Analysis of Movement-Related Cortical Potentials for Brain-Computer Interfacing in Stroke Rehabilitation

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ANALYSIS OF MOVEMENT-RELATED CORTICAL POTENTIALS FOR BRAIN-COMPUTER INTERFACING IN STROKE REHABILITATION

BY
MADS JOCHUMSEN

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AALBORG UNIVERSITY
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Dissertation submitted ….

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Mads Jochumsen received his Bachelor and Master degree in Biomedical Engineering and Informatics from Aalborg University in 2010 and 2012, respectively. Besides the studies at Aalborg University, Mads Jochumsen worked part time as a research assistant at Mech Sense, Aalborg University Hospital, under the supervision of Professor Asbjørn Drewes from 2009-2012. In 2012, Mads Jochumsen was enrolled in the doctoral school at the Faculty of Medicine at Aalborg University under the supervision of Associate Professor Kim Dremstrup. In 2014 Mads Jochumsen was awarded with the Elite Research Travel Scholarship from the Danish Ministry of Higher Education and Science. Mads Jochumsen was also selected by the Danish Council for Independent Research to represent Denmark at the 64th Lindau Nobel Laureate Meeting in Physiology or Medicine.

ENGLISH SUMMARY

Stroke is the leading cause of adult disability in the world, and with limited effect of the current therapies, a great body of research has been conducted over the last years to find new innovative techniques to promote motor recovery in stroke rehabilitation. Brain-computer interfaces (BCIs) can potentially reestablish the disrupted motor control; likely through Hebbian mechanisms where somatosensory feedback from e.g. functional electrical stimulation (FES) is casually linked with motor cortical activity. To obtain this causality, the intention to move the affected body part must be detected slightly before the movement onset to account for the time to activate e.g. FES and for the conduction time of the feedback. Movement prediction can be obtained by detecting movement-related cortical potentials (MRCPs) that are observed prior the movement onset in the ongoing brain activity. In addition, movement-related parameters such as force and speed are encoded in the MRCP. By decoding this, it is possible to improve the control of a BCI by introducing more degrees of freedom to systems that can detect movement intentions. It could be used for providing meaningful feedback (replicated movements) to match the movement intention and/or introducing task variability in the training to maximize the retention and generalization of relearned movements. In this thesis, the aim was to test the possibility of detecting movement intentions and extracting different levels of force and speed from single-trial MRCPs and implement this in an online system to be used by stroke patients. Moreover, the possibility of discriminating between different movement types was explored. This was done through a series of studies. In Study 1, healthy subjects performed different foot movements associated with two different levels of force and speed. It was possible to detect and decode movement intentions offline. In Study 2, different spatial filters and feature extraction techniques were evaluated to optimize the offline detection and decoding of MRCPs. Healthy subjects and stroke patients performed similar movements as in Study 1. In Study 3, the optimal techniques from Study 2 were implemented in an online system. The system was tested on healthy subjects and stroke patients performing two different movements associated with different levels of force and speed. In Study 4, only one recording channel was used to promote the technology transfer from the laboratory to the clinic. Similar movement types were performed as in Study 1 and 2, but hand movements were recorded instead to evaluate the possibility of detecting and decoding these as well. It was evaluated in healthy subjects and stroke patients. In the studies, the best performance was obtained in the offline analyses where 60% of the movements were correctly detected and classified; this decreased to 55% in the online study, but it was shown that different levels of force and speed can be detected and decoded. Lastly, in Study 5 it was shown that different movement types (palmar, pinch and lateral grasps) could be detected and discriminated from each other as well. 79% of the grasps were detected and 63% of them were correctly classified.

DANSK RESUME

Slagtilfælde er globalt den hyppigste årsag til invaliditet blandt voksne, og da nuværende rehabiliteringsmetoder har en begrænset effekt, er der gennem de seneste år forsket i nye rehabiliteringsteknikker. Hjerne-computer interface (BCI: brain-computer interface) kan potentielt genetablere den ikke-fungerende motoriske kontrol gennem Hebbianske mekanismer, hvor sensorisk feedback fra f.eks. funktionel elektrisk stimulation (FES) bliver kausalt koblet sammen med motor kortikal aktivitet. For at opnå denne kausalitet skal bevægelsesintention af den afficerede kropsdel detekteres kort tid inden starten af udførelsen af bevægelsen, så der er tid til at aktivere f.eks. FES og for propageringstiden af den sensoriske feedback. Forudsigelsen af bevægelsesintention kan opnås ved at detekere bevægelses-relaterede kortikale potentialer (MRCP: Movement-related cortical potential), som kan ses i hjerneaktiviteten før bevægelsen udføres. MRCP'et indeholder også kinetisk information såsom kraft og hastighed. Afkodes dette er det muligt at forbedre kontrollen af et BCI ved at give flere frihedsgrader til et system, der kun kan detektere bevægelsesintentioner. Dette kunne potentielt bruges til at give meningsfuldt sensorisk feedback fra replikerede bevægelser, som passer til bevægelsesintention samt introducere varierende træning, hvilket kan maksimere fastholdelsen og generaliserbarheden af genindlærte bevægelser. Formålet med denne afhandling var at undersøge muligheden for at detektere og afkode kraft og hastighed samt bevægelsestypen fra MRCP'et og at implementere teknikkerne i et realtidssystem, som kan bruges af patienter, som har haft et slagtilfælde. Afhandlingen består af fem artikler. I Studie 1 udførte raske forsøgspersoner forskellige fodbevægelser, hvor der var to forskellige niveauer af kraft og hastighed. Analysen blev ikke udført i realtid, men det blev vist, at MRCP'et kunne detekteres og afkodes. I Studie 2 udførte raske forsøgspersoner og patienter de samme bevægelser som i Studie 1. Forskellige signalbehandlingsteknikker blev testet for at finde de optimale teknikker til at detektere og afkode MRCP'et. I Studie 3 blev de optimale teknikker implementeret i et realtidssystem, der kunne detektere og afkode to forskellige bevægelser med forskellig kraft og hastighed. Systemet blev først testet på raske forsøgspersoner og derefter patienter. I Studie 4 blev det testet, om det var muligt at afkode de samme bevægelser fra Studie 1 og 2, når der kun blev opsamlet hjerneaktivitet fra én elektrode. Dette kunne potentielt forbedre implementering af BCI i et klinisk set-up. Bevægelserne i dette studie blev udført med hånden i stedet for foden for at undersøge, om det også var muligt at afkode MRCP'et fra håndbevægelser. Dette blev testet af både raske forsøgspersoner og patienter. I studierne, som ikke blev evalueret i realtid, blev 60% af alle bevægelser detekteret og afkodet korrekt, dette faldt til 55% i realtid, men det blev vist, at det er muligt at detektere og afkode bevægelsesintentioner. I Studie 5 blev det vist at tre forskellige håndbevægelser kan detekteres og afkodes. 79% af bevægelserne blev detekteret og 63% blev korrekt afkodet.

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Lastly, I would like to thank my family, girlfriend, friends and collegaues at the institute for making it some enjoyable years.

