Moving towards awareness detection
From Brain-Computer Interfacing to anaesthesia monitoring

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Chapter 1

Introduction

"Can observable electrical brain signals be put to work as carriers of information in man-computer communication or for the purpose of controlling such external apparatus as prosthetic devices or spaceships? Even on the sole basis of the present states of the art of computer science and neurophysiology, one may suggest that such a feat is potentially around the corner."

–Jacques Vidal, 1973

Over forty years have passed since Jacques Vidal proposed the concept of linking brains with computers [Vidal, 1973]. Within that period of time, the field of Brain-Computer Interfacing has seen many innovations and important breakthroughs. In 2005, a patient who could no longer move his arms except for his shoulder and elbow muscles, learned to control a neuroprosthesis for grasping objects, based on neural signals recorded from the scalp [Müller-Putz et al., 2005]. In 2012, Hochberg and colleagues let two patients with tetraplegia control a robotic arm through the use of an implanted micro-electrode array [Hochberg et al., 2012], while 2013 saw the introduction of a brain-controlled quadcopter [LaFleur et al., 2013].

A Brain-Computer Interface (BCI) is a system that interprets brain signals in order to translate them into useful output, such as control of a device. A user may imagine moving his left hand to indicate he wants to switch on the light, and imagine moving his right hand to switch it off. A similar mental task could be used to move a wheelchair around the room. Some systems focus on communication and enable users to type an email by means of attending to certain letters on a
screen. The important factor these various systems have in common, is that they require no muscular control. The computer takes over the function of neural output pathways, allowing communication by thought only. According to Wolpaw [Wolpaw and Wolpaw, 2012] natural central nervous system output can be either replaced, restored, enhanced, supplemented or improved by BCI output. A BCI can therefore be a solution for people who are otherwise unable to interact with their environment. BCI researchers commonly identify patients in a locked-in state, whose cognitive abilities have usually remained largely intact while their muscle control has (almost) completely been eliminated, as the most likely user group.

One group of patients that has thus far not been considered as potential BCI users are people undergoing surgery under general anaesthesia. If a patient awakes during surgery, but is paralysed because of a neuromuscular block, he or she may be considered to be in a temporary locked-in state: conscious but nevertheless unable to move or speak. The phenomenon of awareness during general anaesthesia is a source of anxiety, stress and other psychological problems in patients undergoing surgery, and one of the greatest challenges in anaesthesia research.

This thesis describes the development of a novel BCI that may in the future be used as a monitor of intraoperative awareness. The paradigm is based on the decoding of changes in sensorimotor rhythms during movement. If patients’ attempted movements can be detected by a BCI, they may allow for communication between a patient under general anaesthesia and the anaesthesiologist.

1.1 Brain-Computer Interfaces: unlocking the locked-in brain

BCIs enable people to drive devices directly with their brain signals, without producing any overt behaviour. The BCI decodes brain activity and converts this information to a sensible output such as a command for a device or computer. This technique allows people to communicate their intentions in a very direct way and is especially useful for people with severely disabled motor functioning. For patients who are partially or completely paralysed due to trauma or disease the most simple day-to-day tasks can be very demanding, if not impossible. BCIs may provide a means for these patients to interact with the world around them and regain a certain level of independence, and in some cases the systems may serve as an aid in rehabilitation.

In addition to the above-mentioned clinical purposes, various other types of BCI
applications have been developed, including brain-controlled gaming [Plass-Oude Bos et al., 2010] and painting [Münßinger et al., 2010]. For tracking cognitive and affective states, so-called ‘passive BCIs’ could be employed [Zander and Kothe, 2011], for instance to monitor alertness in flight controllers or truck drivers [Nijholt et al., 2008].

The underlying assumption of active Brain-Computer Interfacing is that a user’s cognitive functioning is - at least to an extent - intact, such that he or she can make a conscious decision. In other words, the user has an intention to convey a certain piece of information. The BCI detects and decodes the information contained in the brain signal. These signals can be obtained through various imaging techniques, usually electroencephalography (EEG), electrocorticography (ECoG) or intracranial recordings. The decoded intention is then converted to the desired output (e.g. moving a wheelchair or robot arm, spelling the letter ‘e’, or sending information about the user’s mental state to a doctor for diagnosis). Figure 1.1 shows the different stages of a BCI.

Figure 1.1: The stages of a Brain-Computer Interface. The user (a) performs a mental task (b), while the brain signals are measured (c) and amplified and digitised (d). The computer (e) decodes the signal and translates this into a certain output (f). The mental control task can be either self-induced or evoked, with or without the aid of an external cue (g) or feedback from the BCI output.

Two types of brain signals can be distinguished: evoked or exogenous signals, and induced or endogenous signals. Exogenous signals are obtained by presenting an external stimulus to the user, as they reflect the processing of the perception of this stimulus. Many of these responses have been well studied and are therefore generally useful and reliable in BCIs. Moreover, in a task depending on exogenous
signals, the stimuli can be controlled very precisely and the specific signal to be used for decoding is known beforehand. One of the most successful BCI systems so far uses evoked responses: the EEG-based matrix speller utilising the P300 odd-ball response [Hillyard and Kutas, 1983]. In classical oddball experiments target stimuli are presented at an infrequent rate compared to other (non-relevant) stimuli. The appearance of a rare stimulus evokes a positive deflection in the EEG response around 300 ms after stimulus onset, the so-called P300 effect. For the amplitude of the P300 to be modulated it is necessary that the target is recognized by the subject, but no verbal or motor response is required. Based on this response Farwell and Donchin [1988] proposed their P300 visual speller. In this paradigm the user selectively attends to a letter or command from a matrix presented on a screen. Since then many variations of the speller paradigm have been developed, including auditory [Schreuder et al., 2010, Höhne et al., 2011] and multimodal [Belitski et al., 2011] spellers. Importantly, the paradigm has proven to be successful in target users [Sellers and Donchin, 2006, Nijboer et al., 2008, Ikegami et al., 2014, McCane et al., 2015].

The downside of evoked responses is that the user depends on the presented stimuli to communicate an intention. Moreover, the user’s visual and/or auditory perception will have to be intact, depending on the modality the task is based on. By contrast, endogenous signals give the opportunity for self-paced control as they are internally generated and do not necessarily rely on an external stimulus. Frequency modulations caused by kinaesthetic imagery of movements are likely the most commonly used induced responses in BCI research. In many cases, an external stimulus serves as a cue for an internally generated task, for example a visual or auditory cue indicating when the user should start imagining to move either the left or the right hand. Induced brain responses may also be used in ‘asynchronous’ BCI designs, in which the task is fully self-paced. Asynchronous BCIs are, ultimately, preferable in most situations, as they provide the user with as much freedom as possible. While progress has been made in designing systems that are reliable despite the lack of a time-lock, these types of BCI are not yet widely used. For now, most paradigms still rely on a cue-based, synchronous design.

A specific type of BCI, mostly described within the context of asynchronous systems, is the so-called ‘brain switch’ [Mason and Birch, 2000, Pfurtscheller and Solis-Escalante, 2009, Qian et al., 2010]. Essentially, a brain switch is the most simple form of BCI as its aim is to detect just one single mental state from ongoing brain activity. While not suitable for every type of control due to the very limited choice of output options, it is the most practical BCI in cases where control is only
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required every once in a while instead of continuously. Not only can the user refrain
from performing a specific mental task when there is no need for system use or change,
but also the distinction between one mental task, e.g. a motor task, and a baseline
state, may be more robust than the distinction between two different types of motor
task [McFarland et al., 2000]. Sometimes, this robustness may therefore be chosen
over a more flexible control paradigm. A brain switch could also function as the
on/off button of a regular BCI, eliminating the need for continuous presentation of
stimuli whilst no control or communication is required [Kato et al., 2011, Pan et al.,
2013]. Brain switch systems have been tested in healthy users and patients alike. For
instance, in one study a patient with spinal cord injury was able to control a grasp
neuroprosthesis with a motor imagery-based brain switch [Müller-Putz et al., 2005].

Imaging methods

An important distinction exists between so-called ‘invasive’ and ‘non-invasive’ brain
measurement techniques. Invasive methods include implanted electrode grids or mi-
croelectrodes. While implanting electrodes in humans is not uncommon in the treat-
ment of neurological and psychiatric disorders, within the context of BCI research
most invasive studies have thus far only involved non-human primates. Examples
of successful studies in humans include the work by Hochberg and colleagues, who
showed the ability of patients with tetraplegia to operate a neuromotor prosthesis for
control of a computer cursor and reaching and grasping with a robotic arm [Hochberg
et al., 2006, 2012], while a patient in a study by Collinger and colleagues was able to
control a seven-dimensional prosthetic limb [Collinger et al., 2013]. Invasive methods
are often regarded to be more reliable than non-invasive BCIs, but while implanted
electrodes may be suitable for certain patient groups, for most BCI applications the
complicated surgery required is too much of a burden. However, technological ad-
vancements are expected to reduce the level of invasiveness of such systems, perhaps
paving the way for increased development of invasive neuroprostheses [Ramsey et al.,
2014].

One of the most important non-invasive brain imaging techniques used in BCI
applications is electroencephalography (EEG), which uses electrodes placed on the
scalp. Besides the fact that it has a high temporal resolution, an EEG setup is also
portable and therefore suitable for home use [Neuper et al., 2003]. EEG makes use
of the electrical potentials produced by large groups of neurons. It is recorded as
the potential for current to pass between the recording electrode and a reference
electrode. Because EEG provides such precise information on time and frequency
features, it is a very useful technique when studying processes with a rich temporal structure such as language or music processing. In BCIs this temporal resolution is an important advantage since it allows for fast communication. The spatial resolution of EEG however is rather low. Due to the low conductance of the scalp, smearing of the electrical signals occurs, resulting in a signal to be picked up by several surrounding electrodes rather than just by the electrode in the nearest location. On the basis of the voltage distribution over the scalp it can therefore not be determined what the exact dipole configuration causing the signal was.

EEG is very sensitive to nonbrain signals: electrical noise from the recording environment as well as artifacts caused by muscle tension and eye movements or blinks. To overcome the low signal-to-noise ratio, commonly repeated trials are averaged to obtain the relevant information and filter out random noise. In BCIs however, single trial classification is often required to allow for fast communication or control. Therefore, BCI research is regularly devoted to increasing the signal-to-noise ratio by improving EEG hardware as well as signal processing and machine learning techniques.

Functional Magnetic Resonance Imaging (fMRI), based on blood oxygenation levels in the brain, is an expensive, cumbersome and relatively slow neuroimaging technique, but in contrast to EEG it provides a very high spatial resolution. Although not a very popular choice for BCI, several fMRI-based studies have been conducted [Weiskopf et al., 2004, Sorger et al., 2012], while it is also an important tool for diagnosis and communication in patients with disorders of consciousness [Owen, 2013].

Recently, functional near-infrared spectroscopy (fNIRS) has gained popularity as an imaging method for BCI. Like fMRI, it measures hemodynamic changes and therefore indirectly detects cortical activation. fNIRS responses are measured by emitting near-infrared light through the scalp and skull using optical fibres. Light in the near-infrared spectrum is not absorbed by human tissue, but it does not entirely penetrate hemoglobin. Oxygenated and de-oxygenated haemoglobin have different absorption spectra. By emitting near-infrared light with two or more different wavelengths and detecting the light received at another optode the activation in the path between the transmitter and the receiving optode can be determined. fNIRS is portable and relatively cheap, and therefore more practical for most BCI setups than fMRI. Moreover, it is largely insensitive to noise caused by movement. Among the first to introduce fNIRS-based BCIs were Coyle and colleagues [2004] and Sitaram and colleagues [2007]. BCIs based on fNIRS have been studied for communication in patients with ALS [Naito et al., 2007] and for rehabilitation in patients with spinal cord
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injury [Koenraadt et al., 2014]. Recently, the use of hybrid EEG-fNIRS systems has been suggested [Fazli et al., 2012], a method that will be discussed here in chapter 5.

BCIs based on sensorimotor rhythms

Motor-based BCIs use the mu rhythm activity (8-12 Hz) and the related beta rhythm (18-25 Hz) in sensorimotor cortex. The mu and beta rhythms have been found to decrease in amplitude during movement or planning of movement (event-related desynchronization or ERD) and to increase right after movement (event-related synchronization or ERS) (Pfurtscheller 1999). Interestingly, these changes in sensorimotor rhythms (SMRs) occur even when the intended movement has no measurable external physical effect. Apart from during motor execution, these responses can be seen during motor imagery [McFarland et al., 2000], attempted movements in paralysed patients [Muralidharan et al., 2011], passive movements [Alegre et al., 2002] and quasi-movements, where subjects are instructed to minimise their intended movements to such an extent that they are no longer detectable with EMG measures [Nikulin et al., 2008]. BCIs based on movement tasks usually employ the spatial distribution of the changes in SMRs to distinguish between left- and right hand motor tasks [Pfurtscheller et al., 1997] or between movement of various body parts [Pfurtscheller et al., 2006, Morash et al., 2008]. Alternatively, spectral changes over the entire motor cortex may be detected during motor tasks as compared to a rest or baseline condition [Qian et al., 2010].

While changes in SMRs can be detected with several imaging modalities, EEG is the most common approach (however, ECoG can detect activity in much higher frequencies, which also contain substantial motor response information [Leuthardt et al., 2004]). In 1991 Wolpaw and colleagues trained users to modulate µ-rhythm activity in order to move a cursor on a screen [Wolpaw et al., 1991]. This setup was later improved to two-dimensional control and also validated in disabled users [Wolpaw and McFarland, 2004], while in another study successful SMR control was achieved by patients with ALS [Kübler et al., 2005]. SMR-based BCIs have been used for letter spelling [Blankertz et al., 2006b], neuroprosthesis control [Müller-Putz et al., 2005] and wheelchair control in a virtual environment [Leeb et al., 2007].

Users and applications

Most BCI research is aimed at people with severe motor disabilities, including patients with amyotrophic lateral sclerosis (ALS), multiple sclerosis, spinal cord injury, muscular dystrophy, Rett syndrome, Guillain-Barré syndrome and brain stem stroke.
The various potential user groups do not all share the same capabilities for using a BCI, nor the same requirements.

BCIs for communication are mostly aimed at patients with locked-in syndrome (LIS). In this group, while cognitive functioning is mostly intact, the patients’ thoughts and intentions can no longer be translated into muscular action. One of the causes of the locked-in state is ALS, a progressive neurodegenerative disease causing muscle weakness and atrophy. Motor nerve cells in the brain and spinal cord are affected and eventually the entire degeneration of peripheral motor neurons can cause a patient to lose all control of muscle movement. As the paralysis progresses the patients abilities to speak, swallow and breathe can be affected, eventually leading to a complete locked-in state. A recent review of EEG-based BCI studies involving physically disabled users showed that the majority of the participants were patients with ALS [Moghimi et al., 2013]. Although the reason for working with this particular group is not commonly specified, the progressive nature of the disease causes other types of access technology (e.g. mechanical switches) to become increasingly difficult to operate [Huggins et al., 2011]. Successful EEG-based BCI studies with patients with ALS so far only involved people in a classical or incomplete locked-in state, i.e. the patients had retained at least some form of muscle control, like vertical eye movements or blinking. Communication by people in a complete locked-in state may be problematic because of some form of cognitive impairment. It has been suggested that the main cause could be the loss of goal-directed thinking [Kübler and Birbaumer, 2008]. However, recently communication with a patient in the complete locked-in state was established with an fNIRS-based BCI [Gallegos-Ayala et al., 2014].

A special case of a ‘locked-in’ situation is encountered in patients with disorders of consciousness. Diagnosis of patients with reduced levels of consciousness is conventionally based on behavioural measurements. However, this may lead to misdiagnosis in cases in which a patient is fully paralysed yet (periodically) retains a certain level of conscious awareness and is thus in a locked-in state. Introduction of brain imaging techniques for determining a patients level of consciousness may therefore alter the current view on Vegetative State (VS, no evidence of awareness) patients, who might in some cases turn out to be in a Minimally Conscious State (MCS, evidence of periods of awareness) instead [Stins and Laureys, 2009, Cruse and Owen, 2010]. A major breakthrough was achieved when Owen and colleagues asked a patient who was behaviourally diagnosed as being VS to imagine playing tennis during an fMRI scan. The observed brain activity was indistinguishable from that of healthy volunteers performing the same task. The same was true for the activity observed when she was asked to navigate through her own house [Owen et al., 2006]. In a larger follow-up
study similar results were found for 4 out of 23 patients who were considered to be in a vegetative state [Monti et al., 2010]. In order to test whether it might be feasible to include neuroimaging methods in the routine assessment of awareness, EEG was later evaluated as an alternative method. Interestingly, significant changes in SMRs were observed in a patient diagnosed as VS when he was instructed to attempt moving [Cruse et al., 2012]. While BCIs could initially aid in diagnosing a patient’s state of consciousness, potentially they could be used for actual communication for patients who have proven to be in MCS. While this is a promising development, it is important to consider the practical and ethical implications [Kübler and Kotchoubey, 2007, Tamburrini and Mattia, 2011].

Another important user group comprises patients with varying degrees of partial paralysis. For these patients, control rather than communication is the purpose of using a BCI. The BCI could serve as an access technology to assistive devices such as wheelchairs, or for restoring lost motor functions by means of a neuroprosthesis [Millán et al., 2010]. However, concurrent physical, sensory and cognitive impairments, such as spasms or epilepsy, may further complicate BCI use for these patients [Nijboer et al., 2014].

Spinal cord injury, multiple sclerosis, muscular dystrophy, cerebral palsy and earlier-stage ALS are among the causes of paraplegia, where movement of the lower extremities is partially or completely lost, and tetraplegia, where both lower and upper extremity movement is impaired. In these patients, lost motor functions like grasping or walking can potentially be restored by means of BCI-controlled functional electrical stimulation (FES) [Müller-Putz et al., 2005, King et al., 2014]. Another strategy for regaining motor control is the actual restoration of natural motor functioning. Rehabilitation studies aim to utilise the brain’s plasticity and train the production of ‘normal’ brain activity. This is a promising research direction gradually receiving more attention by the BCI field [Daly and Wolpaw, 2008, Severens et al., 2014].

1.2 Awareness during general anaesthesia

General anaesthesia is administered to patients in order to facilitate a safe surgical procedure, while the patient is unaware of the events. However, insufficient depth of anaesthesia may lead to awareness during surgery [Ghoneim et al., 2009]. General anaesthesia involves the simultaneous administration of hypnotics (to achieve and maintain unconsciousness and prevent memory formation), analgesics (for pain relief), and neuromuscular blocking agents (for immobilization). Pharmacological
immobilization is the most important factor contributing to accidental awareness because paralyzed patients cannot seek attention from the anaesthetist or surgeon. The depth of anaesthesia is influenced by the balance between the dose of the anaesthetics and the amount of surgical stimulation. Furthermore, there is a large inter- and intra-patient variability in the response to anaesthetics; their actual pharmacodynamic effect can hardly be predicted or measured. As a consequence, attempts to measure whether adequate anaesthesia has been established basically come down to methods of probability [Kent and Domino, 2009].

Risks arise in both too light and too deep anaesthesia. On one hand, if the depth of anaesthesia is too low, awareness may occur with potential effects of intra-operative pain, panic and feelings of anxiety and helplessness. Serious psychological sequelae may develop afterwards including nightmares, anxiety or posttraumatic stress disorder (PTSD). On the other hand, deep anaesthesia can potentially lead to dangerous physiological changes, e.g., hypotension and longer durations of recovery [Kent and Domino, 2009]. Therefore, an adequate, well-titrated amount of anaesthetic is required to obtain optimal conditions for both patient and surgeon without inducing risks to the functioning of the central nervous system (CNS) and other vital organs.

