MI classifier [80], we also examined whether training with other participants' PM data yields results similar to those obtained by training with MI.

Eighteen healthy volunteers (5 males, 13 females, age 27.7 ± 5.0 y, 3 left-handed by self-report) were recruited for Study II. Two of the subjects had participated in Study I, and the others had no previous BCI experience. The experimental protocol consisted of 80 PM and 80 MI epochs, both involving 40 left- and right-hand epochs. The online classifier was trained by each subject's own PM. The PM and proprioceptive feedback in the MI task were delivered via the pneumatic stimulators. In the MI task, feedback was elicited only when the online classification result was consistent with the target; otherwise, the stimulators did not move.

The decoding accuracy was evaluated offline using 1) MI and 2) PM as training data, separately for MEG and EEG. The evaluated decoding methods were based on either 1) CSP combined with linear discriminant analysis (LDA) classifier, or 2) logistic regression with $l_{2,1}$ - or l_1 -norm regularization. For the CSP-based methods, the following approaches (abbreviation in parentheses) were used for decoding:

- CSP, classification with LDA (CSP+LDA)
- CSP, classification with bootstrap aggregating & LDA (CSP+bagging)
- Regularized CSP, classification with LDA (regCSP)

Inspired by the results of Study I, we used SSD for dimensionality reduction prior to CSP in order to improve classification performance, and preliminary tests proved that SSD indeed yielded better accuracy than CSP alone.

The functions included in MTJFL [56] and MALSAR [81] Matlab toolboxes were modified and used for the logistic regression –based methods. The following approaches, implemented in the MTJFL toolbox, were used for decoding:

- Pooling with logistic regression and l_1 -norm regularization (pooling)
- MTL with logistic regression and l_1 -norm regularization (L1-MTL)
- MTL with logistic regression and $l_{2,1}$ -norm regularization (L21-MTL)

In addition, we calculated the accuracies for within-subject decoding for comparison with the inter-subject decoding results. In this case, each subject's own PM or MI data were used for training. PM training for MEG was tested in the online BCI paradigm using CSP+LDA. For EEG, similar PM training paradigm was conducted for the offline data.

Results

The online accuracy was below the sample-size-adjusted chance level of 58.7% [82] for 7 subjects. However, as the online decoding was done with PM training, we assumed these results probably did not reflect the robustness of MI or the ability to perform MI. Therefore, the decoding accuracy was also calculated offline with MI training in order to evaluate the individual MI performance. The mean accuracy for each subject was calculated as the average of online and offline within-subject accuracies. Five subjects with the lowest mean accuracy were discarded from the training data in further analyses, i.e. the poorly performing subjects were used only for testing the decoders.

When the classifiers were trained with MI, the best inter-subject mean accuracies of 70.6% for MEG and 67.7% for EEG were obtained with L21-MTL. For MEG, also pooling and L1-MTL yielded above chance level results (66.5% and 67.8%, respectively). For EEG, L1-MTL yielded an average accuracy significantly better than chance ($p=0.01$).

In contrast, training with passive movements was not successful. For all subjects, the online within-subject MEG decoding yielded an average accuracy of only 62.8%, compared to 75.0% with MI training. For EEG, the difference was not that clear: the offline within-subject decoding resulted in an average accuracy of 66.8%, compared to 69.3% with MI training. For both MEG and EEG data, none of the inter-subject methods yielded accuracies significantly above chance level.

The results are summarized in Fig. 5.2.

Conclusions

The accuracy of L21-MTL was better than that of the other inter-subject decoding methods both for MEG and EEG data, when other subjects' MI was used for training. In addition, with this method we achieved accuracies significantly above chance level for both modalities. As the method is rather simple and fast to calculate, it can be applied to online BCI paradigms.