TABLE OF CONTENTS

TABLE OF FIGURES

CHAPTER 1. STROKE

Stroke is one of the leading causes of death and adult disability in the world. The World Health Organization defines stroke as (1):

> "rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or until death, with no apparent non-vascular cause"

Stroke is an acute onset of neurological dysfunction and abnormality caused by either ischemic or hemorrhagic lesions (see figure 1-1) caused by closure or bleeding from a blood vessel, respectively (2). Interruption of the blood flow can initiate pathological neuronal events, which eventually lead to cell death. Several deficits are associated with stroke: changing levels of consciousness, impaired cognitive, perceptual and language functions and sensory and motor impairments. The motor impairments can be characterized by weakness or paralysis of muscles, often in one side of the body opposite to the location of the lesion. The level of motor impairment depends on the location and extent of the lesion.(3)

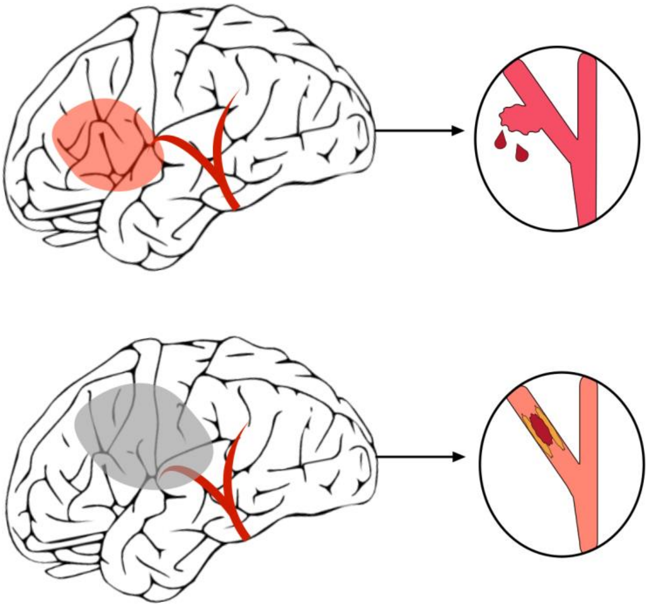

Figure 1-1 Schematic representation of a hemorrhagic (top) and ischemic (bottom) lesion.

1.1. STROKE IN NUMBERS

In 2010, the prevalence of stroke was 33 million worldwide out of which 16.9 million were people having a stroke for the first time (4). Out of this number, 5.8 million people died; this is the second leading global cause of death after ischemic heart disease (5). The incidence of stroke increases with age, and 69% of the first strokes was observed in the population older than 65 years of age (6). The mortality rate due to stroke decreased from 1990-2010, but the daily-adjusted life years (DALYs) lost increased (5). DALY is defined as years of life lost added with years lived with the disability. This increase in DALYs lost indicates that stroke is a huge burden globally for patients and their relatives and for the society; this is expected to increase over the coming years (6). In USA the direct and indirect costs of stroke were 33.6 billion dollars (6). For rehabilitation, the yearly approximate expenditure for one patient was 7500 dollars in USA and 10000 dollars in Denmark (6, 7). One of the most common impairments after stroke is the one affecting the motor functions. About 80% of the stroke survivors suffer from motor impairments initially such as hemiparesis affecting the face and upper and lower extremities (8). With impaired balance and muscles in the lower extremities, locomotor (gait) function is affected. The majority of the patients gain independent gait, but about 35% of them do not reach a level sufficient to perform all their activities of daily living due to reduced walking speed and endurance (9, 10). For arm and hand function, up to 80% of the patients still have some degree of motor impairment 3 months post stroke (11, 12). 50-70% of the patients gain independence 6-12 months post stroke (13), but approximately 50% has some degree of functional disability after the rehabilitation has ended and require assistance for some activities of daily living (14-16). Up to 33% of the stroke patients are left permanently disabled (13). These motor impairments, added with psychological sequelae such as depression, lead to reduced health-related quality of life (17).

1.2. STROKE REHABILITATION

After the injury, neurons in different regions die from apoptosis or necrosis and some of the tissue adjacent or connecting to the lesion become unresponsive (18). Changes are observed following these events in terms of modifications in excitability, cortical networks and maps (18, 19), which can lead to cognitive, speech, sensory and especially motor impairments that require rehabilitation. It is important that the rehabilitation is initiated early (a few days after the injury) to maximize its effect, but it may be detrimental for the outcome if it is initiated too early (18, 20). The greatest improvements in functional level and motor recovery are seen in the first three months, especially the first four to eight weeks, and after this it reaches a plateau (21). The early recovery of function is mainly due to 1) resolution of diaschisis and cell repair, 2) changing properties of existing neuronal networks and 3) formation of new connections (22, 23). Besides stroke recovery, the latter two are also associated with motor learning in healthy subjects. The underlying mechanisms in stroke recovery and the different techniques and technologies that can promote this will be outlined in the following sections.

1.2.1. MECHANISMS OF MOTOR RECOVERY

The term stroke recovery can include motor recorvery and functional recovery which are different types of recovery (24). Motor (or true) recovery refers to the ability of performing the voluntary movements in the same way as before the injury, while functional recovery refers to improvements in the ability to perform activities of daily living independently (24). Functional recovery can be obtained through compensation and not by using the same movement pattern as before the injury. Both motor and functional recovery is influenced by the brain’s ability to adapt to changes following learning or injury; this is known as plasticity. Motor recovery may be seen as a form of motor learning, which can be either skill acquisition or motor adaption (25). There is a consensus that neural plasticity is the best candidate for the underlying mechanisms of motor learning (26, 27). The changes associated with motor learning may be based on Hebbian plasticity or Hebbian-based learning (18, 28, 29). This can be expressed as synaptic modifications in the form of long-term potentiation and long-term depression, which have been linked to learning and memory formation, and cortical reorganization (28, 30). These changes may be due to unmasking of previously existing connections, synaptogenesis, dendritic branching and axonal sprouting, which are important to take over the function over neural tissue that has suffered irreversible damage (22, 23). These plastic changes may be induced or promoted using different interventions, where many of them rely on motor learning principles such as task specificity, repetition, intensity, attention and variable training schedules to maximize retention and transfer ability of relearned movements (24, 25, 31).

1.2.2. TECHNIQUES AND TECHNOLOGIES

No single definite and well-documented rehabilitation technique has been found for stroke recovery; therefore, eclectic approaches are selected rather than one specific intervention (8, 16, 24). This is mainly due to the complexity of the brain and the way it repairs itself and a number of factors affecting the recovery leading to great heterogeneity in this patient group. These factors include, among others, the size and location of the lesion, prestroke comorbidities, acute stroke interventions, severity of initial stroke deficits, age, and amount and types of stroke therapy (20). Gold-standard therapy is a combination of task-specific and task-oriented training through physiotherapy and occupational therapy and general aerobic exercise to improve strength and endurance (16, 27). The patients do not receive motor rehabilitation for more than six months (16).

Several other techniques and interventions have been proposed to improve the recovery; examples of interventions are medical treatments, such as molecules (e.g. amphetamine), growth factors, cell-based therapies, device-based rehab and non-invasive stimulation techniques (32). Especially the latter types of interventions are based on motor learning principles and try to induce neural plasticity. The effect of different interventions was investigated in a review (8), where constrained-induced movement therapy, biofeedback, motor imagery (mental practice) and robotic rehabilitation showed improvement in arm function. Improvements were seen for gait and balance after physical exercise, high-intensity physiotherapy, repetitive task training and biofeedback (8). Other techniques and technologies also exist such as virtual reality-based training where patients can be engaged in the training (25) and electrical and functional electrical therapy to assist them in performing movements while augmenting sensory feedback (25, 33). The effect of non-invasive brain stimulation has also started to be investigated for improving motor function by inducing neural plasticity in the motor cortex. Examples of these techniques are transcranial direct current stimulation, repetitive transcranial magnetic stimulation and paired-associative stimulation (34). Another recent intervention that has been proposed for inducing neural plasticity to promote motor recovery is a brain-computer interface (35-37). With this technology different motor learning principles can be incorporated, e.g. repetition, sensorimotor integration and attention. Moreover, different rehabilitation techniques may be combined such as motor imagery and electrical stimulation or robot-assisted movements. The first results from clinical studies have started to emerge (37-39).