Currently the incidence of intraoperative awareness lies around 0.1 to 0.2% [Ghoneim, 2007]. Estimates show this amounts to approximately 26,000 cases annually in the United States alone [Sebel et al., 2004]. Two more recent studies report even higher incidences of 1% (Spain, [Errando et al., 2008]) and 0.4% (China, [Xu et al., 2009]). On the other hand, a much lower incidence rate of 0.015% was reported in the first stage of a large-scale trial in the United Kingdom [Pandit et al., 2013], a number that has been reported before in the United States as well [Pollard et al., 2007]. Apart from possible demographical differences, two factors are relevant when considering the discrepancies between the outcomes of these studies. First, there is a dissociation between cases of awareness with and without explicit recall. Whether anaesthetists should always aim for full unconsciousness or whether the lack of recall may be sufficient remains a topic of debate [Sanders et al., 2012, Pandit, 2014]. Second, even when taking into account only cases of awareness with explicit recall, patients may not always report episodes of awareness spontaneously. Whereas some incidence studies report only those cases where awareness was spontaneously reported by the patient, in other studies they were questioned directly about whether they had experienced awareness during the period of intended general anaesthesia. Without explicit questioning, many cases may be missed [Mashour et al., 2009].

This discussion aside, the fact remains that patients may experience awareness during surgery. Therefore, several ways of monitoring depth of anaesthesia are in
practice, such as measurement of changes in blood pressure, heart rate, sweating and tear production. Commercial EEG-based monitors have been introduced such as the Bispectral Index (BIS, Aspect Medical Systems, Massachusetts) and the Entropy Module (GE Healthcare, Helsinki), looking for specific (changes in) features in the ongoing EEG signal. These monitors do not provide a straightforward indication of the patients state of awareness, but rather a dimensionless number reflecting a surrogate measure of the effect of anaesthetic drugs on the brain response. Measures are obtained through EEG sensors placed on the forehead and therefore only reflect changes in cortical activity in the frontal areas of the brain. The reliability of the current commercial systems has been questioned repeatedly [Bruhn et al., 2000, Schneider et al., 2002, Avidan et al., 2008, Ozcan et al., 2009, Kaskinoro et al., 2011], which could be the reason that EEG-based monitoring does not seem to be common in day-to-day clinical practice [Pandit et al., 2013].

1.3 Towards a BCI-based anaesthesia monitor

If BCIs could be used for awareness detection in patients with locked-in syndrome or disorders of consciousness, perhaps the technology could be applied to detect intraoperative awareness as well. After all, a patient becoming aware during general anaesthesia but paralysed by a neuromuscular blocking agent, is in a temporary locked-in state. Several studies have reported patients trying to move in order to alert the surgeon or anaesthetist when becoming aware during surgery [Ghoneim et al., 2009, Sandin et al., 2000]. What if those movement attempts could be detected from the brain signals? Indeed, motor imagery and attempt are known to produce a clear neural response and are therefore a common strategy used for BCI control. It is therefore useful to investigate the feasibility of detecting movement attempts during anaesthesia, and the applicability of this detection in either a stand-alone monitor, or as one component or feature of another system.

Two important aspects of the proposed BCI-based monitor would, theoretically, be an improvement over current commercial EEG monitors:

- it has a more intuitive interpretation as it is based on a specific neural response to motor tasks. This is in contrast to systems providing a dimensionless number reflecting the overall EEG state

- it is based on the brain response of the individual patient, rather than a population-based probability of awareness at a given pharmacodynamic (surrogate) EEG effect
Moreover, development of the system within the context of BCI research enables quick adaptation to other breakthroughs in the field, whether in terms of technical improvements (hardware or software) or gained knowledge with regard to cognitive processing and its neural signatures.

However, it is unclear whether current BCI paradigms can simply be transferred to the operating room. The following chapters will shed light on the requirements and feasibility of an 'anaesthesia brain switch'.

1.4 Outline of the thesis

In this thesis several empirical studies are presented, each addressing one of the fundamental questions underlying the proposed paradigm of a movement-based BCI to detect intraoperative awareness. Chapters 2, 3 and 4 are feasibility studies in which healthy volunteers performed various movement tasks under various conditions, after which the BCI performance was evaluated offline. In chapter 2, the aim was to define the parameter settings that would enable a feasible and reliable BCI for use in a clinical setting. Specifically, this study answers the questions of how many EEG channels are required to provide a good accuracy-efficiency tradeoff, and whether an acceptable true positive and false positive rate can be achieved. Chapter 3 presents the first of two EEG studies performed in an operating room, rather than a lab setting. In this study, the influence of temporary paralysis, induced by a neuromuscular blocker (rocuronium), on movement-related EEG signatures was studied. In other words, while subjects attempted to move, actual neuromuscular output was chemically blocked, providing insight in the question how these attempted movements relate to executed and imagined movement. In chapter 4 the effect on the EEG of another component of general anaesthesia was evaluated: volunteers were sedated by means of the hypnotic agent propofol. So, chapters 2, 3 and 4 describe the first steps in the development from the concept of the well-known movement-based BCI to a concept that may be feasible to use in an operating room during general anaesthesia procedures.

Chapters 5 and 6 go further into an interesting topic that was touched upon in chapter 3: how do executed, attempted and imagined movements relate, in terms of their respective EEG signatures and usability for BCI? In chapter 5 both attempted and imagined finger movements were carried out by patients with tetraplegia, to examine whether the first type of task would lead to improved BCI control as compared to the latter. Moreover, EEG and fNIRS were measured simultaneously. The results show that a multi-modal system may be more accurate, and could even be a solution
for 'BCI illiteracy'. In chapter 6 a case is made for switching from motor imagery to motor attempt in BCI research and applications, backed up by the results from both healthy volunteers (chapter 3) and patients (chapter 5).

Finally, theoretical questions arising from the topics presented in this thesis as well as directions for future research are discussed in chapter 7.
Chapter 2

Paradigm Development

Abstract

During 0.1-0.2% of operations with general anesthesia, patients become aware during surgery. Unfortunately, pharmacologically paralyzed patients cannot seek attention by moving. Their attempted movements may however induce detectable EEG changes over the motor cortex. Here, methods from the area of movement-based brain-computer interfacing are proposed as a novel direction in anesthesia monitoring. Optimal settings for development of such a paradigm are studied to allow for a clinically feasible system. A classifier was trained on recorded EEG data of ten healthy non-anesthetized participants executing 3-second movement tasks. Extensive analysis was performed on this data to obtain an optimal EEG channel set and optimal features for use in a movement detection paradigm. EEG during movement could be distinguished from EEG during non-movement with very high accuracy. After a short calibration session, an average classification rate of 92% was obtained using nine EEG channels over the motor cortex, combined movement and post-movement signals, a frequency resolution of 4 Hz and a frequency range of 8-24 Hz. Using Monte Carlo simulation and a simple decision making paradigm, this translated into a probability of 99% of true positive movement detection within the first two and a half minutes after movement onset. A very low mean false positive rate of <0.01% was obtained. The current results corroborate the feasibility of detecting movement-related EEG signals, bearing in mind the clinical demands for use during surgery. Based on these results further clinical testing can be initiated.
2.1 Introduction

In 0.1-0.2% of surgeries involving general anesthesia, patients experience unintended intraoperative awareness [Sebel et al., 2004]. Two more recent studies report even higher incidences of 1% and 0.4% [Errando et al., 2008, Xu et al., 2009]. The phenomenon is frequently described [Ghoneim et al., 2009, Kent and Domino, 2009, Leslie and Davidson, 2010] and several monitors of depth of anesthesia (e.g. Bispectral Index; Entropy Module) are now in clinical use. Nevertheless, current technology cannot prevent awareness in every patient.

Up until now, development of electroencephalography (EEG)-based monitors of depth of anesthesia has focused on general state changes in the EEG caused by administration of anesthetic drugs. As clear neural correlates of consciousness have not yet been found, current measures rely on neural processes that are unclear and cannot be properly controlled. Contrastingly, in Brain Computer Interface (BCI) research, mental tasks with clear neural responses are used as input to control a device or provide other means of communication without the use of overt behaviour. BCIs decode information from brain activity, commonly measured by EEG, and convert this information to a sensible output, e.g. a command for the connected device or computer [van Gerven et al., 2009]. Potential users of BCIs are, for instance, patients suffering from neurodegenerative diseases such as Amyotrophic Lateral Sclerosis, where despite severe motor impairment, cognitive functioning usually remains largely intact. BCIs circumvent the route of overt movement and directly interpret the user’s intentions from the brain signal.

A commonly used paradigm is the movement-based BCI. It uses the mu rhythm activity (8-12 Hz) in the sensorimotor cortex and the related 18-25 Hz beta rhythm. These have been found to decrease in amplitude during movement or planning of movement (event-related desynchronization or ERD) and increase right after movement (event-related synchronization or ERS) [Pfurtscheller and Lopes da Silva, 1999]. This holds for executed as well as imagined movement. So, by detecting ERD and/or ERS, the BCI can infer that the user was executing or imagining a certain movement.

Patients have consistently reported trying to move when they became aware during surgery [Ghoneim et al., 2009, Sandin et al., 2000]. However, neuromuscular blocking agents may entirely prevent the patient to move. The above evidence shows that movement, whether covert or overt, has very clear neural correlates that can be detected with high reliability. We propose a monitor relying on these specific correlates to detect attempted movement, and therefore awareness, during anesthesia.

The specific system settings required for a feasible clinical paradigm have not
yet been determined. Numerous parameters influence the setup and performance of a BCI, depending on the desired application, while each application also has its own requisites. Most importantly, the paradigm presented here requires 1) a small, generic electrode set, thus ensuring a short setup time, and 2) a minimal false positive rate (FPR). False positives occur when the system detects a hit when attempted movement is in fact absent. Contrastingly, false negatives occur when the system fails to detect the presence of an attempted movement. Therefore, they increase the reaction time of the system as several attempts may be required for a correct detection. Although for some applications speed may be prioritized over accuracy, for the current application it is important that false alarms are kept to an absolute minimum. Considering that anesthetists are obliged to remain focused at all times, more than one false alarm in two to three hours operating time and a delay of more than 2.5 minutes to detect attempted movement do not seem to be clinically acceptable.

Here, we first investigate what EEG frequency resolution, frequency range, EEG channels and which movement-related brain signals provide the most reliable information for possible intraoperative use. Then, in order to explore the feasibility of this paradigm in clinical situations, these optimized settings are used in a simulation of a running system, showing that the resulting false positive rate and true positive rate meet our clinical requirements.

2.2 Methods

Ethics statement

The protocol was approved by the Ethical Committee of the Faculty of Social Sciences of the Radboud University Nijmegen. All subjects gave written informed consent and procedures were according to the Declaration of Helsinki.

Participants

The electroencephalogram of ten healthy, non-anesthetized and non-paralyzed participants (24-44 yrs, 4 males) was obtained while they were performing a series of movement tasks. All participants had normal or corrected-to-normal vision and hearing and none had any known neurological impairments.
Figure 2.1: Stimulus sequence. Each sequence started with an auditory sequence instruction, i.e. No Movement or Both Arms Movement. Following the instruction were nine trials consisting of a cue (task) and their corresponding baseline periods used for analysis.

Materials and procedure

Sequences of nine consecutive movement trials were presented to the subjects. Each trial consisted of an auditory 3-second cue preceded by a silence interval of a random duration between 4 and 6 seconds (Figure 1). At the start of each sequence, an auditory instruction was given explaining the task for the upcoming trials. The three types of sequence instruction were Right Hand Movement, Both Arms Movement and No Movement. As the comparison between classifying either Right Hand or Both Arms movement has been reported elsewhere [Blokland et al., 2011] and no major differences were found, the current paper only takes into account the ‘Both Arms Movement’ condition as compared to the ‘No Movement’ condition.

In the ‘Both Arms Movement’ condition subjects made a gross movement with both arms during the auditory cues. In the ‘No Movement’ condition subjects were
instructed to keep still. Participants were asked to keep their eyes closed throughout the entire sequence. However, visual instructions were displayed at all times in case the subject needed a quick reminder of what the task was for that particular sequence. The experiment was self-paced, i.e. between sequences participants could have a short rest and start the next sequence themselves by pressing a button.

In total, 144 trials were collected per condition, equally divided over four experimental blocks, i.e. each block containing 4 sequences of 9 trials for each movement type. Within each block, presentation of the sequences was randomized. A short practice block to get the participants acquainted with the task preceded the actual measurements.

A Biosemi Active-2 system was used for EEG recording of 64 channels placed according to the 10/20 system [Jasper, 1958], sampled at 2048 Hz and then down-sampled to 256 Hz. Additionally, EMG of the right arm was recorded. Electrode offsets were kept below 25 µV before starting the measurement. Stimuli were played through passive speakers (Monacor, type MKS-28/WS) at a comfortable listening level. Additional instructions were displayed on a 17” TFT display with a resolution of 600x800. The experiment was programmed in and run on the BrainStream platform\(^1\) version 1.0, i.e. a Matlab (MathWorks Inc., MA, USA) toolbox especially developed for performing online BCI-experiments, using Psychtoolbox\(^2\) for stimulus presentation.

**Analyses**

A grand average time-frequency plot using a baseline from -1.5 to -0.5 seconds before the start of the task was computed to define the onset and offset of the event-related desynchronization. Based on this plot, trials used for classification were fixed at a period lasting from movement onset (t=0 s) until one second after movement offset (t=4 s). As a post-movement synchronization was also visible in the time-frequency plot, classification rates were computed for the post-movement period (t=4-6 s) as well. From now on, the period from 0-4 seconds will be referred to as the 'ERD period' and the period from 4-6 seconds as the 'ERS period’. To remove slow drift, linear detrending was performed. After calculating the surface Laplacian reference for each channel using Perrins spherical spline interpolation method [Perrin et al., 1989], the power spectral density was computed for 8-24 Hz using Welch’s method [Stoica and Moses, 1997] with a hanning taper applied to 50% overlapping windows. We also

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\(^1\)http://www.brainstream.nu
\(^2\)http://psychtoolbox.org
investigated which were the optimal spectral features in terms of frequency resolution and range, by varying the size of the window (125, 250, 500, or 1000ms) and varying the subset of frequencies in the mu/beta range to keep for further analysis. This subset of power spectral features for each selected channel was then used to train a quadratically-regularized linear logistic regression classifier (rLLR) [Bishop, 2006] to distinguish between each subjects specific pattern of spatial and spectral activation for the 'Both Arms Movement' and 'No Movement' tasks. This classifier uses a subset of the data to find a linear weighting over the input features which gives the best fit to the data (i.e. most accurate predictions), subject to a regularization constraint that excludes unlikely values, e.g. extremely large weights for any feature. What distinguishes rLLR from other similar classifiers (such as Support Vector Machines [Zhu and Hastie, 2005]), is that rLLR gives a natural estimate of the class probability,

$$Pr(x) = \frac{1}{1 + exp(-f(x))}$$  \quad (2.1)

where x is the set of input features, f(x) is the classifiers decision value found by making a weighted summation of the input features x and the classifiers weighting w over these features, with an offset b, i.e.

$$f(x) = \sum_i x(i)w(i) + b$$  \quad (2.2)

Thus, although not used in the present work, with rLLR one obtains a natural estimate of the classifiers confidence in its prediction, which is valuable in a monitoring style application such as the one studied here. The classifier’s performance was estimated using ten-fold cross-validation, thus creating ten non-overlapping test sets. After computing classification results for the ERD period and the ERS period separately, results were also computed for a classifier trained with features from both periods.

A total of six EEG channel combinations was tested in order to find an optimal balance between setup time and accuracy. Classification results obtained with the use of all channels were compared to the results of using an 18-channel set [Tam et al., 2011], as well as a 12-, 9- and 6-channel set. The positioning of the electrodes for each set is shown in Figure 2. As the ERD and ERS are especially prevalent in the motor cortex, channel sets all surrounded C3 and C4. Furthermore, the use of a Laplacian C3 [Qian et al., 2010] was evaluated and its performance was compared to that of the other channel sets. In these analyses, removal of all channels not part of the relevant channel set was done prior to all other preprocessing steps.
The 9-channel set was used to check for possible further optimization. First, in addition to the 4 Hz frequency resolution, i.e. creating one feature in the frequency dimension for each 4 Hz window, classification rates were calculated using resolutions of 1, 2 and 8 Hz. Second, using a resolution of 4 Hz, classification rates were calculated for the additional frequency ranges of 8-20 Hz and 8-28 Hz.

Next, classification rates were recomputed to simulate a clinical scenario with a 10-15 minute pre-operative calibration session for classifier training. Here, we used the first experimental block for classifier training (calibration) and then calculated classification rates for the remaining three blocks (operating time). Results were compared with the results of the ten-fold cross-validation and calculated for the 12-, 9- and 6-channel sets.

The classification results after training on one block, with the 9-channel set and the combined ERD and ERS periods, were used in a simulated decision making paradigm. In this decision-making paradigm, four consecutive positive classifica-
tions (i.e. 'movement') would be required for the monitor to give the corresponding warning.

Given the above assumptions, the cumulative probability of a true positive detection after an increasing number of movement trials was calculated. As each experimental sequence consisted of nine trials, this cumulative probability could be determined from the collected data up to nine trials (72 seconds) for each subject. To further extend this period, another nine trials were simulated using a Monte Carlo method [Mooney, 1997].

The false positive rate was also determined, with a similar requirement of four consecutive positive classifications in a row, calculating it as $(1 - \text{classification rate})^4$. This number represents the average duration of monitoring before a false positive event will occur.

All software was developed 'in-house' using Matlab, and is available as part of the Brainstream platform or directly from the authors on request.

2.3 Results

The average time frequency plot of the Both Arms Movement trials of all participants is given in Figure 3. A clear power decrease during the movement period (ERD) and power increase after movement offset (ERS) are seen, especially in the channels located over the motor cortex. For example, in channel C3, in the 10-14 Hz range the mean power values for the ERD period decreased with 30.4% (SE 0.9%) during 'Both Arms Movement' as compared to 'No Movement', whereas in the 14-18 Hz range mean values for the ERS period increased with 27.4% (SE 2.1%) during 'Both Arms Movement' as compared to 'No Movement'. An extended ERD period after task offset is visible. The corresponding extended muscle activity observed in the participants EMG data suggests this can most likely be attributed to task response time.

The classification rate decreased when reducing the amount of channels (Figure 4). Single trial results are shown using only the ERD or ERS period as well as using them simultaneously. For the ERD period, the average classification rate was 98% when using all 64 channels, whereas for the 18-, 12- and 9-channel sets the rates were all approximately 95%. When reducing further to a 6- and 4-channel set, rates decreased to 92% and 90%, respectively.

Although the post-movement period between 4 and 6 seconds, associated with ERS, gave slightly lower classification performance than the information from ERD during movement, combining these results further increased single trial results. The
18-, 12- and 9-channel sets yielded an average rate of 96%, the 6-channel set yielded 95% and the Laplacian C3 (4 channels) benefited most from incorporating the ERS feature, with rates increasing to 94%.

Tables 1 and 2 show that the use of different frequency resolutions and frequency bands yielded nearly unchanged classification results.

Compared to the classification results when using ten-fold cross-validation over all collected data, results of the three final blocks with the first block used as training session were slightly lower (Table 3).

<table>
<thead>
<tr>
<th>Subject #</th>
<th>1 Hz</th>
<th>2 Hz</th>
<th>4 Hz</th>
<th>8 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>99</td>
<td>98</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
<td>95</td>
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</tr>
<tr>
<td>3</td>
<td>89</td>
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<tr>
<td>4</td>
<td>96</td>
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<td>93</td>
<td>94</td>
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<td>98</td>
</tr>
<tr>
<td>Average</td>
<td>96</td>
<td>96</td>
<td>96</td>
<td>96</td>
</tr>
</tbody>
</table>

Table 2.1: Single trial classification rates in % per subject using different frequency resolutions. Calculations were done using 9 channels and the combined ERD and ERS periods.

In Figure 5 the results of the mathematical simulation of the decision making paradigm are shown, in which 4 trials in a row classified as 'Both Arms Movement' define a positive monitor output. The cumulative probability of a true positive monitor output with an increasing delay after movement onset was calculated. These results are for a classifier trained on 1 block of data only (10-15 minutes), using the 9-channel set and both the ERD and ERS periods. Actual performance was calculated for the 9-trial sequences, results for the remaining 9 trials were obtained by means of a Monte Carlo simulation.