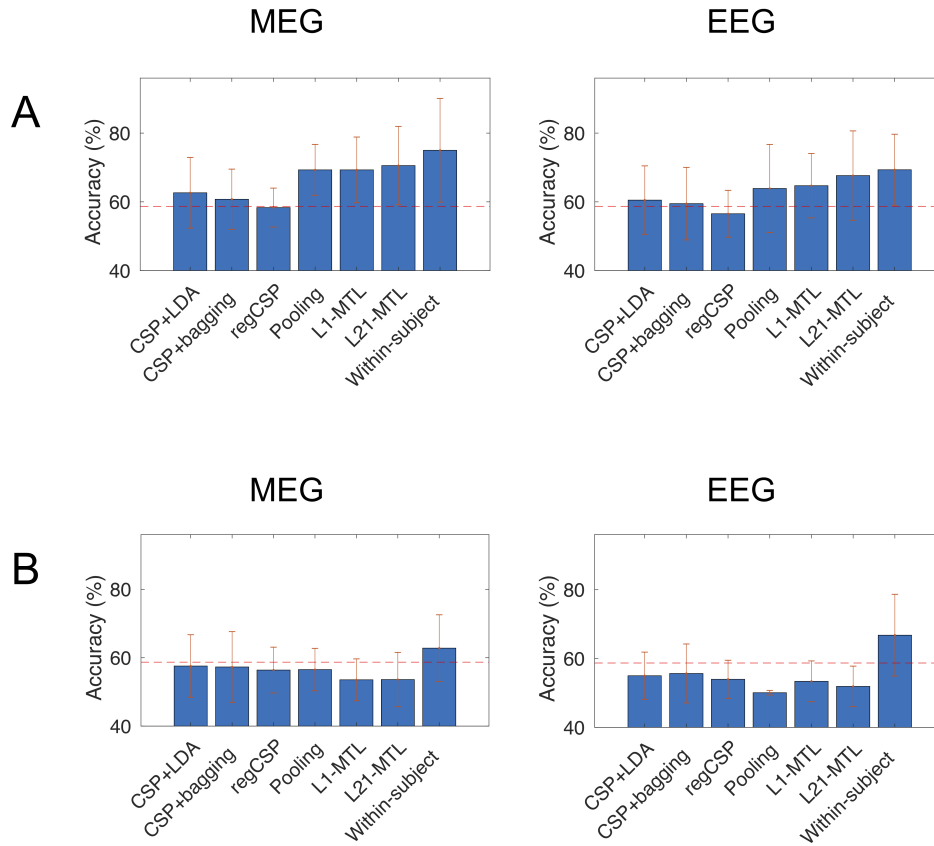


Figure 5.2. Classification results for (A) Motor-imagery-trained MEG and EEG, (B) Passive-movement-trained MEG and EEG. The chance level is indicated with a dashed line. Error bars represent the standard deviation.

However, further optimization of the decoder parameters should be done before using the approach in clinical BCI applications.

Besides the average accuracy across subjects, it should be validated how inter-subject decoding affected the performance of individual subjects. Many subjects showed poor performance during the online BCI task, when the decoder was trained using their own PM data. By using the subject's own MI data and cross-validation, the accuracy was improved for most of the poor online performers. However, some subjects have poor decoding performance simply because of insufficient SMR modulation. For example, Subjects 3 and 5 did not show any discernible SMR modulation during MI, and their accuracy remained under chance level even when their own MI was used for training. In case of the mentioned subjects, inter-subject decoding did not remarkably improve the results. On the contrary, for Subjects 11, 12 and 14, L21-MTL yielded better results with MEG (also with EEG for Subjects 11 and 14) compared to within-subject L1. In

conclusion, inter-subject decoding might improve the accuracy of poorly performing subjects.

Training the classifiers with PM resulted in poor accuracy with all decoders and both MEG and EEG, even in within-subject decoding. With regard to this finding, it can be argued that in inter-subject learning the performed mental task should be as similar as possible for the train and test subjects.

6. Discussion

6.1 Feature extraction for within-subject decoding

In Study I, we evaluated methods for decoding left- and right-hand MI using each subject’s own data for training and testing. The results showed that spatial filtering methods in general outperformed time–frequency methods in both left-vs-right and MI-vs-rest classification. In addition, CSP filtering improved the discrimination capability of time–frequency domain features. Among the evaluated methods, the best results were obtained with the combination of SSD and CSP, which outperformed other signal decomposition methods (SSD, CSP and Filter-Bank CSP) in both left vs right and MI vs rest classification.

As has been shown by Blankertz and colleagues [83], CSP is an efficient method for extraction of variance differences between two classes, and a prior linear decomposition does not add any new information to that. The increase in classifier performance was probably due to decreased overfitting compared to CSP alone, as suggested by Haufe and coworkers [84], or improved signal-to-noise ratio because of spectral filtering.