CHAPTER 2. BRAIN-COMPUTER INTERFACE

A brain-computer interface (BCI) is a device that can translate the intention of a user to a device command using only the activity of the brain (40, 41). Traditionally, BCI was developed for communication and control for patients suffering from e.g. amyotrophic lateral sclerosis, locked-in syndrome and spinal cord injury (41). Over the past years the use of BCI technology in neurorehabilitation has been outlined (35, 36).

2.1. CLASSIFICATION AND SCHEMATIC OVERVIEW OF BRAIN-COMPUTER INTERFACES

BCI systems may be classified as either dependent or independent, where dependent BCIs rely on some activity in the normal outputs from the brain e.g. gaze direction, on the contrary to independent BCIs that do not have this assumption (41). Also, BCIs may be classified according to the mode that they are operated in; this can be in an asynchronous or synchronous one. In the asynchronous mode, the BCI is always active, and the user determines when to control the BCI; this is also called a self-paced BCI. In the synchronous mode, the user depends on a protocol or cues to perform tasks from e.g. a program; this is a cue-based approach.

Generally, a BCI consists of the following parts: recording the brain activity (signal acquisition), processing the brain activity to extract intended information from the user and transform this into control commands (signal processing), and lastly, an external device that the user intends to operate (see figure 2-1).

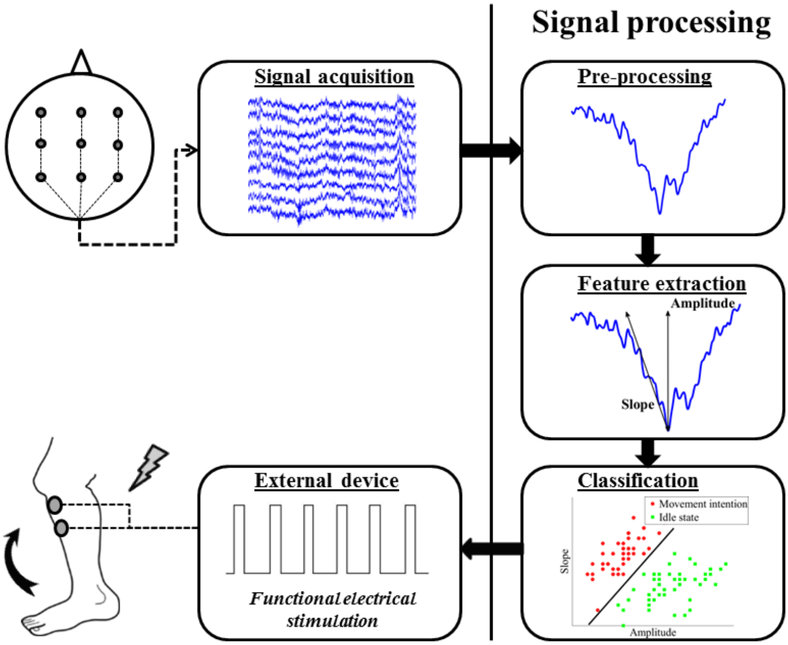

Figure 2-1 An example of a user (e.g. hemiplegic stroke patient) initiating functional electrical stimulation by imagining a dorsiflexion of the ankle joint for neurorehabilitation. Initially, EEG is recorded followed by signal processing to decode the intention to move. Once the computer has decoded the intention to move, a device command is sent to the electrical stimulator to initiate the muscle stimulation resulting in a dorsiflexion of the ankle joint.

2.1.1. SIGNAL ACQUISITION

In theory, any type of voluntary produced brain activity can be used to control a BCI. This can e.g. be electrical activity, magnetic fields or blood flow. Electrical activity is the most common type of activity that is used to drive BCIs (42). This can be acquired using electroencephalography (EEG) through surface electrodes placed on the scalp and more invasive techniques such as electrocorticography (electrodes placed on the cortical surface) and local field potentials (electrodes inserted into the cortex). The advantage with the electrophysiological recording techniques is a great temporal resolution, and for the expense on the invasive procedure electrocorticography and local field potentials have god spatial resolution on the contrary to EEG due to volume conduction. Other techniques such as near-infrared spectroscopy, positron emission tomography and functional resonance imaging have longer time constants compared to the electrical or magnetic measures. Also, positron emission tomography, functional magnetic resonance imaging, and magnetoencephalography are expensive and technically demanding; thus they may not be practical to use. (35, 41)

2.1.2. SIGNAL PROCESSING

Electrical activity recorded from the brain, such as EEG, has a poor signal-to-noise ratio (SNR) that makes it a challenge to extract intentions from the user and translate it into device commands to control the external device. The signal of interest is often of a magnitude that is 5-10 smaller than the artifacts, such as those arising from eye movements and blinking.

2.1.2.1 Pre-processing.

Initially, the signals are pre-processed to improve the SNR. This has been done using various techniques such as bandpass filtering or wavelet denoising to remove signal components from unwanted frequencies or scales, respectively (43, 44). For EEG, volume conduction is a problem that leads to recording of a blurred image of the actual underlying activity. Spatial filters have been applied to correct for some of this blurring and enhancing the SNR (45). Other techniques that have been used for pre-processing include blind source separation, principal component analysis, averaging and Kalman filtering (46).

2.1.2.2 Feature extraction and classification.

After the signals have been processed, features can be extracted from the signals that can be used to discriminate between different states. An example can be to discriminate between an idle state and an active state, or between left and right hand motor imagination; this will lead to a system with a binary outcome. If more classes are included, more degrees of freedom will be added to the system; however, this may impede the performance of the system due to more incorrect decisions. Various types of features have been extracted such a changes in amplitude of evoked potentials, power changes in different frequency bands, complexity measures and parametric modelling (46). To determine the intention of the user, the features must be classified. Some of the most popular classifiers in BCI research are linear discriminant analysis and support vector machines (SVMs), but many different classifiers have been applied in BCI research over the past years (46, 47).

2.1.3. EXTERNAL DEVICES

After the brain signals have been acquired, and the system has decoded the intention of the user, a control signal is sent to an external device that the user can control. For communication purposes, a speller can be controlled which enables the user to select characters. Examples of control applications are web browsing, motor substitution (prosthetics), wheel chairs and gaming. Also, electrical stimulators, orthotic devices and rehabilitation robots have been controlled for neurorehabilitation purposes. (41, 48)

2.2. CONTROL SIGNALS

Various control signals can be extracted from the EEG depending on the BCI protocol; these can be seen in figure 2-2.