The calculated rate of a false positive monitor output, using similar settings, with 4 trials in a row falsely classified as Both Arms Movement during No Movement, is <0.03% in all subjects with a mean of <0.01%. This translates into an average duration until a false positive event occurs of >7 hours in all subjects.
Figure 2.3: Grand average time-frequency plot of all 64 channels. Spatial downsampling was performed with a Surface Laplacian; the period from $t=-1.5$ to $t=-0.5$ s was used as the baseline period. Blue colouring represents ERD; red represents ERS. The motor cortex is situated in the central regions (C3-C4). An enlargement of channel C3 is shown in the right-hand corner, with the dashed lines indicating the onset and offset of the auditory cue (task period).
Table 2.2: Single trial classification rates in % per subject using different frequency ranges. Calculations were done using 9 channels and the combined ERD and ERS periods.

<table>
<thead>
<tr>
<th>Subject #</th>
<th>8-20 Hz</th>
<th>8-24 Hz</th>
<th>8-28 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>99</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>97</td>
<td>94</td>
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<td>98</td>
<td>98</td>
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<tr>
<td>Average</td>
<td>96</td>
<td>96</td>
<td>96</td>
</tr>
</tbody>
</table>

2.4 Discussion

The event-related desynchronization (ERD) and -synchronization (ERS) accompanying movement are features commonly used in movement-based Brain-Computer Interface paradigms. A new BCI application, based on these features, has been proposed here: detection of attempted movement to signal intraoperative awareness. A classifier was trained to distinguish movement trials from non-movement trials based on frequency information in the EEG. We tested several paradigm settings in order to find an optimal combination of factors contributing to the BCI, therefore allowing for a system that is clinically feasible.

The principal finding of this study is that a single trial classification of 92% is obtained after a short training period, with only nine EEG channels if the ERD and ERS features are used simultaneously, as well as a 4 Hz frequency bin and a 8-24 Hz frequency range. With the requirement of four trials in a row classified as positive before a positive monitor output is generated, this translates into an extremely high probability of a true positive response within two and a half minutes after movement onset (99.3%) and a minimal false positive rate (<0.01%). Hence, important clinical requirements are met with the proposed setup: minimal setup time because of the small number of EEG channels and high system accuracy because of the strength of the signal. Although not all feature settings chosen here proved to be significantly
Table 2.3: Classification rates using ten-fold cross-validation (10-fold) versus using only the 1st experimental block (1st block) for training.

<table>
<thead>
<tr>
<th># of channels</th>
<th>Time period</th>
<th>10-fold</th>
<th>1st block</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>ERD</td>
<td>95</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>ERD+ERS</td>
<td>96</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td>ERD</td>
<td>94</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>ERD+ERS</td>
<td>96</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>ERD</td>
<td>92</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>ERD+ERS</td>
<td>95</td>
<td>90</td>
</tr>
</tbody>
</table>

Although using 32 to 64 channels for classification is common in BCI research, there are numerous reasons for reducing the number of channels used: reduction of EEG preparation time, reduction of the cost of the acquisition hardware and a reduced risk of overfitting the classifier [Tam et al., 2011]. Rather than aiming to find a minimal electrode set for individual subjects [Tam et al., 2011, Long et al., 2010], we are interested in a generic minimal electrode set that is feasible for all users.

A major reduction in EEG setup time was obtained at a very low cost in terms of information loss. An optimized balance between the number of channels and system accuracy was obtained using a set of nine channels at electrode positions C3, C4, Cz, F3, F4, P3, P4, T7 and T8. After this major reduction in channel set size, i.e. from 64 to 9 channels, single trial classification rates decreased only slightly from 98% to 96%. Further reducing the amount of channels does not decrease EEG setup time by much whereas classification rates are still reduced. Recently, even single Laplacian channel setups have been discussed (using Laplacian C3 to detect hand movement [Qian et al., 2010] and using Laplacian Cz to detect foot movement [Müller-Putz et al., 2010]). However, this type of channel setup still requires three to four surrounding electrodes in order to be able to make the Laplacian derivation. In our study a rate of 90% was obtained for the Laplacian C3 set (4 channels) when using only the ERD period and of 94% when using the ERD and ERS periods combined.

No major differences were found between different frequency resolutions. One might expect generally larger frequency resolutions to be too coarse to specifically capture the movement-induced changes in a specific frequency band of the power spectrum, whereas generally smaller frequency resolutions might have the risk of
Figure 2.4: Decrease in average classification rate with corresponding standard errors when reducing the number of trials, using either information from $t=0-4s$ (ERD), $t=4-6s$ (ERS) or both (ERD+ERS). Channel sets correspond to the channel sets in Figure 2. To clearly show the rates for all time periods, data points are slightly shifted to either left or right. The dashed line represents the binomial confidence interval, i.e. all classification rates above this line are significantly better than chance ($p = 0.01$).

overfitting the classifier. However, these effects cannot be directly derived from our findings.

Our analysis showed that leaving out frequencies above 24 Hz, and even above 20 Hz, does not decrease classification results, implying that frequencies in the upper beta-band / lower gamma-band do not contribute significantly to the classifiability of the signal. Whereas typically movement-induced changes in the alpha- and beta-band are used in BCI algorithms, changes in higher frequency bands (i.e. gamma) have also been used [Grosse-Wentrup et al., 2011, Zhang et al., 2010]. It has been debated whether the higher frequency ranges can actually show cognitive processing or whether they mostly represent EMG. Whitham and colleagues [2007] showed that
Figure 2.5: Cumulative probability of true positive monitor output after start of movement. Movement was assumed to start at trial 1 (t=0 s) with a trial duration of 8 seconds. As in this paradigm 4 positive classifications in a row are needed for a positive monitor output, the first possible positive monitor output is at trial 4 i.e. 32 seconds after movement onset. For each subject plus the average of all subjects, the solid line shows the output for the recorded sequences. The dashed lines show the interpolation of this output for another 9 trials using a Monte Carlo simulation.

Frequency ranges above 25 Hz are largely contaminated by EMG and therefore do not necessarily give much information about EEG signatures. In that particular study, EEG obtained from participants temporarily paralyzed with cisatracurium was compared to data from non-paralyzed individuals. Signals above 25 Hz were hugely reduced in power after paralysis, even in central scalp regions. In the current paper, paralysis is precisely the problem we are addressing; hence we need to make sure that our information is not contaminated by EMG. Therefore, the frequency bands used for analysis were reduced down to 24 Hz, with the results suggesting that we are in fact detecting EEG, not EMG.

The use of awareness monitors based on spontaneous EEG, such as the Bispectral Index or Entropy Module, does not decrease the rate of intraoperative awareness as opposed to simply keeping the endtidal concentration of volatile anesthetics above 0.7 MAC [Avidan et al., 2011]. These monitors do not measure signs of consciousness but instead a pharmacodynamic effect of anesthetic drugs on the spontaneous EEG. Even worse, their ability to help titrating anesthetic drugs during general anesthe-
sia has been questioned recently [Whitlock et al., 2011]. We therefore propose a completely new paradigm to detect intraoperative awareness, based on movement-related BCIs. The main underlying problem of intraoperative awareness is the fact that pharmacologically paralyzed patients under general anesthesia are unable to move and thus cannot seek attention from the anesthesiologist or surgeon. Their attempted movements, consistently described in the awareness literature, would now be translated into a monitor output by an algorithm detecting the movement-induced EEG changes over the motor cortex.

Ideally, such a BCI-based system should be asynchronous allowing the detection of movement at any time. However, despite of their user benefits, asynchronous systems are not widely used in BCI. Their lack of a time lock makes the analysis of the EEG signal more challenging. Here, we propose a cued synchronous design, meaning that patients would be instructed to (try to) move their hands/arms during sounds, continuously played throughout the operation, and not to move during the silence periods. Prior to anesthesia and surgery, there would be a 10-15 minute calibration session in order for the patient to get acquainted with the task and to train the classifier on the patients signals. During the operation, detection of the attempted movements would activate the BCI-based awareness monitor. It might be argued that the need for a 10-minute training session before an operation is prohibitive. Recent results in the movement-based BCI literature on so called ‘zero training’ BCIs indicate that with more advanced signal classification methods this training period may not be required [Reuderink et al., 2011]. This is an area for future research.

Low doses of anesthetic drugs might be present during cases of awareness. Their effect on movement-induced EEG changes is still unknown. It might be questioned whether patients under anesthesia who are somewhat conscious are able to attend well to a task demand of only trying to move when a sound is being played. Further research is required to test the influence of anesthetic drugs on both peoples ability to perform such a task and the corresponding brain signal.

Although in this study actual executed movements were used, eventually we are interested in studying the EEG effects of attempted but pharmacologically blocked movements. Nikulin and colleagues [2008] showed that so-called ‘quasi movements’, intended movements deliberately minimized to such an extent that they become undetectable with EMG, generate a similar but stronger response than imagined movements and therefore qualify as an improved task for BCI over traditional covert movements. Likewise, attempted movements from individuals paralyzed after stroke have been found to be detectable from EEG [Muralidharan et al., 2011].
Despite the abundance of literature on the choice of parameter settings in BCI, there is no widely accepted standard BCI procedure available that can be used unaltered for monitoring of attempted movements during anesthesia. Here, a systematic analysis of such settings was carried out, bearing in mind the specific clinical requirements. Important aspects of this study adding to the field and bringing us closer to the use of this approach in anesthesia are:

1) A generic, subject independent subset of electrodes resulting in very high classification performance in each individual subject. This adds to the scarce data about subject independent channel selection [Sannelli et al., 2010], whereas commonly BCI studies focus on individually optimized channel selection since this is most interesting for the long-term use in neurological patients. For clinical use during anesthesia however, a standard montage of a reduced electrode set, working for all patients, is required. Here we have given a systematic comparison between different electrode sets and shown that the 9 channels mentioned above are sufficient to obtain the true positive and false positive rates required in the context of anesthesia monitoring.

2) The fact that the maximum frequency considered can be lowered down to 24 Hz and even 20 Hz without significantly decreasing classification performance. Whereas in classical BCI paradigms this may be of lesser importance, as conditions during the training period are largely comparable to those during the testing phase, in our case any EMG activity that may be present in the pre-operative training session will certainly be absent after administration of neuromuscular relaxant drugs.

3) The novel suggestion of a four-in-a-row algorithm for decision making, proving to be appropriate for an intended very low false positive rate (0.01%) and a high true positive rate (99% within 2.5 minutes). Based on our experience in clinical anesthesia and anesthesia monitoring, the maximum acceptable rate of false alarms is one per 2 hours operating time, with a delay of no more than 2.5 minutes before detection of attempted movement. These assumptions can be used as blueprints for other BCI groups without a clinical anesthesia background to further improve the suggested concepts.

In conclusion, a highly accurate system has been proposed that, despite its current limitations, can be further developed into a BCI monitor to detect intraoperative awareness in a clinical environment. Future work will test this paradigm in temporarily paralyzed participants and in the presence of low doses of anesthetics.
Chapter 3

Decoding motor responses during neuromuscular block

Abstract

Brain-Computer Interfaces (BCIs) have the potential to detect intraoperative awareness during general anaesthesia. Traditionally, BCI research is aimed at establishing or improving communication and control for patients with permanent paralysis. Patients experiencing intraoperative awareness also lack the means to communicate after administration of a neuromuscular blocker, but may attempt to move. This study evaluates the principle of detecting attempted movements from the electroencephalogram (EEG) during local temporary neuromuscular blockade. EEG was obtained from four healthy volunteers making 3-second hand movements, both before and after local administration of rocuronium in one isolated forearm. Using offline classification analysis we investigated whether the attempted movements the participants made during paralysis could be distinguished from the periods when they did not move or attempt to move. Attempted movement trials were correctly identified in 81 (68-94)% (mean (95% CI)) and 84 (74-93)% of the cases using 30 and 9 EEG channels, respectively. Similar accuracies were obtained when training the classifier on the participants actual movements. These results provide proof of the principle that a BCI can detect movement attempts during neuromuscular blockade. Based on this, in the future a BCI may serve as a communication channel between a patient under general anaesthesia and the anaesthesiologist.
3.1 Introduction

Detecting unintended awareness during surgery remains one of the biggest challenges in anaesthesia research and clinical practice. The incidence of awareness with post-operative explicit recall is currently 0.1-0.2% [Sandin et al., 2000, Sebel et al., 2004]. While these numbers are still a topic of debate [Pandit et al., 2013, Avidan and Mashour, 2013] the possible psychological sequelae for a patient are not.

As the clinical signs of inadequate anaesthesia have proven to be unreliable, depth of anaesthesia monitors have been developed. Clinical estimates of depth of anaesthesia, such as the PRSTscore (based on the observation of systolic blood Pressure, heart Rate, Sweating and Tears), are particularly masked by the effects of cardiovascular active medication in an ever-increasing proportion of the patients [Bruhn et al., 2006].

Most commercially available depth of anaesthesia monitors are based on spontaneous frontal EEG activity [Mashour et al., 2012]. With increasing anaesthetic drug concentrations characteristic changes in the spontaneous frontal EEG appear. After an initial increase in the beta band activity, the EEG slows down with a shift in the frequency spectrum to the theta and delta frequency bands. With further increasing anaesthetic drug concentrations burst suppression patterns appear with increasing phases of suppression until complete iso-electric activity. A simple way to track these changes with a single parameter from the power spectrum after Fourier Transformation is the median frequency, describing the frequency where 50% of the total power is above and 50% of the total power is below this frequency. Another parameter is the spectral edge frequency 95, describing the frequency where 95% of the total power is below this frequency. Both frequencies decrease with increasing anaesthetic drug concentrations. The disadvantages of these two approaches are paradoxical increases at lower anaesthetic drug concentrations caused by the beta increase and at high anaesthetic drug concentrations caused by the high frequency, high amplitude bursts during burst suppression [Rampil, 1998].

These issues have been solved by the commonly used Bispectral Index (BIS) [Bruhn et al., 2006, Sigl and Chamoun, 1994]. The BIS is a multi-parameter index which incorporates a parameter from the frequency spectrum like the relative beta-ratio, parameters from the bispectrum and a burst suppression ratio. The BIS is the weighted sum of these features, trained and tested against data from patients who underwent different kinds of anaesthesia. The monitors output is a user-friendly number on a 0-100 scale (100=awake, 0=iso-electric). BIS values decrease with increasing anaesthetic drug concentrations. BIS values of 40-60 have been recommended as
target during surgery under general anaesthesia. Use of the BIS monitor has been shown to reduce the incidence of intraoperative awareness [Myles et al., 2004, Ekman et al., 2004].

Nonetheless, the BIS monitor has several shortcomings. If using volatile anaesthetic drugs, like isoflurane or sevoflurane, the BIS is not superior to a regimen based solely on end-tidal drug concentration measurements regarding the incidence of intraoperative awareness [Avidan et al., 2008]. The BIS also does not adequately reflect the effects of anaesthetic drugs like ketamine or nitrous oxide [Palanca et al., 2009]. The standard frontal montage does not give insight in the deeper brain structures involved in consciousness and memory formation but the BIS is a constructed abstract quantity that is not directly linked to any physiological parameter [Musizza and Ribaric, 2010]. Therefore it is not surprising that even the use of the bispectral index reduces but does not eliminate the incidence of intraoperative awareness. Furthermore a clear cut-off value derived from the processed EEG discriminating consciousness from unconsciousness is also missing. Whereas a range of BIS values of 40 to 60 is recommended during surgery, these values are quite arbitrarily chosen and the upper limit of 60 does not mean that every patient with a BIS value above 60 is conscious and every patient with a BIS value below 60 is unconscious [Russell, 2007, Whyte and Booker, 2003]. Therefore, frontal cortical EEG measures a dose-dependent pharmacodynamic effect of anaesthetic drugs, but does not per se measure consciousness. The interested reader is referred to the literature for further details on monitors of anaesthetic depth [Bruhn et al., 2006, Rampil, 1998, Palanca et al., 2009, Musizza and Ribaric, 2010, Whyte and Booker, 2003].

General anaesthesia involves the simultaneous administration of different components including a neuromuscular blocker for immobilization. Consequently, patients cannot communicate their awareness to the surgeon or anaesthetist even though they attempt to move [Sandin et al., 2000]. We propose a novel monitor of intraoperative awareness based on detection of these movement attempts.

This paradigm follows the principles and techniques from the field of Brain-Computer Interfacing. A Brain-Computer Interface (BCI) measures a users brain signal, usually with electroencephalography, and translates this information to commands to drive a device or to enable communication. As it does not depend on overt behaviour such as speech or movement, a BCI can be beneficial for motor-impaired persons such as locked-in patients [Laureys et al., 2005]. Patients under insufficient levels of anaesthetic drugs but nevertheless fully paralyzed by a neuromuscular blocker find themselves in a similar situation.

A well-known BCI paradigm is detection of imagined and attempted movement.
Patterns of a power decrease in the mu and beta frequencies during motor tasks can be detected over the motor cortex to distinguish between left- and right hand motor tasks [Pfurtscheller et al., 1997], between movements of various body parts [Pfurtscheller et al., 2006, Morash et al., 2008], or simply between movement and lack of movement. The latter type of setup is often referred to as a brain switch, where one specific mental task is to be distinguished from a baseline state, and has been studied within the context of motor imagery on several occasions [Pfurtscheller and Solis-Escalante, 2009, Qian et al., 2010]. A natural response for patients experiencing intraoperative awareness is trying to move [Sandin et al., 2000]. Therefore, movement attempts are one of several possible indicators of awareness. Recent studies have shown that attempted movements could be distinguished from rest periods in patients with complete hand paralysis following stroke [Muralidharan et al., 2011] and patients with tetraplegia [Blokland et al., 2014]. Similar results have been found even for patients in a locked-in state [Höhne et al., 2014]. If attempted movements can also be detected during a drug-induced neuromuscular blockade, they could be used as input for a BCI-based monitor of intraoperative awareness.

We have previously discussed the requirements of such a monitor and shown that it is technically feasible, if based on detection of actual movements [Blokland et al., 2012]. However, it is clinically important that the BCI is able to detect attempted movements as well. In the current proof-of-principle study we therefore obtained the electroencephalogram (EEG) from volunteers with a temporary paralysis of the forearm induced by administration of rocuronium, a commonly used neuromuscular blocker as a component of general anaesthesia. Using offline classification analysis we investigated whether the attempted movements the participants made during their paralysis could be distinguished from the periods when they did not execute or attempt movement.

3.2 Methods

The principles of a Brain-Computer Interface

A Brain-Computer Interface (BCI) is a system that, by means of a computer algorithm, interprets a user's brain signals in order to convert them into some form of output that may aid the user in interacting with the environment.

EEG is the most commonly used brain measurement modality in BCI research because of its portability, relative affordability and high temporal resolution. It is recorded as the potential for current to pass between a recording electrode and
a reference electrode. This potential is modulated when a cognitive task is being performed. Based on these modulations, the computer is required to distinguish between one task (such as movement) and another (such as absence of movement). By presenting the computer with examples of the brain signal produced during each task (from now on: condition) the algorithm learns the signal properties belonging to that condition.

When running a BCI two phases can be distinguished: the training phase and the test phase. In the training phase, prior to actual use of the BCI, a certain number of trials is measured for each condition. This information is used to train a classification algorithm (classifier). In the test phase, for each novel trial the classifier makes a prediction of the intended condition based on what it has learned in the training phase. This prediction can be used real-time to generate a certain output. In our case, this could be an alarm or notification whenever attempted movement is predicted.

In an offline study, such as the one presented here, no real-time output is produced. Instead, after collecting a sufficient number of trials, one part is used as the training data for the classification algorithm and the remainder for testing the algorithm. By determining the percentage of the test trials that has been predicted correctly, the classification accuracy is obtained (e.g. 80% when the classifier makes a correct decision for 8 out of 10 trials). This shows how reliably a certain mental task can be detected and thus how feasible the BCI paradigm is. In a two-class problem, with an equal number of trials for both conditions, the theoretical chance level performance is a classification accuracy of 50%. In other words, classification accuracies significantly higher than 50% mean that the EEG data contain useful information for a prediction of which condition a trial belongs to.

The interested reader is referred to van Gerven et al. [van Gerven et al., 2009] for further details on the technology of BCI.