In Study I, CSP or FBCSP did not yield the best average classification results among different methods, unlike in many EEG-BCI studies. This could imply that CSP, which is effective for EEG decoding, is perhaps not an optimal filter for MEG data. MEG is more high-dimensional than EEG, and head movement causes uncertainty in spatial filter optimization, as the most discriminative channels might change between trials and sessions. Thus, for reliably estimating CSP filters one should either have a large amount of training data or reduce the data dimensionality prior to CSP, as we have done here.

In Study II, we obtained reasonably good results for within-subject MI decoding using amplitude features and l_1 norm regularized logistic regression for decoding and MI data for training. On the contrary, training the classifier with each subject’s own passive movements and testing with MI

was not successful. Our results were contradictory to those obtained by Kaiser and coworkers [80], who trained classifiers with active and passive movements and tested them with MI. A plausible reason for this discrepancy is that they decoded rest vs MI and not left vs right MI. Furthermore, the data dimensionality in the mentioned study was much lower than in our case, as only 15 EEG channels were used for measuring activity over contralateral motor cortex. Thus, the MEG data probably resulted in overfitting when the classifiers were trained with PM. The activation patterns of MI and PM are slightly different, as PM mainly activates the somatosensory cortex and MI the primary motor cortex. Furthermore, PM might cause more bilateral SMR suppression compared to MI [85, 86], which would explain why the hemispheric difference was not sufficiently learned from PM data.

6.2 Methods for inter-subject decoding

Several methods for inter-subject decoding were evaluated in Study II. According to the results, classification with multi-task learning based on logistic regression and l_1 - or $l_{2,1}$ -norm regularization yields fairly good inter-subject decoding accuracy, and the mean accuracy was comparable to that of within-subject decoding. On the contrary, CSP and its generalized variations did not work very well in this context, despite good classification results obtained in previous EEG studies involving inter-subject classification [87]. Again, the high data dimensionality and variation in head position in MEG cause overfitting of CSP. These findings suggest that CSP is not a robust enough method for decoding MI from MEG data.

Decoding MI-related brain activity across subjects is a challenging task due to the wide variety of SMR strength, modulation level, latency and location between subjects. Especially if the dataset contains subjects with poor SMR modulation, inter-subject decoding might not even be feasible. Therefore, in order to calibrate an inter-subject generalized classifier one should always check the within-subject performance of each training subject in advance. In Study II, only subjects having high accuracy in within-subject decoding were used for training the inter-subject decoding algorithms. Using these well-performing subjects for training and L21-MTL for classification we managed to improve the accuracy of two subjects showing poor within-subject accuracy.

6.3 Comparison of MEG and EEG in MI-BCI

Study II investigated the efficacy of MEG and EEG in decoding of MI. It was found that MEG yielded slightly better results than EEG in both

within-subject and inter-subject decoding, when similar methods were applied to both modalities. However, the differences were not statistically significant. The minor differences might be due to the higher number of measurement channels in MEG, or simply a result of higher signal-to-noise ratio of MEG compared to EEG. However, in this study we only included signals from parietal sensors in both modalities, which may not give a reliable estimate of modality differences.

MEG and EEG are complementary methods, as EEG is most sensitive to radial current sources and MEG to tangential ones. Thus, it could be argued that the combination of them would be the most sensitive modality for detecting MI-related signals, as suggested in a recent study [88]. However, a practical issue related to this kind of multimodal measurement is that attaching the EEG electrodes is time-consuming. Thus, simultaneous measurement of MEG and EEG requires more preparation time than MEG alone. In addition, due to the EEG cap the distance of the sources from MEG sensors is increased with a few millimeters, which reduces the SNR of MEG signal. It should be further investigated whether simultaneous measurement of both modalities brings relevant additional information to MI decoding compared to MEG or EEG alone.

6.4 Practical considerations

Certain practical issues were considered when designing the studies included in this thesis. One of the most important factors in a BCI is the modality of feedback. Study I involved visual feedback, whereas in Study II proprioceptive feedback was used. In addition, in Study II the experiment began with a passive movement session, in which the subjects were given a "model" of the movement they were supposed to imagine during the BCI task. Most subjects reported that the initial passive movement session helped them to perform MI. Proprioceptive stimulation might enhance the SMR modulation as it inherently provides the somatosensory stimuli corresponding to those elicited during actual finger movements.