2.2.1. P300

This potential is evoked by frequent stimuli that can be auditory, visual or somatosensory. It is seen as a positive peak approximately 300 ms after the stimulus in the parietal cortex (49). One of the most used applications of P300-based BCIs is spelling, since relatively high information transfer rates (decisions per second) can be obtained. Another advantage is that such a system does not require initial user training. (41)

2.2.2. SENSORIMOTOR RHYTHMS

Sensorimotor rhythms are observed in different frequency bands. The mu rhythm is observed from 8-12 Hz in the EEG activity over the sensorimotor cortex. It can be associated with idle activity, but the spatial location and frequency are modulated with sensory input and motor output. In addition, the beta rhythm, from 13-30 Hz, can also be modulated in association with the mu rhythm. The mu and beta rhythms can be decreased during motor preparation (executed or imagined movement); this is known as event-related desynchronization. After the movement or relaxation, an increase is observed in the mu and beta rhythms; this is known as event-related synchronization. Oscillating activity from the mu and beta rhythms has mainly been used for communication purposes, but more recently, it has been used as a control signal in neurorehabilitation as well (50). (51)

2.2.3. VISUAL EVOKED POTENTIALS

Visual evoked potentials are recorded over the visual cortex to determine a fixation point (direction of the gaze). This potential has mainly been used for communication and control where characters in grids are selected or the direction of a cursor is controlled, respectively. It is possible to obtain high information transfer rates with this control signal. (40, 41)

2.2.4. SLOW CORTICAL POTENTIALS

Slow cortical potentials are seen as a slow increase in negativity in the EEG, and they are associated with executed or imaginary movements and functions that require cortical activation (52). The potentials are mainly recorded over the parietal cortex, often close to the vertex. The potentials have been used for communication purposes in patients with late-stage amyotrophic lateral sclerosis (total motor paralysis) since these patients have difficulties in using other types of communication (53). The information transfer rate is relatively low since the potentials are so slow in nature (2-10 s). Slow cortical potentials can also be called movement-related cortical potential (MRCPs) (54), and they will be described in more detail in the next chapter. Besides the application in communication and control, the MRCP has been proposed as control signal for BCI in neurorehabilitation as well (55).

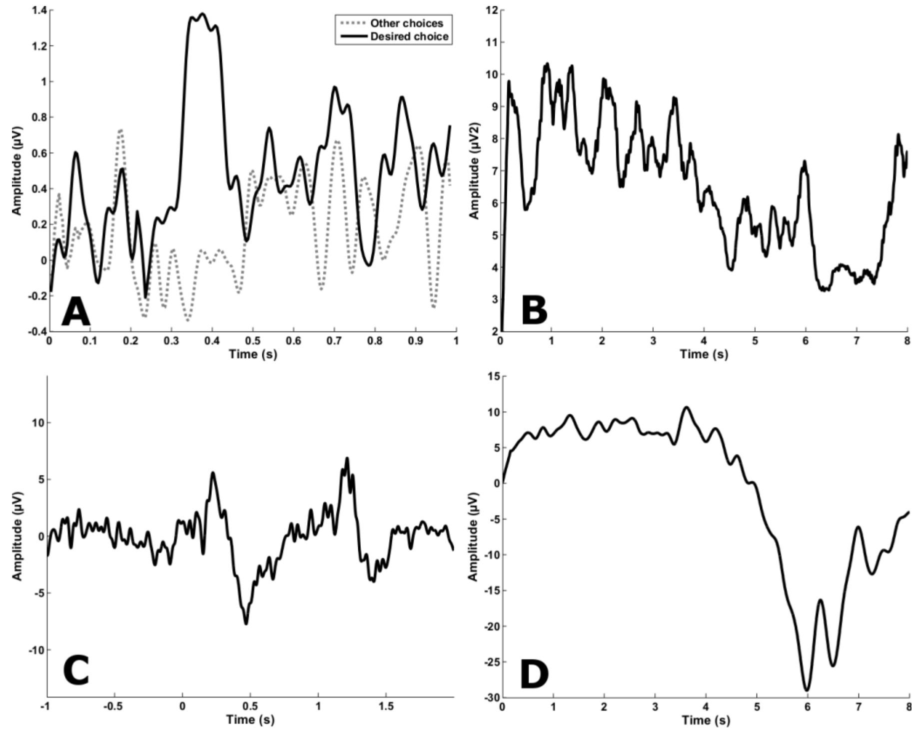

Figure 2-2 Illustrations of commonly used control signals in BCI: A) P300, B) Sensorimotor rhythm (mu rhythm), C) Visual evoked potential, and D) Slow cortical potential. In part A and C, a stimulus is delivered at t=0 s. In part B and D, the control signals are associated with motor execution intiated at t=6 s.

2.3. BRAIN-COMPUTER INTERFACES IN NEUROREHABILITATION

BCIs have been proposed to be used in neurorehabilitation of different diseases such as epilepsy, chronic pain, ADHD, schizophrenia, anxiety disorders, Parkinson's disease, dystonia, spinal cord injury and stroke (36, 37, 56). Especially stroke rehabilitation has been investigated, where BCIs potentially can promote neural plastic changes (37). Several reviews exist regarding how BCIs can be, and have been, used to induce plastic changes (35-37, 57-60), but up until now only a limited number of studies, with a relatively large number of patients, has reported the clinical effects of BCI-based training as a means for stroke rehabilitation (38, 39, 61).

As outlined previously, motor recovery in stroke rehabilitation and induction of plasticity can be promoted using motor learning principles. BCIs have been developed to integrate different forms of rehabilitation techniques such as mental practice through motor imagery, augmented afferent feedback from electrical stimulation, rehabilitation robots and virtual reality. It is possible to obtain task specific training that can be intensive and repetitive. In addition, it requires attention from the patients to operate the BCI, so they do not become passive in the rehabilitation since they are driving it. Another principle that can be incorporated is sensorimotor integration. This is obtained by closing the motor-control loop where sensory feedback is provided in response to cortical activation of the areas associated with movement preparation through e.g. motor imagination. In the closed-loop paradigm, reward is also incorporated when the patients produce sufficient cortical activation to receive sensory and/or visual feedback (62). Visual feedback can be useful for reward and assisting the patients in operating the BCI, but to enhance the induction of plasticity for motor recovery/learning, afferent somatosensory feedback is crucial (63). Functional and peripheral electrical stimulation (55, 64), orthotics and rehabilitation robots are examples of devices that can evoke sensory responses when activated (61, 65). The proposed mechanism for inducing plasticity with a closed-loop BCI is Hebbian-associated plasticity if the cortical activation and somatosensory feedback are timely correlated (18, 36). It has been found that the greatest induction of plasticity occurs if the somatosensory feedback arrives at the cortical level during maximal motor cortical activation (e.g. the onset of an imagined or attempted movement) (66). This means that the imagined or attempted movement must be detected with a limited latency, possibly ±200 ms, with respect to the onset of the movement (66). This has been accomplished in several studies, where especially the MRCP and event-related desynchronization have been used, due to the possibility of early detection and also natural activation of the brain areas associated with motor preparation (67-70). In most of the work for inducing plasticity with a BCI, intentions to move have been detected from the idle state or rest where the BCI works as a binary switch (55, 61, 65). As outlined, several motor learning principles can be incorporated in such a

BCI, but by extending a binary switch to have more degrees of freedom, e.g. by decoding movement-related parameters of the intended movement, another motor learning principle can be incorporated – task variability. Task variability in training has been shown to maximize the retention of relearned movements and increase the generalization of these (transfer ability) (25). Examples could be performing different hand movements such as lateral, pinch and palmar grasps, or variations in grip strength when lifting various objects. To accomplish this, the intention to move has to be detected, and the type of movement must be decoded. In this scenario, meaningful somatosensory feedback can be provided according to the efferent activity, and different types of specific movements can be mixed in a single session.