Participants and consent

This study is registered in the EU Clinical Trials Register, identification number 2012-001777-86. All procedures were according to the Declaration of Helsinki and were approved by the local Medical Ethics Committee. Four right-handed healthy volunteers (aged 20-28, one female) participated in this study. None had any known neurological or motor impairments. Subject 1 had former BCI experience, while the other three were all naive to BCI. All participants gave written informed consent prior to the experiment. Measurements took place in an operating room at the Radboud
Materials and procedures

The experimental paradigm consisted of two phases: one before, and one after administration of a neuromuscular blocker. In the first phase, participants were asked to perform four different types of movement: actual movement, isometric movement, imagined movement and no movement. For subjects S1 and S2, the actual movement task consisted of a repeated grasping movement of the right hand. For subjects S3 and S4, the actual movement performed was a repeated movement of the right-hand thumb towards the right-hand little finger. In the imagined movement condition, participants had to perform kinesthetic motor imagery of the same movement as they performed in the actual movement condition. During kinesthetic motor imagery, as compared to visual motor imagery, one imagines the feeling of performing movement rather than imagining seeing oneself perform that movement [Neuper et al., 2005]. During isometric movement, the participants were instructed to perform the actual movement task, but reduce muscle movements as much as possible. This was used as an alternative to motor imagery as it was expected to more closely resemble the attempted movements [Nikulin et al., 2008]. In the no movement condition subjects were instructed to keep still.

In the second phase, i.e. after drug administration, only two conditions remained: actual movement and no movement. The instructions were identical to those in the first phase. Although participants were no longer able to physically perform the actual movement task, they (mentally) performed the task as if they were. From now on, the actual movement condition in the second phase will be referred to as attempted movement.

Sequences of nine movement trials were presented to the subjects. Each trial consisted of an auditory 3-second cue, with a four-second silence interval between consecutive trials (Figure 1). At the start of each sequence, an auditory instruction was given explaining the task for the upcoming trials. The participants had to perform the instructed task during the auditory cues, and rest during the silence intervals. Participants were asked to keep their eyes closed throughout the entire sequence. Between sequences participants could have a short rest, then start the next sequence by pressing a button. In total, 81 trials were collected for each of the four conditions in the first phase, divided over three experimental blocks, and 54 trials for both conditions in the second phase (single block). Within each block, presentation of the sequences was randomized. A short practice block to get the
participants acquainted with the task preceded the actual measurements.

EEG was recorded with a 32-channel actiCAP system (Brain Products), with the channels positioned according to the international 10/20 system. Impedances were kept below 25 k before starting the measurement. The signal was digitized with a sampling rate of 2500 Hz. Two electrodes were removed from the EEG cap and instead used to record the right forearm electromyogram (EMG) for S1 and S2, and the right-hand thumb EMG for S3 and S4. The experiment was programmed in and run on the BrainStream platform Version 1.0 (http://www.brainstream.nu), i.e. a Matlab (MathWorks Inc., MA, USA) toolbox especially developed for online BCI-experiments, using Psychtoolbox (http://psychtoolbox.org) for stimulus presentation.

**Drug administration**

After phase one was finished, an iv-needle was inserted into a dorsal vein of the right hand to allow administration of the neuromuscular blocking agent rocuronium. An
additional iv-needle was inserted into the left hand to enable quick administration of rescue medication if necessary. Then, after elevation of the right arm for two minutes, a tourniquet was applied to the right upper arm at 50 mmHg above the participants systolic blood pressure to separate the arm from the systemic circulation. Via the iv-needle 0.04 mg/kg rocuronium diluted with NaCl 0.9% to 20 ml was injected into the right arm. According to the protocol, a maximum of two extra doses of 0.01 mg/kg could be administered if the first dose was insufficient to establish full relaxation of the grasp muscles, bringing the maximum dose administered to 0.06 mg/kg. Subjects were asked to try to move every few minutes after drug administration. The level of relaxation was determined by visually inspecting both actual muscle movement and the EMG signals.

After phase 2, i.e. after the final experimental block had been completed, the tourniquet was deactivated. During the entire procedure heart rate, blood pressure and oxygen saturation (pulse oximetry) were monitored. Participants remained in the OR complex until their movement abilities were fully restored.

Analyses

EMG
EMG recordings were used to determine the muscle output for each movement condition. EMG signals were re-referenced using a bipolar reference for the two channels and high-pass filtered at 10 Hz to reduce the effect of artifacts such as electrode drift. These signals were converted to power over time by taking the absolute magnitude of the analytic signal as found using a Hilbert transform, and then averaged for the period between 0.1 and 3.5 seconds (task onset is at 0). For each movement task and each subject the average power was calculated as a percentage of the average power during actual movement for that subject.

Classification
The typical brain response to be seen during motor tasks is a power decrease in mu rhythm (8-12 Hz) and beta rhythm (18-25 Hz) activity in the sensorimotor cortex, with a short period of power increase in roughly the same frequencies after movement has stopped. These changes are commonly referred to as event-related desynchronization (ERD) and event-related synchronization (ERS) [Pfurtscheller and Lopes da Silva, 1999]. Thus, these were the main features the classifier was expected to use for its decisions.

To visually inspect the brain responses and ascertain the presence of ERD and
ERS, for each subject and each movement condition a time-frequency plot was computed using a relative baseline from -1 to 6 seconds.

For the classification procedure, the data were first linearly detrended to minimize analysis artifacts due to large DC offsets. The surface Laplacian reference was calculated for each channel to reduce artifacts and increase signal strength, using Perrins spherical spline interpolation method [Perrin et al., 1989]. In many SMR studies Common Spatial Patterns (CSP) [Koles, 1991] is used for this purpose, however our initial comparison of both approaches showed no performance benefit when using CSP. Thus, we use the simpler unsupervised Laplacian reference here. Then, the power spectral density was computed for 8-24 Hz using Welch’s method [Welch, 1967] with a resolution of 4 Hz and a Hanning taper applied to 50% overlapping windows (i.e. windows of 250ms with overlap of 125ms were used), using separate features for ERD (data obtained during movement, i.e. 0-3 s) and ERS (post-movement, i.e. 3.5-6 s). This subset of power spectral features (9 channels x 5 frequencies x 2 time ranges per epoch) was used to train a quadratically regularized linear logistic regression classifier (rLLR) [Bishop, 2006] to distinguish between each subjects specific pattern of spatial and spectral activation for the actual movement, isometric movement and imagined movement conditions as compared to the no movement (first phase) condition, and between the activation for the attempted movement condition as compared to the no movement (second phase) condition. Regularization is used to limit the complexity of the classifier which prevents over-fitting in the high-dimensional input feature space. The optimal regularization strength (or equivalently classifier complexity) was found using a simple grid search with strengths of [.001 .01 .1 1 10 100] times the total data variance and selecting the strength which maximized validation set performance. Validation set performance was estimated using ten-fold cross-validation. So, for each condition the trials were split up into ten subsets (folds), with each fold used for testing once while the remaining nine folds were used for training the classifier.

Additionally, to more closely simulate a realistic clinical scenario including a pre-operative calibration phase, the classifier was trained on each movement condition from the first experimental part (as compared to the no movement (first phase) condition) and then tested on the attempted movement condition (as compared to no movement (second phase)). As in this case the training and test sets consisted of different movement conditions by default, no cross-validation was needed for performance estimation.

Classification analyses were performed separately for two different channel sets. The first included all 30 EEG channels, the second consisted of a 9-channel subset
located over the motor cortex (C3, C4, Cz, F3, F4, P3, P4, T7 and T8). The latter set is deemed more practical for clinical applications and has been found to lead to only a minimal reduction in classification performance.14

Statistics
For each condition, the 95% confidence interval (CI) for the mean classification accuracy was calculated using IBM SPSS Statistics version 20 (IBM Corp., NY, USA). As the number of movement and no movement trials was always equal, the theoretical chance level was 50%. Therefore, a 95% CI lower limit above 50% for a given condition means that the classifier performs better than chance (p = 0.05).

To determine significance at the individual subject level, we determined the 95% binomial CI for each classification accuracy (calculated in Matlab). Again, lower CI limits above 50% mean above-chance performance (p = 0.05).

3.3 Results
The average time until full muscle relaxation was 18 minutes (range: 8-27). In one participant neuromuscular block was established within 8 minutes following a single dose of rocuronium (0.04 mg/kg). For three participants, an additional dose of 0.01 mg/kg was administered approximately 12 minutes after administration of the first dose. Of these three participants, one required a final dose of 0.01 mg/kg after another 10 minutes until full relaxation was established. The average duration of tourniquet activation was 32 minutes (range: 22-42). None of the participants reported tourniquet-induced pain or systemic effects of rocuronium after tourniquet deactivation. Within approximately one hour after tourniquet deactivation all participants left the OR facilities with their motor functioning restored to normal.

Subjects reported varying subjective experiences of the attempted movement task. Although three out of four considered the task difficult, they all reported the sensation was to some extent similar to actual movement, more so than imagined movement. Only one subject reported having the sensation of actually moving during the attempted movement task, although the EMG power during the neuromuscular block was only 0.8% of the power during actual movement. Subjective experiences of isometric movement were very inconsistent, suggesting that despite extensive instructions and some practice trials, this task may have remained unclear or have been interpreted differently by each subject.

Analyses of the EMG measurements confirmed that muscle movement was blocked
during the attempted movement condition, with comparable power levels to the no movement condition. The average EMG power per movement condition as a percentage of the power for actual movement is shown for each participant in Table 1.

<table>
<thead>
<tr>
<th>Subject #</th>
<th>actual movement</th>
<th>no movement</th>
<th>isometric imagery</th>
<th>attempt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>0.6</td>
<td>1.8</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>0.2</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>0.4</td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>0.8</td>
<td>0.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 3.1: EMG power per condition as a percentage of EMG power during 'actual movement'.

Individual time-frequency plots of the EEG were examined for each subject and movement condition. ERD and ERS were visible in all subjects for actual movement, attempted movement, isometric movement and imagined movement, with the exception of imagined movement in subject 2. Figure 2 shows the grand average EMG power levels along with the time-frequency plot of the EEG for channel C3 for each movement condition.

Tables 2 and 3 show the classification results for both channel sets, along with their 95% CIs. Overall classification accuracies for ‘imagined movement’ tended to be lower than for ‘actual movement’, ‘isometric movement’ and ‘attempted movement’. For the 30-channel set the average single trial classification accuracies were 84% for actual movement, 80% for isometric movement, 69% for imagined movement and 81% for attempted movement. For the 9-channel set the rates were 87%, 78%, 71% and 84%, respectively. When training the classifier on actual movement (first phase) and testing it on attempted movement (second phase), single trial accuracies were 79% using the 30-channel set and 77% using the 9-channel set. For all conditions, the lower limit of the 95% CI was higher than 50%.

Table 2 shows that the lower limits of the 95% binomial CIs for individual classification accuracies were above 50% for each movement condition, except for imagined movement in one subject. So, classification performance was significantly better than chance for actual, attempted and isometric movement in every subject.
Figure 3.2: Grand average EEG time-frequency plots for channel C3 (top figures) and EMG power plots (bottom figures) per condition. For each movement condition the top plot shows EEG power over time per frequency in relative units (r.u.). These plots were computed to ascertain the presence of event-related desynchronization (ERD, blue) and -synchronization (ERS, red), the main features the classifier uses for its decisions. Actual movement, Isometric movement, Attempted movement and Imagined movement each show ERD during the movement task (t= 0-3 s), followed by ERS. A relative baseline over the entire trial was used, so that a value of 1 (white) represents average power, a value <1 a power decrease or ERD and a value >1 a power increase or ERS. The average EMG power over time is shown in the bottom plot. For the EMG plots a logarithmic scale is used on the y-axis.

3.4 Discussion

This study showed that attempted movements of the forearm paralyzed by a neuromuscular blocker can be detected from the EEG with a similar accuracy as movements that are truly executed. The average single trial classification accuracies were between 77% and 84%, irrespective of the number of EEG channels used, both when
training on attempted movement (same task) and on actual movement (different task). Even the lowest of these mean classification accuracies with its associated 95% CI (77 (61-93)%), shows that the classifier performs significantly better than chance. Also on the level of individual classification accuracies the performance was found to be significant.

Therefore, like actual movements in healthy users and attempted movements in (partly) paralyzed patients, attempted movements blocked by a neuromuscular blocker may be used for communication. We propose the use of a Brain-Computer Interface converting detected movement attempts during surgery into an alert for the anaesthetist.

Compared to current EEG monitors, our proposed system has a more intuitive interpretation as it is based on a well-known neural response to motor tasks. Moreover, a BCI-monitor is based on the brain response of the individual patient, in contrast to current monitors that use a population-based probability of awareness at a given pharmacodynamic (surrogate) EEG effect.

Our finding that using actual movement rather than attempted movement for classifier training has little effect on the classification performance has important practical implications for the usability of the proposed monitor. For detection of attempted movement during general anaesthesia, pre-operative system calibration could be based on actual movements. However, it would be even better if a calibration session for each individual user would be made superfluous altogether by implementing a generic classifier [Fazli et al., 2009, Reuderink et al., 2011, Niazi et al., 2013].

Another important result for the clinical usability of the proposed system was the confirmation of our previous findings12 that the average performance does not decrease when reducing the number of channels to nine. A system consisting of only nine EEG channels rather than a full standard cap with e.g. 32 channels would allow for a quick setup and is therefore clinically feasible.

This study used a cued design, meaning the user (patient) would have to perform the attempted movements during the indicated time periods. Ideally, the system would be able to detect spontaneous movement in an asynchronous setting. However, the time-lock now allows for easier incorporation of the post-movement beta-rebound (ERS). Converting the proposed paradigm to an asynchronous system is an important area for future research.

Although this study provides proof of our proposed concept, the paradigm requires further validation before it could be adopted in clinical settings. The most important limitation is that the participants were awake and no drugs other than the
neuromuscular blocking agent were administered. As a first step towards building a BCI for use during general anaesthesia, we have shown the feasibility of detecting attempted movements during a state of awake paralysis. Patients might find themselves in such a state in various clinical situations, including settings on an intensive care unit. However, intraoperative awareness situations are generally not caused by a complete lack of general anaesthetics, but rather by a dose that is too low. Hence, the monitor should be able to detect (attempted) movement from the EEG even in the presence of low-dose anaesthetic drugs, which might influence the background EEG as well as the movement response (e.g. the latency, duration and kind of movement). Also the baseline state during sedation may be different from the instructed no movement task in this study. To get a full understanding of the applicability of the paradigm during general anaesthesia, further studies are being conducted to determine the influence of those anaesthetics. The presence of movement (attempt) alone might not be sufficient to conclude the patient is conscious, which represents another possible limitation [Pandit, 2013]. Further research may be required to define the relationship between attempted and intended movement [Sanders et al., 2012].

Because of the burden of the study for the volunteers and the nature of the study - a feasibility test of a novel concept - the Medical Ethics Committee approved the study only for an absolute minimum number of participants. The number of four participants was found to be sufficient to show the strength of the brain response we aim to utilise, albeit with an expected broad confidence interval.

It is likely that the performance of the proposed system will improve when moving from the feasibility test presented here towards actual development of the BCI. This novel paradigm was evaluated in its simplest form: for a small participant group, single trial classification accuracies were determined using a basic classification algorithm. After this initial feasibility check, a number of steps can be taken to further improve the performance.

First, the amount of information the classifier uses for its decision could be increased. In this paper we reported the performance when a decision is made after only 6 seconds. Previously we have shown that performance increases when a longer movement period is used, with true positive response probabilities up to 100% within 2.5 minutes. Moreover, the system can be adjusted such that it can run for several hours without producing any false alarms. To get an impression of the true positive/false positive tradeoff for attempted movement, we used a simple combination of detection threshold optimisation and combination of multiple classifier predictions for the current dataset, applied on the classification problem of training on actual
movement and testing on attempted movement. An average false alarm rate of 0% with an average true positive rate of 87.5% was achieved when using approximately one minute of data.

Second, the movement task could be changed. For practical reasons of administering the neuromuscular blocker, the movement task in this study was limited to the right hand only. Because of the generally contralateral nature of ERD and ERS, the responses were especially strong in the left but not the right hemisphere of the brain. When moving both hands, the response will be elicited in a larger part of the brain, likely resulting in higher classification accuracies.

Third, the quality of EEG recordings in general is likely to increase. The current measurements took place in an operating room, with the full standard clinical setup. Conditions in such a location differ from the EEG rooms commonly used for BCI experiments. Although we acquired high quality signals, resulting in acceptable classification performance, we expect that future advancements in EEG hardware development will make BCI performance outside of the lab comparable to current performances acquired inside the lab within a few years.

Fourth, extended incorporation of sophisticated machine learning techniques should be investigated to further improve classification performance.

Concluding, despite its current limitations, the proposed paradigm has the potential to become a reliable addition or even an alternative to existing depth of anaesthesia monitors. We believe BCI technology in general and the attempted-movement-based monitor in particular are a promising new direction in the field of anaesthesia monitoring.
Table 3.2: Single trial cross-validated classification accuracies, expressed as percentages, for each movement condition and EEG channel set.

First, separate classifiers were trained on each of the named movement conditions, using a subset of the recorded trials. Then the classification performances were estimated for each classifier on another set of trials belonging to that condition. For this procedure of performance estimation ten-fold cross-validation was used. Results are given as classification accuracy (95% CI): for each individual classification accuracy the binomial 95% CI is given, for the mean classification accuracy the standard 95% CI is given.

<table>
<thead>
<tr>
<th>Subject #</th>
<th>30 EEG channels</th>
<th>9 EEG channels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Training &amp; test conditions</td>
<td>Training &amp; test conditions</td>
</tr>
<tr>
<td></td>
<td>actual movement</td>
<td>isometric movement</td>
</tr>
<tr>
<td>1</td>
<td>81 (73-89)</td>
<td>83 (75-91)</td>
</tr>
<tr>
<td>2</td>
<td>83 (75-91)</td>
<td>68 (58-78)</td>
</tr>
<tr>
<td>3</td>
<td>93 (89-97)</td>
<td>89 (83-95)</td>
</tr>
<tr>
<td>4</td>
<td>79 (71-87)</td>
<td>81 (73-89)</td>
</tr>
<tr>
<td>mean</td>
<td>84 (74-94)</td>
<td>80 (66-94)</td>
</tr>
</tbody>
</table>
Table 3.3: Single trial classification accuracies for 'attempted movement', expressed in percentages, for each EEG channel set.

First, separate classifiers were trained on each of the named movement conditions. Then, classification performances were estimated on 'attempted movement'. Results are given as classification accuracy (95% CI); for each individual classification accuracy the binomial 95% CI is given, for the mean classification accuracy the standard 95% CI is given.
Chapter 4

Decoding motor responses during sedation

Abstract

Objective. Patients undergoing general anesthesia may awaken and become aware of the surgical procedure. Due to neuromuscular blocking agents, patients could be conscious yet unable to move. Using Brain-Computer Interface (BCI) technology, it may be possible to detect movement attempts from the EEG. However, it is unknown how an anesthetic influences the brain response to motor tasks.

Approach. We tested the offline classification performance of a movement-based BCI in twelve healthy subjects at two effect-site concentrations of propofol. For each subject a second classifier was trained on the subject’s data obtained before sedation, then tested on the data obtained during sedation (‘transfer classification’).

Main results. At concentration 0.5 $\mu g$/ml, movement-related changes in the motor cortex EEG could be reliably detected in all subjects despite an overall propofol EEG effect. At 1.0 $\mu g$/ml, the mean single trial classification accuracy was 81% (95% CI 76-86%), and 72% (95% CI 65-80%) for the transfer classification. At this propofol concentration for 4 subjects the movement-related brain response had been largely diminished. These subjects showed a slower and more erratic task response, indicating an altered state of consciousness distinct from that of the other subjects.

Significance. The results show the potential of using a BCI to detect intra-operative awareness and justify further development of this paradigm. At the same time, the
relationship between motor responses and consciousness and its clinical relevance for intraoperative awareness requires further investigation.

4.1 Introduction

Brain-Computer Interfaces (BCIs) are systems directly translating brain signals into useful output, such as control of a device. By eliminating the need for muscular control, BCIs can therefore provide a means of interaction with the environment for partially or completely paralysed patients (e.g. in [Nijboer et al., 2008]). Patients under general anesthesia are often temporarily paralysed with a neuromuscular blocking agent. If they awake during surgery, they may find themselves in a situation where they have a certain degree of consciousness but are nevertheless unable to move or speak. This experience, known as ‘unintended awareness with postoperative explicit recall’, has an estimated incidence of 0.1-0.2% [Ghoneim, 2007]. Therefore we propose to extend BCI research into the domain of anesthesia awareness.