The pneumatic stimulator was also considered comfortable and easy to get used to. Many clinical studies have used functional electrical stimulation (FES) of target muscles as feedback [6, 89–91]. FES is found to be effective for activation of the paretic muscles, and undoubtedly works well as a feedback modality for MI-BCI. However, proprioceptive stimulation might be a more gentle option for patients, and it is able to produce more delicate movements than FES, which typically stimulates multiple muscles at a time. Furthermore, the pneumatic stimulators used in Study II could be useful for other researchers working with MEG, since they are fully MEG-compatible and can be modified for various forms of tactile and proprioceptive stimulation.

It is also crucial to consider how the subjects are instructed to perform the MI task. In both studies of this thesis, the subjects were specifically asked to imagine the somatosensory aspect of hand movement instead of visual imagination of moving fingers. It has been previously reported, not very surprisingly, that visual imagery activates mainly the visual areas and kinesthetic imagery the motor areas [92]. A BCI designed for motor cortex rehabilitation is practically unusable if the user does not actually activate the motor areas. Thus, practising MI beforehand and careful instructions for the subjects are important.

As SMR modulation via MI is among the most challenging BCI tasks [93], it should be acknowledged that it is a skill that improves with practice (see discussion about this issue by McFarland & Wolpaw [94]). MI and concurrent SMR modulation requires active contribution from the subject, and it might feel difficult especially in the beginning of MI-BCI training. Nevertheless, the feedback of the BCI should reliably indicate whether the SMR modulation was sufficient or not, even if that leads to only a few successful trials in the first training sessions. This also means that a high classification accuracy is not always desirable, if it is not based on motor cortex activity. Although robust machine learning classifiers are essential for flexible usability of a BCI, especially in noisy measurement conditions, it is not appropriate to adapt them to any possible brain activity. Instead, the BCI should reward the user if and only if the desired activity is originated in the targeted motor areas.

6.5 Future directions

All decoding approaches evaluated in this thesis suffer from one substantial limitation: the analysis is restricted to two-class classification. However, three and more classes should preferably be classified in real-life experiments. For example, in a MI-BCI experiment the subject might imagine moving left hand, right hand or no hand at all. Extending the decoding into multi-class paradigms is an essential improvement for future clinical applications. In a recent study of our research group [59], convolutional neural networks (CNN) were trained offline to distinguish between left-hand MI, right-hand MI and rest. The online performance of CNN was validated using two healthy participants, who achieved high accuracy for two-class classification. This approach should be further tested with more participants and three-class classification.

One possible extension of MEG-BCI would be source-level analysis for the real-time paradigm. Oscillatory SMR could be captured with e.g. synthetic aperture magnetometry (SAM; [95]) or dynamic imaging of coherent sources (DICS) beamformer [96]. However, cortically-constrained source estimation requires additional acquisition and processing of head MRIs,

which might not be feasible in real-time applications. In addition, source modeling requires more computation than sensor-level signal analysis, and thus could cause longer delays in the feedback. Furthermore, the signal quality of single-trial MEG might not be sufficient for reliable source localization in real time. Despite these challenges, the efficacy of source-level and sensor-level signals in MI decoding should be compared, as previous studies have yielded promising results also for source-level neurofeedback. Florin and colleagues [10] successfully provided feedback to the subjects by measuring oscillatory components at predefined sources. Also Battapady and colleagues [97] reported high accuracy for decoding motor execution and MI from SAM-filtered MEG data; however, the analysis was done for offline data and thus is not directly indicative of good online performance.

The future generations of multi-sensor OPM arrays will most likely benefit the development of MEG-BCIs as well. Improved signal-to-noise ratio and diminishing of movement artifacts due to on-scalp sensors could improve the accuracy and robustness of real-time signal analysis and decoding. For inter-subject decoding, however, this might constitute a challenge, if the sensor locations are at different positions with respect to the brain for each subject. On the other hand, also in current MEG measurements the head position with respect to the sensors varies between subjects, and even after head position correction the anatomical regions are not necessarily aligned. In the future, it should be evaluated whether current decoding methods designed for SQUID-MEG are robust enough also for OPM-MEG.

Another important extension of the current BCI paradigms is clinical use, e.g. with patients suffering from hemiplegia. The MEG-based MI-BCI could be useful especially in the beginning of rehabilitation, since the higher signal-to-noise ratio of MEG allows more efficient detection of small SMR modulations than EEG. Thus, the patients could receive concurrent proprioceptive feedback for generating even minor SMR suppression during MI or attempted movements. Also in this case, OPM-MEG will likely further improve measurement sensitivity. If the BCI therapy improves the patients' SMR modulation, they could continue practising with similar EEG-based BCI system.

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