CHAPTER 3. MOVEMENT-RELATED CORTICAL POTENTIALS

The MRCP is a slow cortical potential that can be observed in the EEG up to 2 s prior self-initiated and cue-based movement. The MRCP associated with a self-paced movement is known as the Bereitschaftspotenial (BP) or readiness potential (71), and the MRCP associated with a cue-based movement is known as the contingent negative variation (CNV) (72). The MRCP reflects motor preparation or an intention to move, and it is also observed when imagining movements (see figure 3-1) (54). The MRCP can be divided into different segments; the initial negative phase of the MRCP is comprised of the early BP or CNV (CNV1), the late BP or CNV (CNV2) and the motor potential. There is an initial increase in negativity starting from 2 s prior the movement onset until 400 ms prior the movement onset (early BP or CNV), and from 400 ms prior the movement onset to the movement onset there is a further increase in negativity. The initial negative phase of the MRCP is followed by a decrease in negativity (and increase in positivity); this is known as the movement-monitoring potential or reafferent potential, and it is considered to reflect control of the performed movement and the inflow of kinesthetic feedback. (54, 73)

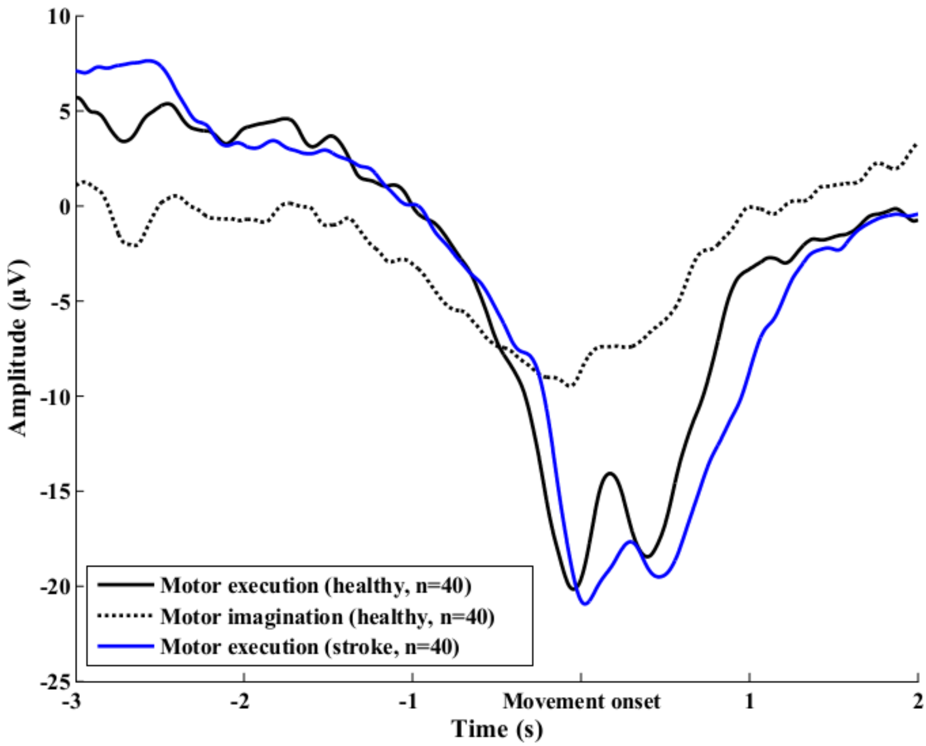

Figure 3-1 Example of MRCPs associated with foot movements averaged over 40 trials for motor execution and motor imagination performed by a healthy subject, and motor execution performed by a stroke subject with the affected foot.

3.1. NEURAL GENERATORS

Different regions of the brain contribute to the generation of the MRCP. The initial part of the MRCP is thought to be produced mainly in the supplementary motor area, the premotor cortex and prefrontal cortex with no site-specificity (54). The steeper increase in negativity preceding the movement onset is generated by the site-specific primary motor cortex (54), e.g. for hand right hand movements it is around C1-C3 according to the International 10-20 system. Other areas contribute to the generation of the MRCP as well; these include the primary sensory cortex, basal ganglia, thalamus and cerebellum (54). The MRCPs associated with imagined movements are generated by the same neural structures (74). The BP and CNV share the neural generators, but it has been found that the supplementary motor area is most active in the generation of the BP compared to the CNV. In addition, the dorsal premotor cortex is most active in the generation of the CNV compared to the BP (75). (73)

3.2. FACTORS MODULATING MOVEMENT-RELATED CORTICAL POTENTIALS

Several factors influence the MRCP in terms of e.g. amplitude modulations in signal morphology. The start of the negative depression occurs earlier for the CNV compared to the BP, while the BP has been reported to be more prominent (76). The MRCP is also modulated by the level of intention and attention to a task, which can be affected by fatigue (54). The MRCP has also been used to evaluate the effect of motor learning in healthy subjects since learning modulates the amplitude of the initial negative phase of the MRCP (77, 78). The amplitude increases with learning; this is the case for healthy subjects (79). For stroke patients who are recovering lost motor function, however, a decrease in amplitude has been observed when pre- and post-rehabilitation measurements were compared, potentially due to less mental effort needed for performing the movements after the rehabilitation had ended (80, 81). Stroke and other conditions and diseases such as pain, spinal cord injury, dystonia and Parkinson’s disease affect the MRCP. In general, evident MRCPs are observed in the EEG for stroke (see figure 3-1), while the amplitudes of the different phases seem to decrease in the other pathological conditions (54, 82). Lastly, several movement-related parameters about the intended movement are encoded in the MRCP. This can e.g. be seen as modulations of the amplitude of different phases associated with different levels of force and speed (83, 84), where higher levels of force and speed seem to increase the amplitudes (see figure 3-2). In addition, the type of movement modulates the initial negative phase of the MRCP. Complex movements have been found to have larger amplitudes compared to simple movements (54).

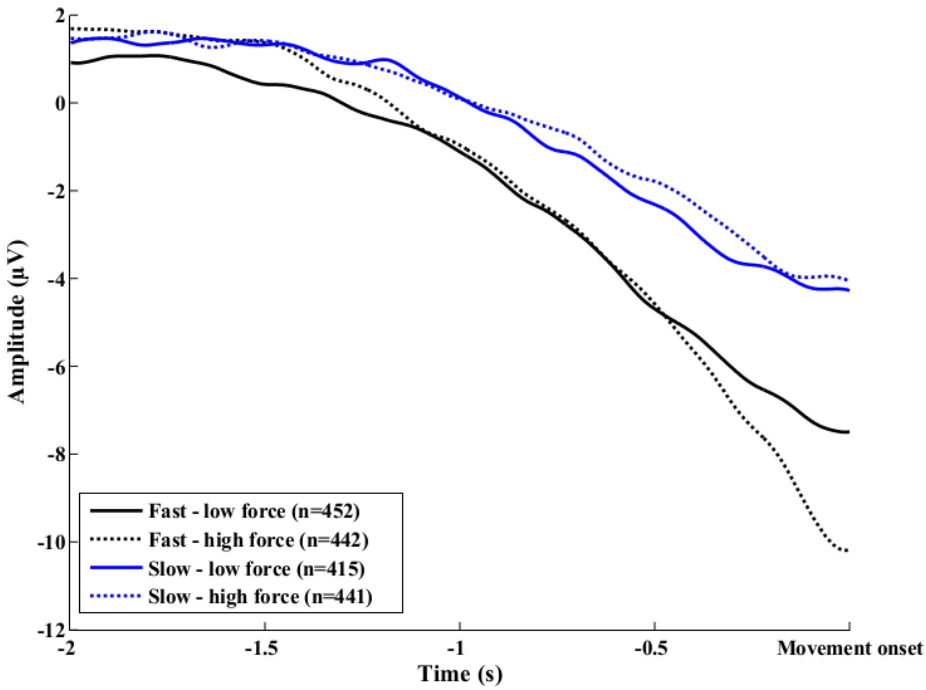

Figure 3-2 Example of how speed and force modulate the initial negative phase of the MRCP. The MRCPs are obtained by averaging more than 400 ankle movements from healthy subjects.