One of the best known and most successful BCI paradigms is detection of changes in sensorimotor rhythms from the EEG during attempted and imagined movement [Yuan and He, 2014]. For instance, it has been shown that attempted movements can be detected from patients with tetraplegia [Kauhanen et al., 2007]. Likewise, motor tasks may be used as a diagnostic tool in determining states of altered consciousness in patients recovering from coma [Cruse et al., 2011]. This evidence shows the potential of using patients’ movement attempts during general anesthesia as an indicator of awareness. Intentions of movement could replace or complement the features currently used in anesthesia monitoring, such as entropy or bispectral analysis [Musizza and Ribaric, 2010].

Our proposed BCI paradigm proved successful in awake volunteers intending gross movement [Blokland et al., 2012] and also in awake volunteers trying to move one isolated forearm temporarily paralyzed by a neuromuscular blocking agent [Blokland et al., 2015]. However, hypnotics are known to change EEG characteristics [Purdon et al., 2013, Mukamel et al., 2014]. Sensorimotor rhythm modulations normally occurring when a person is engaged in a motor task may be altered or disappear altogether.

In this study we therefore investigated the influence of low doses of propofol on sensorimotor rhythms. Healthy participants performed a motor task in a baseline state as well as in altered states of consciousness induced by propofol. For each
state, offline classification accuracies of movement as compared to rest were determined. If the specific brain response normally seen during movement is retained after administration of hypnotic drugs, it may be used for BCI-based communication.

4.2 Methods

Participants

Twelve right-handed healthy volunteers (aged 18-28, 5 females) participated in this study. None had any known neurological or motor impairments, nor contraindications for the use of propofol. All participants gave written informed consent prior to the experiment. Measurements took place in an operating room at the Radboud University Medical Centre in Nijmegen, the Netherlands.

Experimental design

All procedures were according to the Declaration of Helsinki and were approved by the local Medical Ethics Committee.

The experiment consisted of three blocks. The first experimental block was a baseline block in which the subjects performed the movement tasks without administration of propofol (block 0). In the subsequent blocks, propofol was administered via a TCI (target controlled infusion) pump in steps of 0.5 µg/ml (target concentration). So, the target concentration was 0.5 µg/ml for the second block (block 0.5) and 1.0 µg/ml for the third block (block 1.0). An Alaris PK infusion pump (Carefusion, Basingstoke, UK) was used in the TCI mode (Schnider model, effect-site targeting). When the target concentration had been reached, participants waited for another 10 minutes before proceeding with the experiment, to ensure equilibration between the body compartments. Only subjects S1, S2 and S3 received an additional propofol dose increase with 1.5 µg/ml as target concentration. During the entire procedure heart rate, blood pressure and oxygen saturation (pulse oximetry) were monitored. After the end of the experiment participants remained in the OR complex until they were fully recovered.

In each block, sequences of nine movement trials were presented to the subjects. Each trial consisted of an auditory 3-second cue, with a four-second silence interval between consecutive trials. At the start of each sequence, an auditory instruction was given explaining the task for the upcoming trials: either ‘move’ or ‘don’t move’. The participants had to perform the instructed task during the auditory cues, and
rest during the silence intervals. Participants were asked to keep their eyes closed throughout the entire sequence. Between sequences participants could have a short rest, then start the next sequence by pressing a button. Per block, between 54 and 63 trials were presented for each of the two task conditions. Within each block, presentation of the sequences was randomized. A short practice block to get the participants acquainted with the task preceded the actual measurements.

The experiment was programmed in and run on the BrainStream platform\textsuperscript{1} Version 1.0, i.e. a Matlab (MathWorks Inc., MA, USA) toolbox especially developed for online BCI-experiments, using Psychtoolbox\textsuperscript{2} for stimulus presentation.

**EEG, EMG and BIS recording and analyses**

EEG was recorded with a 32-channel actiCAP system (Brain Products), based on the international 10/20 system. Impedances were kept below 25 kΩ before starting the measurement, and the sampling rate during recording was 2500 Hz. After recording, signals were downsampled to 128 Hz.

Two electrodes were removed from the EEG cap and instead used to record the left forearm electromyogram (EMG). Muscle outputs as recorded by EMG were used to determine if and when participants had executed the wrong task. EMG signals were rerereferenced using a bipolar reference for the two channels and high-pass filtered at 10 Hz to reduce the effect of artifacts such as electrode drift. Then, the signals were converted to power over time by taking the absolute magnitude of the analytic signal as found using a Hilbert transform, and the mean power per subject and movement condition was determined for the period between 0.1 and 3.5 seconds (task onset is at 0). Trials for which the EMG power deviated more than 3 times the standard deviation from the mean for that subject and condition were excluded from further analysis. For the remaining trials, the mean amplitude per subject per condition was determined, as well as the mean movement onset time and standard deviation for the movement tasks by identifying the first rising edge of the EMG amplitude increase.

Additionally, Bispectral Index (BIS) was measured using the Philips M1034AX Bispectral index (BIS) Solution plug-in module (Philips Medical Systems, Eindhoven, The Netherlands). BIS is a commercial depth of anesthesia monitor, providing a number between 0 (no brain activity) and 100 (completely awake) [Escallier et al., 2014]. Values were recorded manually every 1-2 minutes during the experimental blocks.

\textsuperscript{1}http://www.brainstream.nu
\textsuperscript{2}http://psychtoolbox.org
Classification

To test the feasibility of detecting movement during propofol sedation, offline classification analyses were performed separately for each of the three experimental blocks. Data obtained at a propofol effect-site concentration of 1.5 $\mu$g/ml were not used for analysis, as explained below. The parameter settings used have been validated for this paradigm in a previous study [Blokland et al., 2012]. Specifically, the classifier used information from only nine EEG channels, as this would be more practical in clinical settings than using a full standard EEG cap. Moreover, frequencies above 24Hz were disregarded. Even though they may contain useful information, in the current setup involving actual movements these higher frequencies may be prone to class-related artifacts [Pope et al., 2009].

The typical brain response to be seen during motor tasks (actual, attempted or imagined movements) is a power decrease in mu rhythm (8-12 Hz) and beta rhythm (18-25 Hz) activity in the sensorimotor cortex, with a short rebound period in roughly the same frequencies after movement has stopped. These changes are commonly referred to as event-related desynchronization (ERD) and event-related synchronization (ERS) [Pfurtscheller and Lopes da Silva, 1999]. Thus, these were the main features the classifier used in this study was expected to use for its decisions.

Trials were constituted of 3 seconds of movement (or no movement) followed by 3 seconds of rest. For the classification procedure, the data were first linearly detrended to minimize analysis artifacts due to large DC offsets. After calculating the surface Laplacian reference per channel using Perrins spherical spline interpolation method [Perrin et al., 1989], the power spectral density was computed for 8-24 Hz using Welch’s method [Welch, 1967] with a resolution of 4 Hz and a Hanning taper applied to 50% overlapping windows, using separate features for ERD (data obtained during movement, i.e. 0-3 s) and ERS (post-movement, i.e. 3.5-6 s). This subset of power spectral features for each channel was then used to train a quadratically-regularized linear logistic regression classifier (rLLR) [Bishop, 2006] to distinguish between each subjects specific pattern of spatial and spectral activation for the movement condition as compared to the ‘no movement’ condition. Validation set performance was estimated using ten-fold cross-validation. So, for each condition the trials were distributed over ten subsets (folds), with each fold used for testing once while the remaining nine folds were used for training the classifier.

Additionally, we calculated the performance of the classifier when it was trained on block 0 (baseline: no propofol), then tested on the data from block 0.5 (propofol effect-site concentration 0.5 $\mu$g/ml) and block 1.0 (propofol effect-site concentration 1.0 $\mu$g/ml), respectively. The rationale behind this lies in the eventual clinical ap-
plication, where it would make sense to train a classifier before general anesthesia, then apply it after drug administration. Here, no cross-validation was required for performance estimation. Inspection of the power spectra revealed a $\beta$-increase in the sedation conditions, a known effect of anesthetic drugs [Kishimoto et al., 1995, Bruhn et al., 2006]. In order to cancel out these dose-dependent shifts, which are unrelated to the movement task, trials were first baselined using a relative baseline over the entire trial (-1 to 6 s). After that the classifier could be trained on the baseline (no propofol) data and then transferred to the data obtained during sedation.

**Statistical analyses**

To test whether the classifier can make any meaningful decision at all, it is important to compare its results to those of a 'random' classifier. For a binary problem with balanced classes, such as in this study, the theoretical chance level performance is 50%. Using the binomial distribution for proportional data, taking into account the number of trials per condition, confidence intervals for a random classifier can be calculated [Müller-Putz et al., 2008]. Individual classification accuracies were compared to the upper limit of the 95% confidence interval of a random classifier.

Additionally, for each condition the 95% confidence interval (CI) for the mean classification accuracy was calculated, using GraphPad Prism version 5.03, GraphPad Software, San Diego California, USA. A 95% CI lower limit above 50% for a given condition means that the classifier performs better than chance, i.e. the true mean in the population is higher than 50% (p=0.05).

**4.3 Results**

All participants performed the tasks well. During the administration of propofol, however, participants started to show signs of sleepiness, and gradually needed to increase their efforts to stay alert and perform the required task. The table shows that the mean BIS values decreased from 92.1 during baseline to 90.5 and 83.1 during propofol administration. As the experiment progressed, reaction times increased and some participants started making a few errors. Based on the EMG responses, 0.6%, 1.7% and 3.9% of trials were judged to have been wrongly executed in blocks 0, 0.5 and 1.0 respectively. For the movement conditions, the mean EMG amplitude as a percentage of each subject’s baseline EMG amplitude was 86% and 74% at propofol effect-site concentrations of 0.5 $\mu$g/ml and 1.0 $\mu$g/ml, respectively. The mean movement onset time increased by 65 ms (from 273 ms to 338 ms) between
block 0 and block 1, but there was no difference between block 0 and block 0.5 (see Table).

<table>
<thead>
<tr>
<th>Block</th>
<th>Target Concentration</th>
<th>BIS</th>
<th>Task execution errors (%)</th>
<th>EMG amplitude (%)</th>
<th>Movement onset time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 0</td>
<td>0 µg/ml</td>
<td>92.1 (4.56)</td>
<td>0.6 (0.8)</td>
<td>100</td>
<td>273 (24)</td>
</tr>
<tr>
<td>Block 0.5</td>
<td>0.5 µg/ml</td>
<td>90.5 (4.05)</td>
<td>1.7 (3.3)</td>
<td>86 (16)</td>
<td>273 (33)</td>
</tr>
<tr>
<td>Block 1.0</td>
<td>1.0 µg/ml</td>
<td>83.1 (3.81)</td>
<td>4.1 (3.7)</td>
<td>74 (20)</td>
<td>338 (59)</td>
</tr>
</tbody>
</table>

Table 4.1: Overview of the experimental blocks with the propofol target concentrations, along with the results for BIS (Bispectral Index) and EMG analyses. Numbers are given as mean (SD).

Only the first three participants received propofol aiming at 1.5 µg/ml effect-site concentration. For all three, awareness levels were reduced so much that they were unable to perform the task. Therefore the data obtained at this concentration were not analysed and the final nine participants did not receive this dose.

Figure 1 shows the paired data for single trial classification accuracies for each subject. Mean accuracies were 87.5% (95%CI 82.4-92.5%) for block 0, 84.9% (80.9-88.9%) for block 0.5 and 80.9% (76.1-85.8%) for block 1.0. For each subject and condition the performance was significantly higher than chance level (p<0.05). After correcting for dose-dependent EEG shifts (Figure 2), a classifier was trained on data from the baseline block and then applied on data from blocks 0.5 and 1.0. The mean accuracy for this transfer classification was 83.4% (79.3-87.5%) for block 0.5, and 72.4% (65.7-79.1%) for block 1.0. The transfer classification performance was significantly higher than chance level (p<0.05) for all subjects at 0.5 µg/ml, but only for 8 out of 12 subjects at 1.0 µg/ml. All transfer classification accuracies are shown in Figure 3.

To find possible indicators as to why the transfer classification was not significantly better than chance in subjects S1, S2, S3 and S6, the propofol-associated changes in the BIS and EMG measures were reanalysed post-hoc for the effect-site concentration of 1.0 µg/ml. The mean BIS-value for these four subjects was 80.6, as compared to 84.4 for the remaining subjects. Regarding the EMG, S1, S2, S3 and S6 not only had the highest movement onset times (range 370-448 ms versus range 264-348 ms in the other subjects), but also the standard deviations of the movement
onset times were highest for these subjects (range 181-292 ms versus range 64-158 ms), meaning their responses were both slower and more erratic.

In Figure 4 details are shown for one participant for whom the transfer worked (S7) and for one participant for whom it did not (S2). The plots reveal that the desynchronization in 8-24 Hz (ERD) remains constant in S7 after propofol administration, whereas for S2 the effect is greatly reduced at 1.0 μg/ml target concentration.

Figure 4.1: Single trial classification accuracies in percentages per subject per propofol effect-site concentration. The twelve subjects entered the study in an order designated by the integers from 1 to 12. The dashed line shows the binomial confidence interval (α = 0.05) for the minimum number of trials used for performance estimation (46 trials for S1 at 1.0 μg/ml). For the remaining subjects and conditions the line would be slightly lower.
Decoding motor responses during sedation

4.4 Discussion

Principal findings

This study showed that motor responses could be detected from the EEG of volunteers during altered states of consciousness, with an average single trial classification accuracy of 85% at a propofol effect-site concentration of 0.5 µg/ml and 81% at a propofol effect-site concentration of 1.0 µg/ml. Single trial 'transfer' classification accuracies of 83% and 72% were obtained at propofol effect-site concentrations of 0.5 µg/ml and 1.0 µg/ml, respectively. Adding this to previous findings showing the possibility of detecting attempted movement during neuromuscular block [Blokland et al., 2015], we conclude that further development of the proposed Brain-Computer Interface is justified. During various conditions of drug administration, including both hypnotics (propofol) and neuromuscular blocking agents (rocuronium), movement can be distinguished from rest with high accuracy.

For eight of the twelve subjects it was possible to 'transfer' between the baseline state and the highest level of sedation. In other words, a classifier trained on the subjects’ data obtained prior to administering propofol was able to detect the movements at the target concentration of 1.0 µg/ml with an accuracy above chance level.

Figure 4.2: Frequency powers at propofol effect-site concentrations 0.0 and 1.0 µg/ml, averaged over all subjects, channel C3. At 1.0 µg/ml a β-increase is seen, as well as a reduction in γ.
Figure 4.3: Transfer classification rates (single trial) per subject for two propofol effect-site concentrations. Classification accuracies were obtained after classifier training using data from the baseline condition (no propofol administered). The dashed line shows the binomial confidence interval ($\alpha = 0.05$). This fact is useful for subsequent steps in development of the paradigm, specifically for determining the most efficient way of system calibration. The transfer of the BCI from a baseline condition to the sedation conditions is relevant because of the inter- and intrasubject variabilities in the brain signal. Currently, most BCIs require a calibration phase for each individual user and session. Especially in the developmental phase of BCI paradigms, system calibration is an essential step. In the near future however, end-user applications may no longer require this phase, as novel methods are being developed in which a generic classifier can be applied to every user’s data. This means there is not only a transfer between different states in an individual user, but also between users. Promising results have recently been
reported on such so-called zero-training BCIs for a spelling paradigm [Kindermans et al., 2014], and also movement-related BCIs may be feasible without (or with very limited) user-specific calibration [Fazli et al., 2009, Lotte and Guan, 2010, Reuderink et al., 2011, Niazi et al., 2013].

The successful transfer was partly based on adequate compensation of propofol-induced effects. Most conventional EEG-monitors in anesthesia, like Bispectral index or Entropy module, use only frontal electrodes to detect drug-induced EEG changes. However, hypnotic drugs like propofol have substantial effects on the EEG measured at other electrode locations as well [Gugino et al., 2001]. Accordingly, we found a clear propofol effect with a $\beta$-increase at the central electrodes, where the main EEG effect of (attempted) movement is located. By baselining each individual trial this increase was cancelled out. As a result, the classifier only took into account relative motor response effects. Because the exact change of the background EEG does not have to be known, this crucial compensation seems to be a large benefit of using a BCI algorithm during general anesthesia.

Unexpectedly, for four subjects (33%), a classifier trained on the baseline data could not distinguish between movement and rest at a propofol effect-site concentration of 1.0 $\mu$g/ml. If these subjects were excluded, the transfer classification performance would increase from 72% to 79% (95% CI 74-85%). In speculating on the reason for the low classification performance for these four subjects, a few aspects may be considered. First, visual inspection of the individual time-frequency spectra of these subjects revealed a large reduction or even absence of the ERD/ERS pattern at the effect-site concentration of 1.0 $\mu$g/ml. Second, remarkably, the first three subjects entering the study all belonged to this group. They were the only participants in whom we attained the highest propofol concentration, i.e. 1.5 $\mu$g/ml. At this effect-site concentration, all three subjects became unable to follow commands. Afterwards, none of these subjects exhibited recall of events from after administration of this third and final dose. Third, the four subjects for whom the transfer classification performed below chance level were the four who had the largest increase in both mean movement onset times as well as the largest spread between said onset times. For two of these subjects, S2 and S6, the mean EMG amplitude at 1.0 $\mu$g/ml target concentration was less than 50% of the amplitude at 0.0 $\mu$g/ml target concentration, pointing to a change in task intention (note that a reduction or absence of motor output itself does not necessarily mean a reduced brain response; the intention itself seems to be the most important factor [Blokland et al., 2015]). Fourth, S1, S2 and S3 had made relatively many errors in executing the movement task as compared to the remaining subjects at 1.0 $\mu$g/ml target concentration, while S6 had made the most
mistakes at 0.5 $\mu g/ml$ target concentration. This may indicate a misinterpretation of sensory information and therefore a lower level of awareness and command following. Finally, the mean BIS value at 1.0 $\mu g/ml$ target concentration was lower for these four subjects (80.6) than the mean of the other eight subjects (84.4).

Models of Consciousness

The current study was based on the assumption that a patient under general anesthesia would either be unconscious and hence not move while being stimulated, or the patient would be conscious and move, unless paralysed. Our findings indicate that instead a more detailed model of consciousness should be adopted.

While the above observations may not be sufficient to draw any hard conclusions, they do indicate that the group of four volunteers may have been close to a state described by Pandit [Pandit, 2013] as ‘dysanesthesia’ at the target concentration of 1.0 $\mu g/ml$. In this state, one may respond to simple commands but not to surgical stimuli. There is a certain degree of consciousness, but perception and sensory input are uncoupled such that memory formation is unlikely. This state is, according to Pandit, the minimum requirement for satisfactory general anesthesia [Pandit, 2014]. Our findings seem to be in line with the functional model of consciousness proposed by Pandit as well as his view on the isolated forearm technique (IFT,[Tunstall, 1977, Russell and Wang, 2014]).

While reviewing results from IFT, Pandit has suggested that patients may have retained some limited capacity for responsiveness to simple command, but that this does not always mean consciousness. The method of IFT is simple but its interpretation is controversial. One arm of the patient is isolated from the circulation so that it remains unaffected when a neuromuscular blocker is administered. The patient is asked to respond to command by moving the unparalysed hand. An awake patient would thus be able to communicate his/her state of awareness. According to the Global Workspace Theory specialized neuronal networks can execute movements on verbal command without the subject being conscious. This could explain why in some IFT studies patients responded to command, but did not show any spontaneous response to surgery [Pandit, 2013]. In addition, movements during IFT are not correlated with any recall of events in most of the studies on IFT [Sanders et al., 2012].

It might be hypothesised that in our study the movements were executed on a subconscious level at a certain propofol target concentration. For the four volunteers showing – to a certain extent – deviating results, the progressive loss of the
respective functions constituting consciousness could have been more rapid than in
the other participants. If Pandit’s model is right and if the group of four shows signs
of dysanesthesia, then they would no longer belong to the primary target population
of our research project.