3.3. PROCESSING MOVEMENT-RELATED CORTICAL POTENTIALS

As outlined in the previous sections, the MRCP can be observed in the EEG prior to the onset of the executed or imaginary movement; it opens up the possibility of predicting when a subject or patient intends to perform a movement. This intrinsic feature of the MRCP has been exploited in several BCI systems that have been used for communication/control and rehabilitation purposes. By detecting MRCPs from the continuous EEG, different asynchronous brain-switches have been developed over the years (55, 65, 68, 85-93).

3.3.1. DETECTION

It is a challenge to detect MRCPs on a single-trial level due to a low SNR and great trial-trial variability. In order to overcome these challenges for detecting the movements (see figure 2-1 for an example), the MRCPs must be pre-processed to enhance the SNR before features can be extracted and classified. Several techniques have been used to pre-process MRCPs, but among the most used techniques are bandpass filtering with a narrow passband located at low frequencies (43). In addition, spatial filtering techniques (45) are often utilized as well as blind source separation (94) and channel selection techniques (86). After pre-processing the signals, features are extracted to discriminate between movement-related and idle activity. To do this, different types of features have been proposed; these include template matching (67, 68, 70, 94-98), data transformation (68, 99), wavelets (93), power modulations (70, 85) and slope and amplitude of the MRCP (100). Besides the different features that have been proposed, different classifiers have been used as well such as SVMs (101, 102), linear discriminant analysis (68), Neyman-Pearson classification (67), k-nearest neighbors (99), Gaussian Mixture Model (103), Mahalanobis distance (85), Bayes classification (43) and logistic regression (70).

Different types of executed and imaginary movements have been detected in self-paced and cue-based paradigms. Movements of different body parts have been detected such as finger (43, 88, 89, 91, 93, 95, 97, 98, 104-107), hand (108), wrist (85), elbow (100), arm (69, 70, 101, 102, 109, 110) and ankle movements (55, 65, 67, 68, 96), but also complex movement patterns involving several joints such as sitting/standing (103) and gait initiation (94, 111).

3.3.2. DECODING

The MRCP also contains movement-related information; it has been attempted to decode some of this information from single-trial MRCPs in offline analysis. Movements of different body parts have been classified as well as kinetic and kinematic information of individual joints. Recently, grasping different objects have been decoded (112). In addition, various movements of the upper extremity have been classified e.g. left versus right hand movements (113-115), various wrist movements (flexion/extension/rotation) (116-119). Movements involving the lower extremities have also been classified such as discrimination between sitting and standing (103).

Other movement-related information, kinematics and kinetics, has been decoded as well. Trajectories and movement direction (120, 121) and muscle synergies have been extracted for the upper and lower extremities (122), and different levels of force and speed have been classified for ankle (123-125), wrist (116, 117) and finger movements (126).

CHAPTER 4. THESIS OBJECTIVES AND FINDINGS

In the previous chapters it was outlined that there is a need of new and innovative techniques or technologies that can promote motor recovery after stroke. One such technology could be BCI with the MRCP as control signal. It is too early to be conclusive about if BCI training in stroke rehabilitation is superior to other techniques since there is a lack of large-scale randomized clinical trials. Since BCI for motor recovery is a relatively new field, several areas need to be investigated to obtain a functional BCI that can be used daily in the clinic. Some of these areas are summarized in figure 4-1. The optimal hardware and electrodes, as well as signal processing techniques, can improve the performance of a BCI, but it must be designed and implemented in a way that it can be set up fast and operated by clinicians without the expert knowledge by those that developed the systems. Proposed examples of this could be the use of wireless EEG, dry electrodes and BCI systems that require no training or calibration. Besides the technical aspects, the effect of several factors must be investigated to optimize the design of rehabilitation protocols. This could be the optimal type (or combination) of feedback modality to use for motor recovery such as visual feedback or somatosensory feedback from electrical stimulation or robot-assisted movements. Another important factor to be addressed in the design of an optimal rehabilitation protocol is to find ways to motivate the patients and for them to maintain attention during the training. Virtual reality and gaming could be ways for patients to maintain the motivation to train with the BCI. To evaluate the effect of rehabilitation protocols using BCI, randomized clinical trials are needed.

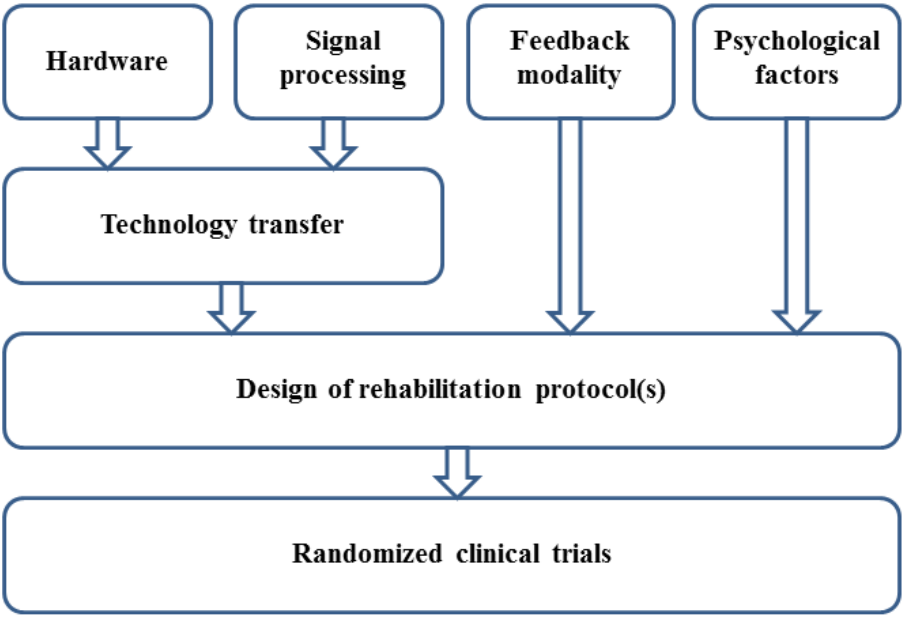

Figure 4-1 Research areas in BCI for stroke rehabilitation.

4.1. AIM OF THE THESIS AND FINDINGS

The aim of this thesis was to extend the work of detecting MRCPs for BCI in stroke rehabilitation by decoding different levels of force (low/high) and speed (slow/fast), and different grasps (pinch, palmar and lateral grasp); this can potentially be used in the design of rehabilitation protocols. The focus of the thesis is on the signal processing to detect and decode MRCPs and test if a BCI, based on these techniques, can be transferred to stroke patients in the clinic (see figure 4-2).

The thesis consists of five studies. In Study 1, the aim was to test if it was feasible to detect and decode MRCPs associated with foot movements performed with two levels of force and speed from healthy subjects in offline analysis (see figure 3-2). In Study 2, different spatial filters and feature extraction techniques were evaluated to optimize the performance of detection and decoding of the same foot movements as in Study 1; motor execution and imagination were performed by healthy subjects and motor execution by stroke patients. In Study 3, the optimal techniques from Study 2 were implemented in an online BCI, where the performance of it was tested with healthy subjects and stroke patients performing two different types of foot movements associated with different levels of force and speed. In Study 4, hand movements from healthy subject and stroke patients were performed instead of foot movements to investigate if it was possible to detect and decode different levels of force and speed. It was evaluated using only a single recording electrode to see how the performance was affected with a view to have an easy electrode setup in the clinic. In Study 5, the aim was to discriminate three different grasp types from background EEG activity and to discriminate the grasps from each other. This was tested in an offline analysis using principal component analysis (PCA) and sequential forward selection (SFS) of spectral and temporal features extracted from 25 electrodes covering the cortical representation of the hand.