As the BCI detects real cortical involvement during movement, it may be an even
better measure of intraoperative awareness than the BIS or the IFT. Nevertheless,
we must recognize that the state of dysanesthesia might represent a precursor for
awareness [Pandit, 2014].

Limitations and future research
To find more conclusive answers on the matters discussed here, future studies on our
proposed paradigm could be expanded with behavioural measures to track memory
formation after drug administration. Moreover, it would be highly interesting to
measure the EEG above the motor cortex during the IFT and to correlate this with
memory formation. A difficulty presented by that type of research setting, however,
is that it is very sensitive to the Heisenberg uncertainty principle with a marked
observer effect: every behavioural measurement of consciousness itself is potentially
altering the state of consciousness by being an arousal stimulus.

Despite this study being conducted in an operating room, the question still re-
 mains to which extent this controlled research setting mirrors the real clinical sit-
uation. The focus of a patient awakening during surgery who follows movement
commands for seconds to escape this situation is different from that of a paid volun-
teer performing a non-demanding repeating task in a non-stimulating environment
for more than an hour. This may explain the marked sedation of the volunteers at
relatively low propofol concentrations, as the actual state of sedation is always the
result of the balance between sedating drug effect and environmental arousal. For
example, Röpcke and colleagues [Röpcke et al., 2001] studied the effect of surgical
stimulation on the EEG. They found a shifted dose-response relationship for the ef-
eect of anesthetic drugs on the EEG depending on the presence or absence of surgical
stimulation.

This study was a first exploration as to whether motor response detection after
hypnotics administration may be feasible. Meanwhile, BCI research is continually
bringing forth further advancements, of which many may be applied to the paradigm
proposed here. For example, improvement of motor detection performance could be
gained by taking into account multi-trial classification (i.e. increasing the amount of
information the classifier uses for making its decision) and by adapting the system
to achieve a certain true positive/false positive trade-off rate. Moreover, with the development of more advanced EEG systems a reduction in setup time and signal noise can be expected in the near future. The introduction of wireless and dry electrodes will also mean an improvement in comfort and user-friendliness, which is important for clinical use [Hairston et al., 2014, Jakab et al., 2014, Chi et al., 2012].

Conclusions

To conclude, despite a clear effect of propofol on the EEG, changes in sensorimotor rhythms could still be detected in sedated volunteers. These findings are encouraging for the further development of a BCI for detecting attempted movements during intraoperative awareness. Importantly, in contrast to existing monitors, it is based on active communication by the patient, rather than a passive interpretation of the brain signal. However, alongside further technical development of the proposed system, a more precise model of the relationship between motor responses and consciousness is required. Because some volunteers moved without a clear correlated EEG response, future studies are needed to investigate the exact state of consciousness in these cases, as well as its clinical relevance for intraoperative awareness. This provides an opportunity for deeper insights in this challenging field of research. At the very least, anesthesiology research could benefit from BCI technology in general. Much insight could be gained by connecting with this field of research as anesthesiologists and BCI experts pursue a similar goal: communication by patients in a conscious locked-in state.
Decoding motor responses during sedation

Figure 4.4: Relative power spectra for the movement period and time-frequency plots for S7 (left-hand subfigures) and S2 (right-hand subfigures), channel C3. Subfigures (c)-(f) show the relative power increase or decrease per time point as compared to the mean of the trial. The dashed lines indicate the movement task period.
Chapter 5

Decoding motor responses in patients with tetraplegia

Abstract

Combining electrophysiological and hemodynamic features is a novel approach for improving current performance of brain switches based on sensorimotor rhythms (SMR). This study was conducted with a dual purpose: to test the feasibility of using a combined EEG-fNIRS SMR-based brain switch in patients with tetraplegia, and to examine the performance difference between motor imagery and motor attempt for this user group. A general improvement was found when using both EEG and fNIRS features for classification as compared to using the single-modality EEG classifier, with average classification rates of 79% for attempted movement and 70% for imagined movement. For the control group, rates of 87% and 79% were obtained, respectively, where the 'attempted movement' condition was replaced with 'actual movement'. A combined EEG-fNIRS system might be especially beneficial for users who lack sufficient control of current EEG-based brain switches. The average classification performance in the patient group for attempted movement was significantly higher than for imagined movement using the EEG-only as well as the combined classifier, arguing for the case of a paradigm shift in current brain switch research.
5.1 Introduction

Motor-impaired individuals, such as tetraplegia patients, could potentially benefit from the use of a Brain-Computer Interface (BCI). Such a system would enable them to control e.g. a wheelchair or orthosis, driven partially or completely by mental actions [Müller-Putz et al., 2005, Ortner et al., 2011]. Many BCIs are based on changes in sensorimotor rhythms: Event-Related Desynchronization (ERD) and -Synchronization (ERS) [Pfurtscheller and Lopes da Silva, 1999], which can be detected in the electroencephalogram (EEG) of an individual who is intending, imagining or executing movement.

'Brain switch'-type BCIs detect one specific mental state from ongoing brain activity, i.e. the default or 'rest' state. Therefore, their output is limited to a binary decision: either keeping the system in its current state or switching it to the second state. However, this drawback comes with the benefit of a low level of complexity on the part of both the system and the user. The user is only required to perform a certain task when there is an intention for communication or system change. In the remaining time the user can relax or focus on a different task. As for the detection performance, the distinction between one motor task and a baseline state may be more robust than the distinction between two different types of motor task, thus limiting the number of errors [McFarland et al., 2000]. A brain switch could also function as the 'on/off button' of a regular BCI, which in turn may have a more complex set of tasks or instructions and therefore a larger range of outputs [Kato et al., 2011].

Although brain switch systems driven by motor tasks are typically based on electrophysiological signals, some studies have shown the feasibility of using functional near-infrared spectroscopy (fNIRS) instead [Coyle et al., 2004, Sitaram et al., 2007]. Optical BCIs make use of concentration changes in the cerebral blood flow during increased neural activity, for instance motor tasks during which an increase of oxygenated hemoglobin (oxy-Hb) along with a decrease in deoxygenated hemoglobin (deoxy-Hb) occurs [Obrig et al., 1996]. Recently a few studies have looked into the possibility of combining these hemodynamic responses with their electrophysiological counterparts, in a multimodal or 'hybrid' BCI [Pfurtscheller et al., 2010]. Fazli and colleagues showed promising classification performance in healthy participants when combining features from both modalities [Fazli et al., 2012]. In the current study, we examined whether this principle works in patients with tetraplegia, an important target user group of brain switch technology.

Secondly, we tested the difference in performance between attempted and imag-
ined movement. In most BCI studies, healthy subjects as well as patients are instructed to perform motor imagery only, regardless of their motor abilities. However, motor imagery requires active inhibition of motor neural activation. Apart from the fact that brain patterns during motor imagery are less distinguishable from rest than motor execution patterns [McFarland et al., 2000], the task may also feel less natural, and therefore more difficult, to perform. Therefore, letting a motor-impaired individual attempt rather than imagine a certain movement may result in higher performance rates. Here, using EEG and fNIRS separately as well as in combination, we test the feasibility of using motor attempt instead of motor imagery as a task for brain switch control.

5.2 Methods

Participants

Ten male patients with tetraplegia (mean age 48.9 years) and twelve male controls (mean age 45.9 years) participated in the study. Nine patients had a complete lesion at C5-C6, one patient had a complete lesion at level C4-C5. Impairments had all been caused by traumatic spinal cord injury (SCI). The time since the injury varied between 11 and 40 years (mean 25.2 years). The protocol was approved by the institutional review board and all participants gave informed consent. After data collection, data from three patients and four controls were excluded from further analysis due to insufficient signal quality and excessive artifacts in one or both modalities.

Materials and procedures

Subjects were presented with six sequences of movement tasks with visual instructions, each sequence consisting of six task trials (Fig. 1). Each trial lasted 15 seconds. The three types of task participants were asked to perform were 'rest' (do nothing), 'movement' (tap your fingers and thumb continuously) and 'imagined movement' (imagine tapping your fingers and thumb continuously). When patients received the instruction of 'movement' they were asked to attempt performing the actual movement even though the movement could not truly be executed. Each type of movement was performed 12 times with the trials equally divided over all sequences. Instructions were presented randomly, with the restriction that the first sequence trial was always 'rest'. Intervals between trials lasted between 27 and 33 seconds to ensure sufficient recovery time (i.e. return to baseline levels) for the hemody-
Figure 5.1: Visualization of experimental sequences. Sequences consisted of two trials of each condition: 'executed/attempted movement', 'imagined movement' and 'no movement'. The five seconds before each movement period were used as a baseline for computing grand average plots of the brain responses.

Dynamic responses. After 'no movement' trials however, the return to baseline period lasted only 5 seconds as no significant deviation from baseline should have occurred. Total recording time per participant, including short breaks, was approximately 30 minutes.

EEG was recorded with an 8-channel passive Porti system (TMSi, Enschede, the Netherlands), the electrodes placed on positions C3, FC3, C5, CP3, C4, FC4, C6 and CP4 according to the international 10/20 system. Data was sampled at 2048 Hz and acquired with the Fieldtrip toolbox in Matlab [Oostenveld et al., 2011].

Two fNIRS channels were recorded with a continuous-wave system (Oxymon MK III, Artinis, Zetten, the Netherlands). Six optical fibers with straight ends were used: two transmitters (wavelengths 764 and 858 nm) and one receiver per channel. For each channel, an inter-optode distance between the target transmitter and the receiver of 35 mm was chosen, whereas the reference transmitter was placed at 10 mm from the receiver in order to correct for hemodynamic noise from e.g. the scalp and skull [Saager et al., 2011]. The channels were positioned around C3 and C4. Data was sampled at 250 Hz and acquired with Oxyssoft version 3.0.43.

EEG electrodes and fNIRS optodes were mounted side-by-side on a specially constructed cap. Fig. 2 shows the full configuration.

All patient recordings and two control recordings took place at the participants’ homes, the remaining control experiments were conducted at the institutional lab.
Decoding motor responses in patients with tetraplegia

Analyses

EEG

After downsampling the EEG data to 256 Hz and removing the DC offset, linear detrending was performed to remove slow drifts. Visual inspection of the data revealed class-specific data contamination in a very low number of trials and channels, which were therefore excluded from further analysis. Spectral features were averaged over all subjects in order to compute a grand average time-frequency plot visualizing the power decrease (ERD) during the movement tasks.

fNIRS

The optical signals from the fNIRS acquisition device were converted to hemoglobin changes using the modified Beer Lambert law [Villringer and Chance, 1997]. This converts the optical density changes to oxygenated (O$_2$Hb) and deoxygenated (HHb) concentration changes (in the literature, O$_2$Hb and HHb are sometimes referred to as HbO and HbR, respectively). The differential pathlength factor (DPF) was selected individually for each subject according to their age [Duncan et al., 1996]. Slow drifts were removed with a 0.01 Hz high pass filter. In order to enhance the signal to
noise ratio, the concentration changes for the reference transmitter were scaled to fit the obtained concentration changes from the target transmitter with a least squares approach [Saager and Berger, 2005]. Subsequently, the scaled concentration changes of the reference transmitter were subtracted from the far transmitter. This was done to correct for systemic noise, including hemodynamic changes from scalp and skull, and was performed for O$_2$Hb and HHb and both channels. Since activities faster than 0.2 Hz were not expected the concentration changes were further low pass filtered to 0.2 Hz and were baselined for each trial and channel to the period from -5 to 0 seconds before task onset. The filtered O$_2$Hb and HHb changes were used as the features for classification.

Computation of the grand average plots included two further preprocessing steps. First, because of the large individual variations in O$_2$Hb and HHb, the concentration changes were normalized so that the actual/attempted movement condition had unit power. Subsequently, the imagined movement condition was normalized for each subject with the same scaling factor as for the actual/attempted movement condition.

Classification

For both modalities, trials were split into 3-second segments. This increases the number of training examples to 60 per movement condition and allows for estimation of the classifier performance for a specific segment and hence time period. For EEG classification power spectral features between 8 and 24 Hz (5 frequency bins x 8 channels) were used, which were computed using Welch’s method with a 4 Hz frequency resolution [Blankertz et al., 2006a]. For fNIRS, three separate classifiers were trained: an O$_2$Hb classifier using the average O$_2$Hb concentration change for both channels (1 average x 2 channels), an HHb classifier using the respective HHb concentration changes and an (O$_2$+H)Hb classifier using both the O$_2$Hb and HHb average concentration changes for both channels (2 averages x 2 channels). The EEG classifier was evaluated on the time period of 0 to 15 seconds while the fNIRS classifiers were evaluated on the time period of 3 to 18 seconds, since a slower response was expected for the latter.

Performance of an L2-regularized linear logistic regression classifier [Bishop, 2006] was computed for both EEG and fNIRS for three binary problems to distinguish each individual movement condition from the ‘rest’ condition: 1) ‘executed movement’ versus ‘rest’ (controls only), 2) ‘attempted movement’ versus ‘rest’ (patients only) and 3) ‘imagined movement’ versus ‘rest’ (both groups). Classification performance was evaluated with a chronological (block-wise) 12-fold cross-validation where a block corresponded to one 15 second trial, i.e. five consecutive 3-second segments. For each
fold 2 blocks (one per condition) were removed from the training set to make the test examples.

In order to facilitate a probabilistic combination of the EEG and each of the three fNIRS classifiers, the obtained linear predictions were calibrated separately for each classifier. The calibration was performed by fitting the classifiers’ linear predictions to the logistic function so each classifier returns valid probabilities [Platt, 1999]. For any set of single predictions (here, we consider the prediction of the EEG classifier and the prediction of the fNIRS classifier(s)) the class membership decision of the segment was based on simple addition of each classifier’s linear predictions. This corresponds to a naive Bayesian combination of the predictions, irrespective of the modality (see appendix).

The binomial confidence with the Agresti-Coull correction [Agresti and Coull, 1998] was used to test for performance significantly higher than chance. The statistical significance between the obtained classification rates of different classifiers and task conditions was evaluated using a one-tailed dependent samples t-test. Statistical significance between the control group and the patient group was determined by means of a two-tailed independent samples t-test.

5.3 Results

Group average responses for all movement conditions show expected patterns in both measuring modalities. Time-frequency plots visualizing spectral features from the EEG during and after the movement tasks (Fig. 3) show a clear ERD/ERS pattern in the control group for actual movement and a relatively similar though weaker pattern for imagined movement, whereas for the patient group only ERD is clearly visible in either condition. In Fig. 4, normalised fNIRS group averages for \( O_2 \text{Hb} \) and HHb are shown, with the two fNIRS channels averaged. A typical increase in \( O_2 \text{Hb} \) can be observed for both groups and movement types. The expected decrease in HHb is observed in all conditions except for attempted movement in the patient group.

The individual classification results for each movement type and measuring modality are shown in Table 1 (control group) and Table 2 (patient group). The EEG single-segment classification rates for the healthy subjects are on average 84% and 77% for actual and imagined movement respectively. For the patient group the average rates are significantly lower (\( p<0.05 \)) at 73% and 63% for the two movement types. The fNIRS single-segment classification rates for the healthy subjects are 77% for actual and 59% for imagined movement, whereas for the patients the rates
Figure 5.3: Average time-frequency plots from the EEG, channel CP3. Blue represents a power decrease, red a power increase. 'AM' is the attempted or actual movement condition, 'IM' is the imagined movement condition.

are 70% and 65% for attempted and imagined movement respectively. Contrary to EEG-classification, the performance of the fNIRS classifiers is not significantly different between the control group and the patient group. For EEG, the difference in classification rates between actual/attempted and imagined movement is significant \( p < 0.05 \) while for fNIRS in the control group actual movement rates are significantly higher than imagined movement rates \( p < 0.01 \), but in the patient group the difference between attempted and imagined movement does not reach significance \( p = 0.19 \).

When the EEG classifier is combined with the fNIRS classifier, a significant increase as compared to EEG classification only is observed in the classification per-
Figure 5.4: Grand average normalised concentration changes for both fNIRS channels. O$_2$Hb (black) and HHb (gray) are shown, along with the variance over subjects (shaded area, one standard deviation from the mean).

Performance for each condition ($p<0.05$), except for motor imagery in the control group ($p=0.12$). Utilising both modalities the classification rates for the control subjects rise to 87% (actual) and 79% (imagined). For the patients the combined rates are 79% (attempted) and 70% (imagined). Also for the combined classifier the performance is significantly higher in the actual and attempted movement condition than in the imagined movement condition ($p<0.05$).

5.4 Discussion

Adding hemodynamic information to the more commonly used electrophysiological features may improve brain switch performance. Here, for an important target user
group of such systems, namely patients with tetraplegia, it was shown that a combination of both modalities indeed improves classification performance as compared to an EEG-only BCI. Secondly, for both EEG alone and the combined EEG-fNIRS classifier it was shown that classification performance is higher when patients are asked to attempt their movement rather than perform motor imagery.

For every condition except the motor imagery condition in the control group, the combined classifier yielded a significantly better performance. Interestingly, Fazli and colleagues [Fazli et al., 2012] found significant improvement for motor imagery but not motor execution. However, that study differs in two major respects as compared to the study presented here. Firstly, classification was based on a traditional left-versus right hand paradigm, rather than the brain-switch approach we adopted here, i.e. movement versus no movement. Secondly the number of channels used was much higher in that study: 24 fNIRS channels and 37 EEG channels, as compared to 2 fNIRS channels and 8 EEG channels in our study.

The fact that performance improves by adding an additional modality, indicates that the decisions made by the individual classifiers are at least to some degree uncorrelated, even though they are derived from the same underlying neurological processes. Indeed, the mean correlation of the decision values between EEG and fNIRS over all groups and conditions turns out to be as low as 0.07. The gain of the combined classifier is apparent for most users whose classification performance based on only EEG is relatively low. This could mean that several users who have been considered to be ‘BCI illiterate’ [Vidaurre and Blankertz, 2010] until now based on low EEG-BCI performance, may in fact turn out to be able to control a BCI relatively well, using the same task, but by expanding the hardware with (or replacing it by) fNIRS channels.

We obtained the classification performance reported here with a relatively low number of channels, which has important implications for practical usability as it allows for a very quick setup. Further research might provide insight into whether a simple montage consisting of any low number (4-10) of combined EEG and fNIRS channels means an improvement over using the same number of channels from a single modality. If that proves to be the case, simply replacing certain EEG channels with fNIRS rather than adding extra channels would mean performance increase of the brain switch without compromising too much on setup time.

The current performance might be improved by using more advanced methods of combining the EEG and fNIRS features as well as by optimizing the experimental paradigm. In this offline study, trials were split into 3-second segments. Additional analysis of the full 15-second trials of the current data set showed a large performance
increase when delaying the time until a decision is made. When the combined EEG-fNIRS classifier decides after the full 15 seconds, accuracy for the patient group is 90% for attempted movement and 82% for imagined movement. To fully determine the possible speed/accuracy tradeoff of brain switch control with the paradigm presented here, an online study using the full trials is required. Furthermore, a limitation of the current study is the relatively low number of trials per participant. Therefore, a more extensive study with larger amounts of data per participant would be an important step towards validation of the setup proposed here. However, a longer experimental duration would be needed, making participation more strenuous for the patients.

As a result of the inherent slowness of the BOLD response [Logothetis, 2003] detection of $O_2$Hb and HHb concentration changes is slightly delayed as compared to detection of ERD. For the same reason, it is also sustained until after movement has stopped. ERD on the other hand disappears almost instantly after movement has stopped and is replaced by ERS. Until a few seconds after movement offset, fNIRS features could continue to be classified in a similar fashion as during the movement, while the post-movement ERS could be incorporated as an extra EEG feature. With a more efficient use of data like this, the movement period could possibly be shortened to e.g. 5 or 10 seconds without performance loss. Although in the time-frequency plots of the current data set ERS is not clearly visible for the patient group, more extensive analysis would need to be performed to quantify the actual benefit of a combined ERD/ERS classifier for this group.

An issue that has not been addressed in the current study is intersession variability. Ideally, a brain switch such as the one proposed here would not require recalibration prior to every single use. As hemodynamic responses especially suffer from variations over time, sophisticated methods for reducing or even eliminating recalibration time are of great importance [Power et al., 2012].