4.2. STUDY 1

Title: *Detection and classification of movement-related cortical potentials associated with task force and speed*.

Authors: *Mads Jochumsen, Imran Khan Niazi, Natalie Mrachacz-Kersting, Dario Farina and Kim Dremstrup.*

Journal: *Journal of Neural Engineering.* ***10*** *(2013) 056015.*

The aim was to detect and decode single-trial MRCPs associated with two levels of force (low/high) and speed (slow/fast) to estimate the performance of a BCI that can be used for neurorehabilitation purposes. Cued isometric dorsiflexions of the ankle joint were performed by 12 healthy subjects while recording EEG. The initial negative phase of the MRCP was detected in the continuous EEG with a template matching technique, and temporal features were extracted from the initial negative phase of the MRCP to classify the different levels of force and speed. Approximately 80% of the movements were correctly detected and 75% of the movements were correctly classified. For a 2-class system, 64% of all movements were correctly detected and classified. In conclusion, it is possible to detect and decode single-trial MRCPs associated with different levels of force and speed.

4.3. STUDY 2

Title: *Comparison of spatial filters and features for the detection and classification of movement-related cortical potentials in healthy individuals and stroke patients*.

Authors: *Mads Jochumsen, Imran Khan Niazi, Natalie Mrachacz-Kersting, Ning Jiang, Dario Farina and Kim Dremstrup.*

Journal: *Journal of Neural Engineering.* ***12*** *(2015) 056003.*

The aim was to determine the optimal spatial filter to use for the detection of single-trial MRCPs and the optimal features, and combination of those, for discriminating between the same foot movement types as in Study 1. Twenty-four healthy subjects either executed or imagined the movements, while 6 stroke patients attempted to perform the movements with their affected lower extremity. The best detection performance, 72% for patients and 78-82% for healthy subjects, was obtained with a large Laplacian spatial filter. Temporal, spectral, time-scale and entropy features were evaluated, and the best combination (temporal and spectral) led to pairwise classification accuracies of 87% for patients and 68-77% for healthy subjects.

4.4. STUDY 3

Title: *Online multi-class brain-computer interface for detection and classification of lower limb movement intentions and kinetics for stroke rehabilitation*.

Authors: *Mads Jochumsen, Imran Khan Niazi, Muhammad Samran Navid, Muhammad Nabeel Anwar, Dario Farina and Kim Dremstrup.*

Journal: *Brain-Computer Interfaces (Under Review).*

Based on the findings in Study 2, an online BCI system was constructed, and the aim was to evaluate the performance of the system when operated by 12 healthy subjects executing and imagining movements and 6 stroke patients attempting to perform movements. Two of the foot movement types, associated with different levels of force and speed, from Study 1 and 2 were performed. Approximately 80% of the movements were detected, and 63-70% of the movements were correctly classified. The healthy subjects performed better than the patients who performed better than chance level. This study indicates that it is possible to detect and decode movements online.

4.5. STUDY 4

Title: *Detecting and classifying movement-related cortical potentials associated with hand movements in healthy subjects and stroke patients from single-electrode, single-trial EEG*.

Authors: *Mads Jochumsen, Imran Khan Niazi, Denise Taylor, Dario Farina and Kim Dremstrup.*

Journal: *Journal of Neural Engineering. **12** (2015) 056013.*

In this study, the detection and decoding of MRCPs were evaluated when using only a single recording electrode. Fifteen healthy subjects performed and imagined hand movements with the two levels of force and speed as in Study 1 and 2. In addition, 5 stroke patients attempted to perform the movements. The same template matching technique was used for detecting single-trial MRCPs, and one spectral and three temporal features were used for classifying the different movement types. Approximately 75% of the movements were detected, and 60% of the movements were correctly classified. The results indicate that it is possible to detect and decode different level of force and speed from hand movements, and that it can be obtained with only one electrode.

4.6. STUDY 5

Title: *Detecting and classifying three different hand movement types through electroencephalography recordings for neurorehabilitation*.

Authors: *Mads Jochumsen, Imran Khan Niazi, Kim Dremstrup and Ernest Nlandu Kamavuako.*

Journal: *Medical & Biological Engineering & Computing (Resubmitted – Minor Revisions).*

The aim was to discriminate pinch, palmar and lateral grasps from background EEG to estimate movement detection. Also, the three movement types were classified to discriminate between them. Temporal and spectral features were extracted from 25 electrodes covering the cortical representation of the hand and classified using linear discriminant analysis. Data filtered in the MRCP frequency range were compared to the use of the data filtered in the full EEG frequency range. 79% of the movements were correctly discriminated from the background EEG (combined temporal and spectral features), and 63% of the grasps were correctly classified (spectral features). The detection performance was similar when comparing the two frequency ranges, but the best grasp type discrimination was obtained using information from the full EEG frequency range. The findings suggest that different grasps can be detected and classified, and that information from the entire EEG frequency range can be beneficial for movement discrimination.

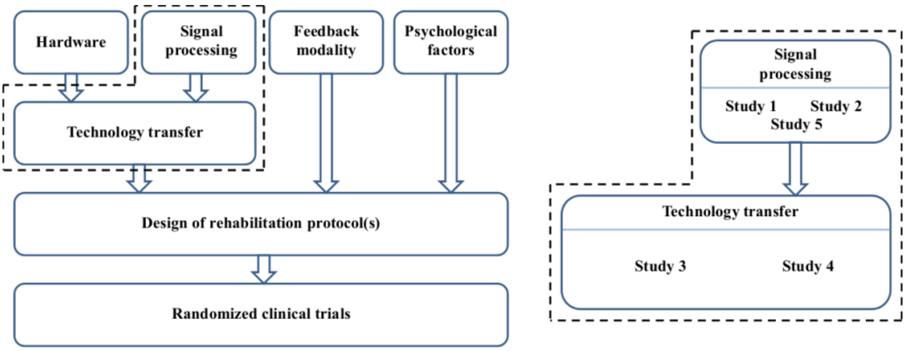

Figure 4-2 Main research area of the studies in the thesis.

CHAPTER 5. GENEREL DISCUSSION

In this series of studies in the thesis, the possibility of detecting MRCPs from healthy subjects and stroke patients was outlined as well as decoding different levels of force and speed associated with the movements and decoding different movement types.

5.1. MAIN FINDINGS

The performance of the detector for detecting the initial negative phase of the MRCP was in the range of what has been found in previous studies (55, 65, 67, 68), which is a true positive rate (TPR) of 70-80%. A similar performance of the detector was obtained in three of the offline studies (1, 2 and 4) and the online study in the thesis. When a classification-based approach was used for detection of hand movements, 79% of the movements were correctly detected on the contrary to 75% in Study 4. This approach was expected to lead to a better detection performance since the detection estimate was based on a 2-class classification problem where the epochs (movement vs background EEG) were extracted with a priori knowledge of when the movements occurred. The results of the detector in Study 5 suggest that better performance of the detector may be obtained in synchronous BCI systems, where the detector is only enabled in specific pre-determined time intervals. In this scenario, the number of false positive detections will also be reduced, but the control will not be self-paced. The TPR was slightly lower for the patients compared to healthy subjects, but it was higher in the current studies compared to a previous study where stroke patients performed self-paced movements (67). This difference can be due to different factors such as severity of the injury and the absence or presence of visual cues. Advanced visual cueing has been suggested to be beneficial for patients to perform movements (127). Detection latencies with respect to the movement onset were obtained in three of the offline studies (Study 1, 2 and 4). The movements were detected around 100-300 ms prior the onset of the movement, which is in the range of what has been found in previous studies, where the onset of movements is predicted (67, 69, 70, 94). It is important to note that the movements are detected with a latency where sensory feedback can be provided, so it becomes timely correlated with the cortical activation associated with the movement intention (66). Also, similar and lower TPRs than what was found in this work have been shown to induce neural plasticity (55, 65).

The classification accuracies of the different levels of force and speed for foot movements were approximately 75-80% for pairwise classification for healthy subjects; this is also similar to what has been reported previously (123-125). The classification accuracies obtained for stroke patients were higher than those obtained for healthy subjects; this can be explained by the detection latencies from which the data to derive features were extracted. With shorter detection latencies (closer to the movement onset) more discriminative information can be included in the analysis, which leads to a higher classification accuracy (128). When the 2-class classification problems were extended to a 4-class problem, the classification accuracies decreased significantly (to 50-60%); this was expected due to the low separability of the MRCPs associated with the different levels of speed and force. The classification accuracy associated with discrimination between three grasps was 63%; this shows that when the number of classes increases, then the classification accuracies decrease. The discrimination of different hand movements is in the same range as what has been reported previously where decoding of different wrist movements was performed (116, 118, 119). In the online decoding of the movement types with different kinetic profiles, the classification accuracies (2-class problem) decreased to approximately 65%, suggesting that the selected features were sensitive to the variability of when movements were detected. A big decrease was seen especially for the stroke patients, which again could be due to the lack of advanced visual cueing and continuous visual feedback (127). Combined detection and classification led to accuracies reaching 65% correctly detected and classified movements in offline studies; this system performance decreased when performing the analysis online, possibly due to the factors described above. For hand movements, the classification accuracies were similar when using one electrode compared to nine electrodes. The performance, however, was relatively low (60% for pairwise classification) compared to that obtained for foot movements. The optimal features for decoding different levels of force and speed of foot movement were applied to hand movements; this suggests that other techniques could be applied and features extracted to improve the decoding of this information, or that subject-dependent features should be derived instead of the subject-independent features in Study 1, 2, 3 and 4. This is supported by the findings in Study 5, where it was found that the most discriminative features differed in terms of time window where they were extracted, spatial location (electrode position) and frequency range.

Even though it has been shown to be possible to detect movements and decode movement-related activity from the MRCP, the findings in Study 2 and 5 suggest that the full EEG frequency range contains additional useful movement discriminative activity to obtain better system performance. It has been shown in several studies that movements can be discriminated from background EEG activity using sensorimotor rhythms, which is one of the state-of-the-art techniques in BCI control (86, 129, 130). The performance of detectors based on MRCPs or sensorimotor rhythms are in the same range, very roughly a TPR of 80%. Recently, it has been explored to use a hybrid approach where the control signals have been combined (70); this has been shown to improve the detection performance. Moreover, sensorimotor rhythms have been used to decode movement-related activity as well such as: hand opening and closing (131), movement direction and trajectories (132, 133), finger movements (134), speed (135), and movement of different body parts (136). Different metrics and research questions make it irrelevant to compare the findings in these studies with those from this thesis. However, as for the hybrid approach for movement detection, it could be interesting to start exploring hybrid approaches to improve the decoding performance.

5.2. METHODOLOGY

The movements were detected well in advance to fulfill the requirements for the temporal association between somatosensory feedback and cortical activity. Therefore, it would be possible to modify the detector, so movements are detected closer to the movement onset. To do this, the detection threshold needs to be higher. The threshold was derived from the turning point of the receiver operating characteristics curve to obtain a trade-off between the TPR and the number of false positive detections. A larger detection threshold, would lead to lower TPRs and false positive detections, but the detection latencies would be shorter. As outlined in the previous section, this could lead to better classification accuracies since more discriminative data can be included in the feature extraction.

A limited number of patients were included in three of the studies as a proof of principle that attempted movement can be detected and decoded. In these studies, the initial negative phase of the MRCPs was similar between patients and healthy subjects (see figure 3-1) which could be an explanation for the similar performance of the detector and classifier. For the patients, however, more false positive detections occurred because many of them had difficulties relaxing in between the movements. More patients should be included to verify these findings. In this work, all patients had residual movement with mild to moderate hemiparesis. More severely injured patients, e.g. suffering from hemiplegia, could be included to investigate if they can operate such a BCI with similar performance. The size of the MRCPs is expected to be detectable in patients with such impairments since MRCPs have been shown to decrease with improved level of functionality after rehabilitation (80). Therefore, it can be hypothesized that a similar detection and decoding performance can be obtained. As outlined in the previous section, subjects could benefit from being visually cued in advance or to receive visual feedback on their performance, on the contrary to the self-paced online system in Study 3. The patients will lose the control of the pace of the movements with this approach, but the classification accuracies will likely improve, and the number of false positive detections could be reduced by having the detector enabled only when they were instructed to perform the movements.

In Study 4, it was tested if it was possible to decode different levels of force using a single electrode. The performance of this was comparable to an optimized channel (based on a linear combinatioin of nine electrodes); however, the performance of the classifier was relatively low. The findings from Study 5 showed that better classification accuracies were obtained when features were extracted from several channels. This may be due to that movement-related activity is better expressed at several sites in different time windows; therefore, it could be useful to use more electrodes to derive features from. Also, the risk of not obtaining a usable control signal in stroke patients (due to the great heterogeneity) will be reduced compared to using a single fixed site such as C3. The SFS outperformed PCA. However, when using SFS the calibration time of the system will increase since the subject-specific features must be selected from a large set of candidate features. The use of such a BCI system for rehabilitation may not be taken up by clinicians and patients if the calibration process becomes more complex and time consuming.

5.3. CONCLUSION

The conclusion of this work is that it is possible to detect single-trial MRCPs from stroke patients and healthy subjects offline and online. Also, different levels of force and speed as well as movement types can be decoded from the single-trial analyses from stroke patients and healthy subjects. However, further studies are needed to improve the online decoding of the MRCPs. With improved decoding, such an online system could have implications for stroke rehabilitation when it is combined with assistive technologies such as electrical stimulation or rehabilitation robots.

5.4. FUTURE PERSPECTIVES

In this thesis, it was outlined that it is possible to detect and decode MRCPs, but with low online performance there is a need to improve this for reliable BCI control. Better control could e.g. be obtained by finding features that are less sensitive to when the movement is detected and the great trial-trial variability. Individualized and larger feature vectors could potentially be derived followed by feature selection prior each use of the system. The longer calibration time of the system would potentially lead to better system performance. Through further research in machine learning reliable control and reduced system calibration time may be obtained. Moreover, it should be investigated how little training data are needed to calibrate a BCI system, so reliable performance is obtained, or if subject-independent detectors and classifiers can be constructed, so training data are not needed (96, 111). Ideally this should be tested in online studies and with large stroke patient groups with different levels of impairment. In this work, it was hypothesized that providing meaningful somatosensory feedback according to the decoded MRCP and introducing task variability in BCI training could promote motor recovery. This hypothesis needs to be tested to see if plasticity can be induced and retained in this way, and if it is a better way of training with a BCI than the current BCI training protocols. Randomized clinical trials are needed to show the efficacy of BCI-based rehabilitation. Besides the technical challenges, several areas need to be researched such as feedback modalities and pschycological factors.

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