Although traditionally SMR-based BCIs exploit signals induced by motor imagery, a few studies have adopted motor attempt instead [Kauhanen et al., 2007, Muralidharan et al., 2011]. BCI paradigms are commonly tested with healthy users, whose actual movements might induce confounding factors as compared to patients in whom no true muscle activation may be present. Motor imagery is considered a relatively representative task of eventual application use: if a patient cannot use actual movement to control the BCI, neither should a healthy user when testing the feasibility of the BCI. However, why the complex task of motor imagery is often retained when moving from healthy subjects to potential users remains unclear. In the current study we compared BCI performance for both types of movement within the same subjects. Here we have shown that for both the individual EEG classifier
and the combined classifier attempted movement yields a significantly higher average classification rate than imagined movement. This may partly be explained by the fact that all patients had retained at least some form of movement in their upper extremities, mostly their wrists. Even though the fingertapping movement could not be executed, the attempt may have triggered slight activation of other arm muscles. In the future, a systematic comparison between patients with different levels of impairment may provide insight into the influence of residual activity in certain muscles on signal strength and therefore chance of detection during attempted movement.

A second explanation could be that motor imagery and attempt are intrinsically different tasks in one very important respect: whereas during attempted movement the intention of moving is in fact present, imagery requires suppression of true movement (intention). Mentally, motor attempt is the exact same task as motor execution, except for the lack of sensory and visual feedback. Imagery on the other hand, although requiring many of the same processes as execution, is driven by a different intention.

Regardless of which of these or other factors mostly contribute to stronger signals during attempted movement, this advantage could and should be exploited, as the gain in performance is apparent. Without trying to generalize over every BCI paradigm and user group, we conclude that at least for the particular application of a brain switch for patients with acquired (rather than congenital) impairments, the actual source of the signals is irrelevant as long as the user retains control. For patients with congenital impairments however, who were not included in this study, somatosensory representations of limbs may be different than for SCI patients.

In addition, EMG signals could be incorporated in the system, thus introducing another component to the hybrid BCI. Instead of using the residual movement and the brain signals for different control outputs, their signals could be merged in order to increase brain switch performance [Millán et al., 2010]. Moreover, in an fMRI study cortical activation patterns of attempted movement in patients with tetraplegia were shown to correspond well to those of executed movement in healthy controls [Shoham et al., 2001], whereas another study showed similar results in patients with paraplegia [Sabbah et al., 2002]. This might be an indication that if motor attempt will be used by patients for BCI control, it is favourable to test the paradigm with healthy users performing actual instead of imagined movement.

On average, the patients in this study became paralysed twenty-five years ago. Nevertheless, movement-related signatures could be detected in every patient in at least one modality and most often in both EEG and fNIRS. In the literature, both invasive and non-invasive recording methods have been demonstrated to be feasible
for neuroprosthesis control in patients with tetraplegia [Hochberg et al., 2006, Müller-Putz et al., 2005]. The current evidence adds to the impression that non-invasive methods, in this case a combined EEG-fNIRS system, could provide adequate brain switch control for motor-impaired individuals. Although non-invasive systems may not (yet) be as robust as invasive alternatives, the advantage of avoiding surgery makes it worthwhile exploring this area further.

Summarizing, we have shown that for an important target group of brain switch technology, namely patients with tetraplegia, a combined EEG-fNIRS classifier yields promising performance rates, especially when the users are instructed to attempt their movements rather than imagine them. Further research is needed to shed light on the feasibility of this paradigm in an online setting.

Appendix

For the EEG-fNIRS combined classifier, as well as for obtaining the predicted labels of the full 15-second trials (see discussion), individual classifier predictions were summed. Here we show that this is equivalent to a naive Bayesian combination of the single example (from now on: ‘trial’) probabilities.

The logistic regression classifier gives the posterior probability $p(c = y|x_i)$ which is the probability that the true class of trial $i$ is $y$ given the trial data $x_i$. When considering multiple predictions we get:

$$p(c = y|x_1, \ldots, x_k) \equiv p(c = y| \bigcap_{i=1}^{k} x_i)$$

Using Bayes theorem and the conditional independence of $x_i$ given the class we get:

$$p(c = y| \bigcap_{i=1}^{k} x_i) = \frac{p(\bigcap_{i=1}^{k} x_i|c = y)p(c = y)}{p(\bigcap_{i=1}^{k} x_i)} = \frac{\prod_{i=1}^{k} p(x_i|c = y)p(c = y)}{p(\bigcap_{i=1}^{k} x_i)}$$

(5.2)

assuming $p(c = y) = p(c = -y)$, using Bayes theorem on $p(x_i|c = y)$ and given that $p(\bigcap_{i=1}^{k} x_i) = \prod_{i=1}^{k} p(x_i|c = y)p(c = y) + \prod_{i=1}^{k} p(x_i|c = -y)p(c = -y)$ gives:

$$p(c = y| \bigcap_{i=1}^{k} x_i) = \frac{\prod_{i=1}^{k} p(c = y|x_i)}{\prod_{i=1}^{k} p(c = y|x_i) + \prod_{i=1}^{k} p(c = -y|x_i)}$$

(5.3)

For logistic regression the mapping of linear predictions is done through the logistic
function:

\[ p(c = y|x_i) = \frac{1}{1 + e^{-yf_i}} \]  \hspace{1cm} (5.4)

where \( f_i \) are the linear predictions based on data \( x_i \). Using the fact that:

\[
\prod_{i=1}^{k} p(c = -y|x_i) = \prod_{i=1}^{k} \frac{1}{1 + eyf_i} = e^{-y\sum_{i=1}^{k} f_i} \prod_{i=1}^{k} \frac{1}{1 + e^{-yf_i}} = e^{-y\sum_{i=1}^{k} f_i} \prod_{i=1}^{k} p(c = y|x_i)
\]  \hspace{1cm} (5.5)

Combining (3) and (5) we obtain:

\[
p(c = y|\bigcap_{i=1}^{k} x_i) = \frac{1}{1 + e^{-y\sum_{i=1}^{k} f_i}}
\]  \hspace{1cm} (5.6)

showing that the naive Bayesian combination of single trial probabilities is equal to the logistic transformation of the summed linear classifier predictions.

**Acknowledgment**

The authors thank Fatma Özin and Betüll Karaman for data acquisition, Koen Koenraadt for his advice on fNIRS data analysis and Twente Medical Systems International for providing the EEG system used in this study.
Table 5.1: Individual and mean classification rates based on single 3-second segments for the control group. Each subcolumn of the fNIRS column represents the single-segment classification rates for only oxy features ($O_2$Hb), only deoxy features (HHb) and when both chromophores are used for classification ($O_2$+H)Hb. The EEG+ subcolumns represent the combination of the classifier outputs of the EEG classifier when combined with either the $O_2$Hb, HHb or the [(O$_2$+H)Hb] classifiers. For EEG classification the segments between 0 and 15 seconds after task onset were used, for fNIRS the segments between 3 and 18 seconds after task onset. The combination was performed by adding the predictions of the EEG classifier for the whole time range (0-15 seconds) and the NIRS classifier for a reduced time range (3-15 seconds). Classification rates above 62% are significantly higher than chance (p=0.05).

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Table 5.2: Individual and mean classification rates based on single 3-second segments for the patient group. See Table 1 for further details. *For P2, EEG channels FC3 and CP3 were removed. Therefore, EEG classification rates for this subject are based on 6 channels only.

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Y. Blokland, L. Spyrou, J. Bruhn & J. Farquhar. (submitted). **Why BCI researchers should focus on attempted, not imagined movement.**
Chapter 6

Why BCI researchers should focus on attempted, not imagined movement

Abstract

For the past decades, developments on non-invasive motor-based Brain-Computer Interfaces (BCIs) have mainly relied on one major assumption: that motor imagery in healthy users is a good model of the strategy a motor-impaired individual would be using for BCI control. Consequently, motor imagery has been adopted as a meaningful task for both healthy and impaired users. However, the brain response is difficult to detect in some subjects and therefore high accuracy cannot always be achieved. We argue that for more reliable and efficient communication and control, patients should use attempted movements instead. Moreover, not imagined but executed movements are the better model of this end user strategy of attempted movement.

6.1 Introduction

An important aim in BCI research is to develop systems which allow paralysed patients to control external devices for movement or communication [Wolpaw et al., 2002]. Movement-based BCIs commonly detect changes in sensorimotor rhythms from the EEG, specifically Event-Related Desynchronization (ERD) and -synchroni-
ization (ERS) [Pfurtscheller and Lopes da Silva, 1999] (BCIs based on other measurement techniques including invasive recordings, as in e.g. [Hochberg et al., 2012], will not be discussed here).

Due to the additional effort required to conduct experiments with patients, most BCI research uses healthy adults. In an attempt to simulate BCI use by paralysed patients, it is common practice to use kinesthetic motor imagery (MI), where the participant imagines as vividly as possible the feeling of moving whilst simultaneously inhibiting motor execution (ME). This lack of movement makes the healthy subjects appear more similar to paralysed individuals. However, there is an implicit assumption that this also makes the brain signatures more similar. Indeed, the seminal work of Pfurtscheller et. al. [Pfurtscheller and Neuper, 1997] showed that MI and ME have similar brain signatures. Later work investigated this more closely in multiple modalities and showed that ME, MI and even observed movement indeed share a common neural substrate in primary motor cortex (PMC) and supplementary motor cortex (SMC) [Schnitzler et al., 1997, Guillot et al., 2012].

However, there is also considerable evidence that the neural response of MI differs significantly from both ME and movement attempt (MA) in paralysed individuals. Indeed, the ERD produced during MI is generally weaker than for ME [Miller et al., 2010]. This difference is not surprising, as MI differs from ME in a number of ways; (1) MI requires an active process of inhibiting movement execution, and (2) MI has no proprioceptive feedback about action execution. Whilst the lack of feedback is similar to the situation in paralysed individuals the inhibitory process is a potential difference. Recent work has investigated the significance of both these aspects using patients with partial paralysis, for example stroke patients who can only move one arm, or Spinal Cord Injury patients who can move arms but not legs. It was found that MI recruits additional networks to actively inhibit motor execution [Guillot et al., 2012]. A study by la Fougère et al. [la Fougère et al., 2010] using fMRI and PET showed that although the basic activation patterns during gait were similar for walking MI and ME, actual locomotion utilised a direct pathway via PMC and MI an indirect pathway via SMC. Further, an fMRI study by Hotz-Boendermaker et al. [Hotz-Boendermaker et al., 2008] comparing attempted and imagined foot movements in patients with paraplegia and execution in matched healthy controls showed that patients retained the ability to distinguish MA and MI. Compared to the controls the strength of activation in the PMC during attempted movement was weaker, whilst there was enhanced activation in regions of the parietal lobe and cerebellum which are important in sensorimotor integration.

Clearly, the situation is complex, and it is unclear whether paralysed individuals
should use MI or MA to control a movement-based BCI. Further one cannot simply assume that imagined movement in healthy individuals is an effective substitute for attempted movement in paralysed individuals. In this paper we aim to address these questions by summarising results from two studies directly comparing attempted and imagined movements in the same subjects.

6.2 Comparing attempted and imagined movements

We briefly describe two recent studies in which both attempted and imagined movements were to be distinguished from a rest condition. Although between the two studies the purpose and user groups were very different, both datasets provide the opportunity to directly compare motor imagery with motor attempt within the same users.

The first dataset was collected from ten patients with tetraplegia performing a fingertapping task with both hands [Blokland et al., 2014]. Trials were collected for three different movement conditions: ‘attempted movement’ (MA), ‘imagined movement’ (MI) and ‘rest’. Nine patients had a complete lesion at C5-C6, one patient had a complete lesion at level C4-C5. The time since the injury varied between 11 and 40 years (mean 25.2 years). EEG was recorded with an 8-channel passive Porti system (TMSi, Enschede, the Netherlands). After data collection, data from one participant were excluded from further analysis due to insufficient signal quality.

The second dataset consists of EEG data recorded from four right-handed healthy volunteers in a two-phase experiment, with the purpose of investigating the possibility to detect attempted movements during general anaesthesia [Blokland et al., 2015]. In the first phase, participants performed actual (ME) and imagined finger movements with their right hand. Afterwards, temporary paralysis of the right arm was induced by administering the neuromuscular blocking agent rocuronium, with the forearm isolated by applying a tourniquet. In the second phase participants performed attempted finger movements. In both phases, ‘rest’ trials were collected as well.

EEG was recorded with a 32-channel actiCAP system (Brain Products). Two electrodes were removed from the EEG cap and instead used to record the right forearm electromyogram (EMG).
Analyses

Both datasets consisted of 3-second cued movement trials. We selected a set of 9 channels over the motor cortex for the analyses of dataset 2, making the input features comparable (though not equal) to those of dataset 1. For both datasets power spectral features between 8 and 24 Hz were used to train a quadratically-regularized linear logistic regression classifier. For each individual movement condition the classification performance on a binary problem (ME, MA or MI compared to the 'rest' condition) was estimated using cross-validation. Only the period during the movement task (0-3s) was used, therefore excluding the beta rebound as a classification feature (in the original paper reporting dataset 2 the beta rebound period was used as a second feature). For dataset 2, transfer classification across movement conditions was also performed. So, a classifier was trained on movement execution and imagery, respectively, and then tested on the attempted movement condition. Classification accuracies between the movement tasks were compared by means of a one-tailed dependent samples t-test. For a detailed description of the setup and analyses for both experiments see [Blokland et al., 2014] and [Blokland et al., 2015].

Results

For study 1, average single trial classification accuracies were significantly higher for attempted movement (76%) than for imagery (67%) (p<0.01), see Table 1(a). A similar result was found for the healthy participants in study 2: 82% for attempted movement compared to 70% for imagery (p<0.05)(Table 1(b)), while EMG levels were similar for both conditions. Classification accuracies did not differ significantly between actual movement and attempted movement. When training on actual movement and testing on attempted movement, the average classification accuracy was 80%, which was significantly higher than for training on imagery and testing on attempted movement (p<0.01).

6.3 Discussion

This paper aimed to answer two questions; firstly, whether motor attempt or imagery is most effective for BCI control in paralysed individuals, and secondly, which of imagined or actual movement in healthy individuals is more similar to attempted movement in paralysed individuals.

Regarding the first question, our results for study 1 show that even for very long term paralysed individuals (on average 25 years) motor attempt produces signifi-
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Table 6.1: Single trial classification accuracies in % for study 1 (a) and study 2 (b). MA = motor attempt, MI = motor imagery, ME = motor execution.

Significantly higher classification rates. Some individuals who may have been classified as 'BCI illiterate' [Vidaurre and Blankertz, 2010] based on their MI results, showed that with MA they were in fact able to produce detectable brain responses. Further, the performance difference between imagined and actual movements in healthy matched control subjects (see [Blokland et al., 2014]) is similar to the difference between imagined and attempted movements in patients. Our second experiment reinforced these results with neurochemically blocked attempted movements generating significantly stronger ERD than imagined movements.

An additional benefit of attempted movements is that in some patients residual muscle activity is present. Hybrid BCI systems may combine muscular output with brain activity to further improve performance [Leeb et al., 2011]. Secondly, MA may have benefits for rehabilitation. Work in BCI for stroke rehabilitation has shown some recovery advantages for combining BCI control with proprioceptive feedback generated by a robot moving the affected limb [Ramos-Murguialday et al., 2013]. Using MA could potentially offer similar benefits for the many patients with some residual motor functioning, as they would also receive a certain level of proprioceptive feedback from these small movements.

The answer to the second question is illustrated by data from healthy subjects performing actual movements, imagined movements and neurochemically blocked attempted movements. Actual and attempted movements have visually very similar time-frequency decompositions (though MA was slightly weaker), see Figure 1. Further, regarding classification accuracies for attempted movement, no significant
difference was found between training a classifier on actual movements and on attempted movements. Conversely, the responses for motor imagery were visually much weaker and classifier performance significantly reduced.

While MI differs from ME in two ways, namely 1) the inhibitory process of MI, and 2) the lack of proprioceptive feedback, MA and ME are only different in the second respect. To further reduce the difference between these motor tasks, even quasi-movements, where subjects are instructed to minimise their intended movements to such an extent that they are no longer detectable with EMG [Nikulin et al., 2008], could be considered. A similar approach was additionally adopted in the second study presented here, demonstrating BCI performance close to that of ME and MA. However, the downside of this approach is that (more extensive) subject training is required.

Considering the combined evidence presented here, we conclude that
(1) Instructions to BCI end users should focus on attempted, not imagined, movement strategies
and
(2) Executed movements form a more realistic model of BCI end user strategies. Therefore BCI testing and validation with healthy users should be based on motor execution rather than motor imagery.
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Figure 6.1: Grand average time-frequency plots for study 2 per movement condition. A relative baseline over the entire trial was used, so that a value of 1 (white) represents average power, a value $<1$ (blue) a power decrease or ERD and a value $>1$ (red) a power increase or ERS. (Adapted from [Blokland et al., 2015]).
Chapter 7

General Discussion

7.1 A BCI-based anaesthesia monitor: outcomes and limitations

Outcomes

In this thesis the development of a Brain-Computer Interface paradigm for awareness detection during anaesthesia was presented. Despite the important position BCI research has taken in the field of patient communication, and the recent expansion of the topic to other domains, thus far the technology had not yet been introduced to the field of anaesthesia monitoring. While on the one hand the application of a BCI to detect awareness during general anaesthesia may seem straightforward, it also brings many difficulties as the system requirements are different from ‘conventional’ BCI paradigms.

First, it was important to design a system with a very low false positive rate. While in a P300-speller it may not present a problem if one in every ten decisions was wrong, in an awareness monitor this would result in a false alarm every minute or so. Considering the fact that an operation may last several hours, this would be unacceptable. The first study (Chapter 2) showed that it was possible to achieve a very low false positive rate along with a high true positive rate. A second important factor is the system setup time. Currently, much time is still required to set up the EEG, including the cap fitting and applying conductive gel. We showed that the BCI can be reliable when only 9 channels over the motor cortex are used, rather than a full 32- or 64-channel setup.
The second step in the development of this paradigm was to test whether attempted movements blocked by a neuromuscular blocking agent would generate the ERD/ERS pattern (Chapter 3). This response has been found during motor imagery [McFarland et al., 2000], passive movements [Alegre et al., 2002], quasi-movements [Nikulin et al., 2008] and attempted movement in patients [Muralidharan et al., 2011, Blokland et al., 2014]. However, the effect of chemically induced temporary paralysis was unknown. Our study showed that attempted movements blocked by a neuromuscular blocking agent produced a very strong ERD/ERS response, much stronger than motor imagery.

Finally, the influence of low doses of hypnotics on the system accuracy, as well as the subjects’ ability to follow commands, was evaluated (Chapter 4). By definition, a patient experiencing awareness during general anaesthesia is conscious, but it is unclear to what extent. In the second clinical study presented in this thesis healthy subjects were therefore lightly sedated before executing movement tasks. While the results demonstrated that the BCI may in principle work in altered states of consciousness, it became clear that sedation may present difficulties with regard to interpretation of the outcome, and thus reliability. Meanwhile, it also provided some interesting insights on the nature of sedation and states of consciousness in general.

Limitations

In both clinical studies the setup did not allow for a fully randomised experiment. Although anaesthetic drugs have a fast onset and offset effect compared to non-anaesthetic drugs, a true ‘baseline’ state cannot be ensured for up to several hours after drug administration. This required that all trials for one particular condition (paralysis in the study on rocuronium, or each of the sedation levels in the study on propofol) were recorded in one experimental block. This may have introduced so-called ‘block effects’. In the later stages of the experiment, the subject may have become better at the task because of learning effects. In this case this is not very likely as the movement task was very easy to perform even without practice. On the other hand however, the subjects may have gotten tired or less motivated over time. Especially in the second study, where subjects received propofol, the duration and repetitive nature of the experiment may have contributed to subjects becoming less alert.

One partly unresolved issue is the system calibration phase. The work presented here shows that a classifier trained on a user’s actual movements can detect the same user’s attempted movements when blocked by a neuromuscular blocker. Similarly, in
two-thirds of the volunteers participating in our studies, a classifier trained on a baseline level could detect movements while the subjects were sedated (1.0 $\mu$g/ml propofol effect-site concentration). However, in the remainder of the volunteers, this transfer classification performed at chance level. While several factors indicate that these subjects may already have been in a mental state where perception and sensation are uncoupled, meaning that they produced the movement tasks at a subconscious level, future studies are required to further investigate this theory.

Even if within-subject transfer of a classifier was fully feasible, i.e. if a classifier trained on a user’s actual movement data obtained before sedation could detect attempted movement while a patient was conscious but nevertheless sedated, this may not be enough to be adopted in clinical practice. Ideally, a calibration phase would be unnecessary. For this purpose, which would be useful in many BCI paradigms, generic (multi-user) classifiers are being developed.

The presented paradigm currently follows a synchronous setup, i.e. it depends on a time-lock and the presentation of auditory stimuli. In practice, some patients may have impaired hearing or not be able to respond to the stimuli for other reasons. An asynchronous design would allow for the detection of spontaneous movement and therefore be more user-friendly and, potentially, more robust. While beyond the scope of this thesis, the developments on asynchronous generic systems are very important for the future of clinical BCI paradigms such as the one presented here.

### 7.2 Theories of consciousness

Despite the fact that the concept of consciousness is often used to describe someone’s mental state, its true nature is still poorly understood. Various theories have been proposed attempting to explain the neural basis of consciousness, such as the Integrated Information Theory [Tononi, 2004] and the Global Workspace Theory [Baars et al., 2003]. This neurobiological perspective will not be further discussed here. A second perspective is of a more philosophical nature: it addresses questions such as ”What does it mean to be conscious?” and ”What precisely does subjective experience entail?”. Finally, there is the pragmatic approach: describing in what situations what level of (un-)consciousness and (un-)responsiveness is problematic, and what would be be required to take these problems away. The following paragraphs will try to shed some light on consciousness, disorders of consciousness and anaesthesia awareness from the philosophical and pragmatic perspectives.
Determining consciousness in unresponsive patients: a Turing test

In 1950, Alan Turing proposed his famous question "Can machines think?" [Turing, 1950]. He devised a hypothetical test in the form of a game, in which a human and a computer are placed in separate rooms. The third participant, a human interrogator, has to determine which of the two others is the human and which is the machine by means of asking them questions. If the machine can convince the interrogator that it is the human, and is thus perceived as being intelligent and conscious, it passes what has later come to be known as the Turing test. According to Stins [2009], determining whether an unresponsive patient is conscious is akin to determining whether a machine is intelligent. What a patient needs to do, is to convince others that he or she is conscious.

In theory, one can never be certain that another person is conscious. This is referred to as the 'problem of other minds'. However, we normally choose to interpret behavioural cues, usually speech and movement, as indicators that another person has similar subjective experiences as we do, and therefore reacts to the world in an expected manner. This behaviourist approach has shown to fail in the circumstances addressed in this thesis: when a person lacks the means for self-reporting their mental state. As Owen [2013] summarises the problem: "absence of evidence is widely accepted as adequate evidence of absence". If a patients does not pass the Turing test, he or she is considered to lack consciousness.

The work by Owen and colleagues shows that a solution may be at hand: the inclusion of neural signals in the set of accepted behavioural responses. Using both fMRI and EEG brain responses were obtained in patients diagnosed to be in Vegetative State that the researchers judged to be signs of consciousness [Owen et al., 2006, Monti et al., 2010, Cruse et al., 2012]. Theoretically, there is no reason to trust brain signals less than muscular output as evidence that a person is conscious. Criticism to Owen's work has mainly revolved around the argument that the brain patterns that Owen and colleagues asserted to a conscious response, may just have reflected an automatic response. There is no direct evidence for the presence of subjective experience. However, the same holds for 'normal' behavioural output. If the patient can convince us that he or she is conscious, it is irrelevant whether that was done by means of verbal, muscular or neural output. If we in principle accept brain responses as true expressions of mental content, only one question remains: how do we map brain activity onto an assumption of consciousness? In other words, what specific signs of expression do we attribute to the presence of consciousness rather than to
random brain activity? Again, it comes down to what the observer interprets to be a meaningful response. The various levels of consciousness encountered in disorders of consciousness illustrate that this interpretation is far from straightforward.

**Subjective experience versus responsiveness**

Consciousness is not a binary mental state, where one is always either fully conscious or fully unconscious. Sleep, coma and general anaesthesia are all states in which someone is considered to be more or less unconscious. During sleep, wakefulness is lost, i.e. someone has no awareness or experience of their surroundings. However, Sanders and colleagues state that one can still experience *disconnected* consciousness during sleep, for instance when dreaming [Sanders et al., 2012]. Another component Sanders distinguishes is ‘responsiveness’. What does it mean when a patient does not respond to command? Someone’s observable (lack of) behaviour is not always sufficient to determine whether they are conscious or not, evidenced by locked-in syndrome, awareness during anaesthesia and disorders of consciousness.

Conversely, the presence of movement (attempt) alone may not be sufficient to conclude the patient is conscious. Pandit describes a view consistent with the notion of disconnected consciousness during general anaesthesia, the concept of ‘dysanaesthesia’ [Pandit, 2013]. In this state sensation and perception are uncoupled, i.e. the brain may respond to external stimuli although subjective experience is absent. This idea is corroborated by the results from Chapter 4. While single trial classification accuracies were significantly better than chance level after sedation, this was only the case in every subject when the classifier was actually trained on data obtained during the same sedation level. At a propofol effect-site concentration of 1.0 $\mu$g/ml, in 4 out of 12 subjects, the strength of the changes in sensorimotor rhythms had been largely reduced or the response had even been diminished altogether. Interestingly, although EMG measures indicated slightly slower and more erratic responses in these subjects, they were clearly still able to follow commands as they executed the desired movement tasks as instructed.

A very similar situation is encountered in various studies using the isolated forearm technique (IFT, [Tunstall, 1977, Russell and Wang, 2014]). With the IFT, one arm is isolated by inflating a cuff before induction of neuromuscular blockade. This allows the patient to communicate by moving the unparalysed hand. Interestingly, in many IFT-studies patients responded to command by moving (i.e. they exhibited goal-directed behaviour), but did not show any spontaneous responsiveness during surgery. In addition, patients who responded to command rarely recalled being awake.
afterwards [Sanders et al., 2012].

Thus, while as discussed above, the lack of a physical response does not necessarily indicate a lack of consciousness, the problem goes even deeper. If a patient does respond in a meaningful way, whether we judge this by their physical movements or their brain activity, we still cannot be sure of the presence of subjective experience.

**Implications for anaesthesia monitoring**

Summarising, is it unclear what the precise relationship is between awareness during anaesthesia and responsiveness during anaesthesia. Pandit concludes that the state of ‘dysanaesthesia’ may be sufficient to consider general anaesthesia successful [Pandit et al., 2013]. In other words, anaesthesia awareness would only be problematic in cases where the patient would have responded spontaneously to surgical stimulation had they not been paralysed, and where they would have reported awareness spontaneously afterwards (‘explicit recall’). Sanders and colleagues draw a similar conclusion stating that disconnecting the patient from the environment may be the minimal requirement for general anaesthesia [Sanders et al., 2012]. However, Pandit admits that an IFT-response during a state of dysanaesthesia is likely a sign that a patient is emerging from unconsciousness. The same would hold then for movement attempts detected from the EEG. Moreover, it is reasonable to assume that in cases of significant pain or other discomfort the patient is likely to produce a spontaneous response [Sanders et al., 2012]. Indeed, the loss of meaningful responses to painful stimuli normally happens after the loss of command following [Noreika et al., 2011].

It would therefore make sense to increase the anaesthetic dose when activity is detected that we would normally interpret as conscious behaviour, in this case movement. A movement response during IFT or attempted movement detected from EEG probably either indicates 1) consciousness or 2) dysanaesthesia or connected consciousness which is likely a precursor for consciousness. Future theoretical as well as empirical work will hopefully provide a more definite answer to the question of what (neural) behaviour during anaesthesia requires intervention.

### 7.3 Future directions

**Anaesthesia monitoring**

One question that has been largely left unaddressed in this thesis is: What would the eventual BCI monitor look like, and how would it be used? Several aspects can
be considered in this regard:

- **Output:** The paradigm could be further developed into a stand-alone system, or alternatively detection of attempted movement could become one of several features in another system. A combined monitor could for instance output the chance of motor attempt in % alongside the dimensionless Bispectral Index output number. While BIS monitors present the raw EEG signals on a screen, the BCI monitor could provide visual details of the power spectral density, specifically displaying details of periods when the patient may have attempted to move. Other features that may be considered in a combined system include EMG and possibly EEG signatures correlated with pain and fear.

- **Sensors:** For practical reasons, the hardware, including the sensors, should be as small as possible. Any cables should not interfere with other machines and cables and not hinder the surgeon. Further development of wireless and dry EEG electrodes [Chi et al., 2012, Hairston et al., 2014, Jakab et al., 2014] will be essential for clinical applications in general and BCI-based anaesthesia monitoring in particular.

- **Usability:** The usability of the system largely depends on the issues discussed above: The system output should be easily interpretable, the hardware should be easy and quick to set up and, naturally, using the system should be safe. If the level of added complexity is too high, anaesthetists will likely be reluctant to include the monitor in their daily procedures. Another factor has been pointed out before: the necessity of a calibration session. It is probably not feasible to calibrate the system for every individual patient, especially when such a procedure would take more than a few minutes. Recently it has been suggested that a small amount of resting state data may be sufficient for calibrating a motor imagery-based BCI [Wang et al., 2012]. That type of data should be relatively easy to obtain while preparing for the surgery. The current setup that still requires individual calibration could perhaps be a solution for patients with an increased risk of intraoperative awareness (e.g. patients with a history of awareness [Aranake et al., 2013] or those undergoing cardiac surgery [Serfontein, 2010]).

An important ethical question also arises when working with a cued design and/or a calibration period: should the patient be informed of the risk of becoming aware during surgery? A specific instruction to try to move during auditory or other cues would require this. One way to work around that may
be for the anaesthetist to ask the patient to respond to command while inducing sedation, much like with IFT protocols (“if you can hear me, squeeze my hand”). In this case it could be an instruction along the lines of “if you hear the beep, move your hand”. It is however unknown whether patients would remember that type of instruction after awaking from anaesthesia.

- **Validation:** A final important issue concerns the validation of the system. Conventionally, novel clinical developments undergo an evaluation process in large clinical trials. That approach would in theory be useful here, to test if the novel paradigm can prevent awareness in every patient and to compare it to existing systems. However, as the incidence of intraoperative awareness is low, the required scale of clinical testing renders such attempts virtually impossible. There is no controllable way of inducing a state of intraoperative awareness on demand. Instead, introduction of the BCI monitor would probably have to be solely based on a proof of principle. This fact alone is one of the greatest difficulties for introduction of the system into daily clinical practice and remains even if all technical difficulties have been dealt with.

**BCI in general**

Many challenges faced in the development of BCIs for other (clinical) purposes apply equally to the system proposed here. Development of truly asynchronous, zero-training BCIs is especially relevant as that would mean a great improvement in general usability. A short hardware setup time, including sensors that are fast to mount, reduces the threshold for using a BCI. Outside the operating room, less bulky hardware is not only important for practical but also for social reasons. Patients value aesthetics and want to prevent further stigmatisation due to the equipment they might be carrying around [Nijboer et al., 2014].

Another interesting development in BCI research is the gradually growing interest in the use of functional near-infrared spectroscopy (fNIRS) instead of, or in addition to, EEG. In Chapter 5 a hybrid EEG-fNIRS BCI was discussed. While it had been shown previously that combining features from both modalities could increase BCI performance in healthy users [Fazli et al., 2012], here a similar result was found in patients with tetraplegia. This study focussed on brain switches for control of assistive devices such a neuroprostheses, but fNIRS may be equally relevant for communication. Already the possibility of fNIRS-based communication in patients with ALS has been shown [Naito et al., 2007], while recently fNIRS studies for disorders of consciousness have been initiated in both the Tübingen [Veser et al., 2014] and Graz
BCI research groups. fNIRS-based paradigms have the potential to be further used and developed in various domains of BCI research, including anaesthesia awareness. As discussed in Chapter 6, the results from Chapter 3 and Chapter 5 point to an interesting principle: motor attempt is a better control task for BCI than motor imagery. Modulation of sensorimotor rhythms is among the most widely used paradigms in BCI research. Consistently instructing patients to adopt attempted movement as a control strategy may well improve current BCI performance and thus increase usability. While the precise underlying mechanisms for the benefit of attempted movement are not yet specified, the intention of actually moving, without inhibition, is likely an important component. Any residual muscle output could be used as an extra feature in a hybrid system and improve the performance even further.

7.4 Overall conclusion

On the one hand, awareness during intended general anaesthesia is a troubling but fascinating topic. For decades, anaesthesiologists have tried to find the ultimate solution to the question of how to detect consciousness in a paralysed patient (the 'anaesthetist’s dilemma, [Pandit, 2014]. On the other hand, the field of Brain-Computer Interfacing is equally fascinating, and in fact often deals with precisely the same question. The types of situations in which a patient may be paralysed yet conscious are numerous: the locked-in state as a result of for instance brain stem stroke or ALS, misdiagnosed cases of minimally conscious state, and indeed intraoperative awareness. For each of these situations ways are being sought to let the patient communicate without depending on motor output. Fortunately, brain signals carry all the necessary information. It is the task of the BCI researcher and the anaesthesiologist to extract the relevant pieces from this high-dimensional data, in a safe, reliable and efficient way.

Brain responses produced by movement attempts have demonstrated to be a reliable source of information. They can be detected from the EEG (as well as from signals obtained with other modalities) in healthy users and patients alike, during neuromuscular block, and even in patients who have lost movement abilities over twenty-five years ago. It is the intention of the motor action that facilitates communication through brain signals. Therefore, movement attempt, more so than motor imagery, may be the key to establishing communication via a BCI.

While important steps have been taken towards communication by paralysed patients, many technical, theoretical and ethical challenges still await. It is to be hoped that researchers from the fields of BCI, disorders of consciousness and anaesthesia
will build further collaborations and share their expertise, in a joint effort to find the ultimate solution to ‘unlocking’ the locked-in patient.
References


References


Nederlandse samenvatting

Vrijwel alles wat de mens doet draait om interactie met anderen en met de omgeving. Door spraak en beweging kunnen we de wereld beïnvloeden en zo onze doelen bereiken. In sommige gevallen wordt deze interactie echter bemoeilijkt: mensen kunnen door ziekte of een ongeluk geheel of gedeeltelijk verlamd raken. Bijvoorbeeld patiënten met de progressieve ziekte ALS, die steeds meer bewegingsfuncties verliezen. Of patiënten die ontwaken uit een coma en daarna in een toestand komen waarbij ze verlamd zijn maar af en toe periodes van bewustzijn hebben (Minimally Conscious State of MCS).

Er zijn ook situaties waarin het de bedoeling is dat iemand tijdelijk niet kan bewegen: tijdens een operatie onder algehele narcose. De patiënt wordt buiten bewustzijn gebracht om niets van de operatie te hoeven meemaken. Onderdeel van de narcose is een spierverslapper die ervoor zorgt dat de patiënt geen onverwachte bewegingen maakt. Echter, in een zeer klein percentage van de operaties verliest de patiënt het bewustzijn niet (geheel) of ontwaakt hij of zij tijdens de operatie. Als de spierverslapper echter wel goed werkt is er sprake van een tijdelijke locked-in-staat, vergelijkbaar met de bovengenoemde situaties als MCS en de laatste fase van ALS. De patiënt is wakker, maar kan dit niet kenbaar maken.

In dit proefschrift wordt een aantal onderzoeken beschreven die als doel hebben om te laten zien of, en hoe, hersensignalen gebruikt kunnen worden als direct communicatiemiddel. Zogenaamde Brein-Computer Interfaces (BCIs) vertalen gemeten hersengolven naar bijvoorbeeld geschreven tekst of de aansturing van een apparaat zoals een robotarm of een rolstoel. Hierbij is het echter van belang dat het duidelijk is wat de gebruiker precies wil communiceren of doen. De computer moet dus een betrouwbare voorspelling kunnen doen over de betekenis van het gemeten hersensignaal op een bepaald moment. De meest gebruikte methode om de hersensignalen te meten voor de aansturing van een BCI is elektro-encefalografie, kortweg EEG. Hierbij worden elektroden op het hoofd geplaatst die de elektrische activiteit in het brein meten.
De computer leert vervolgens om patronen in de hersenactiviteit te herkennen en te onderscheiden. En van de meest voorkomende taken voor aansturing van een BCI is beweging. Het bewegen van een arm of hand, maar ook het inbeelden van eenzelfde beweging, zorgt voor een duidelijke reactie in het EEG-signal. Patiënten die wakker zijn tijdens narcose proberen vaak te bewegen. Het herkennen van deze pogingen tot bewegen zou de basis kunnen vormen voor een BCI die de artsen waarschuwt dat de patiënt bij bewustzijn is.

In hoofdstuk 2 wordt het concept van een dergelijke BCI uitgewerkt en de haalbaarheid onderzocht. Deze studie laat zien dat de EEG-signalen die geproduceerd worden tijdens beweging betrouwbaar te meten zijn. Armbewegingen konden in deze studie in 99% van de gevallen herkend worden. Het aantal false alarm was daarbij minder dan 0.01%. Een lage false positive rate is zeer belangrijk om dit systeem in de praktijk te brengen. Verder werd in deze studie gekeken naar het aantal benodigde elektroden. Het systeem bleek betrouwbaar genoeg bij gebruik van slechts 9 elektroden. Daarmee is het systeem redelijk snel op te zetten, een belangrijke vereiste om het in de praktijk te brengen.

Hoewel het systeem betrouwbaar blijkt te zijn op basis van echte bewegingen, moet het ook werken als de patiënt probeert te bewegen. Bij het onderzoek beschreven in hoofdstuk 3 kregen proefpersonen een spierverslapper toegediend in de rechterarm, waarna ze moesten proberen deze arm te bewegen. De gemeten EEG-signalen tijdens deze gepoogde bewegingen bleken zeer vergelijkbaar te zijn met de signalen tijdens daadwerkelijk uitgevoerde bewegingen.

In hoofdstuk 4 werd gekeken naar de invloed van lage doseringen van sedatieve medicatie. Bij het merendeel van de proefpersonen waren de bewegingen nog altijd duidelijk herkenbaar in het EEG na toediening van de medicatie. Bij eenderde van de proefpersonen was dit echter niet het geval. Dit gegeven biedt een interessant inzicht in de mechanismen van bewustzijn. Vervolgonderzoek is nodig om dit probleem verder uit te diepen.

BCIs zijn niet alleen relevant voor communicatie door patiënten die volledig verlamd zijn. Voor patiënten met een gedeeltelijke fysieke beperking kan het een hulpmiddel zijn om een bepaalde mate van vrijheid en zelfstandigheid terug te krijgen. In hoofdstuk 5 wordt gekeken naar de mogelijkheden van het meten van gepoogde bewegingen in patiënten met tetraplegie. Net als bij de proefpersonen die een spierverslapper kregen toegediend, bleken de gepoogde bewegingen van deze deels verlamde patiënten goed meetbaar in het hersensignaal. Beide studies tonen aan dat gepoogde bewegingen een betrouwbare signaal opleveren dan ingebeelde beweging, hoewel ingebeelde bewegingen meestal verkozen worden in BCI-onderzoek. In hoofdstuk 6
wordt deze kwestie verder bediscussieerd.

Dit proefschrift laat zien dat het herkennen van bewustzijn tijdens algehele narcose een nieuwe toepassing kan zijn binnen het vakgebied van Brain-Computer Interfacing. Hoewel de eerste stappen ter ontwikkeling van een dergelijk systeem hier genomen zijn, zijn er vele aspecten die nog onderzocht moeten worden. Het is daarom van groot belang dat anesthesiologen en BCI-onderzoekers blijven samenwerken. Het uiteindelijke doel is om alle patiënten die, door welke oorzaak dan ook, locked-in zijn, weer de mogelijkheid te geven om met de buitenwereld te communiceren.
Publication list

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Y. Blokland, L. Spyrou, J. Bruhn & J. Farquhar. (submitted). Why BCI researchers should focus on attempted, not imagined movement.


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